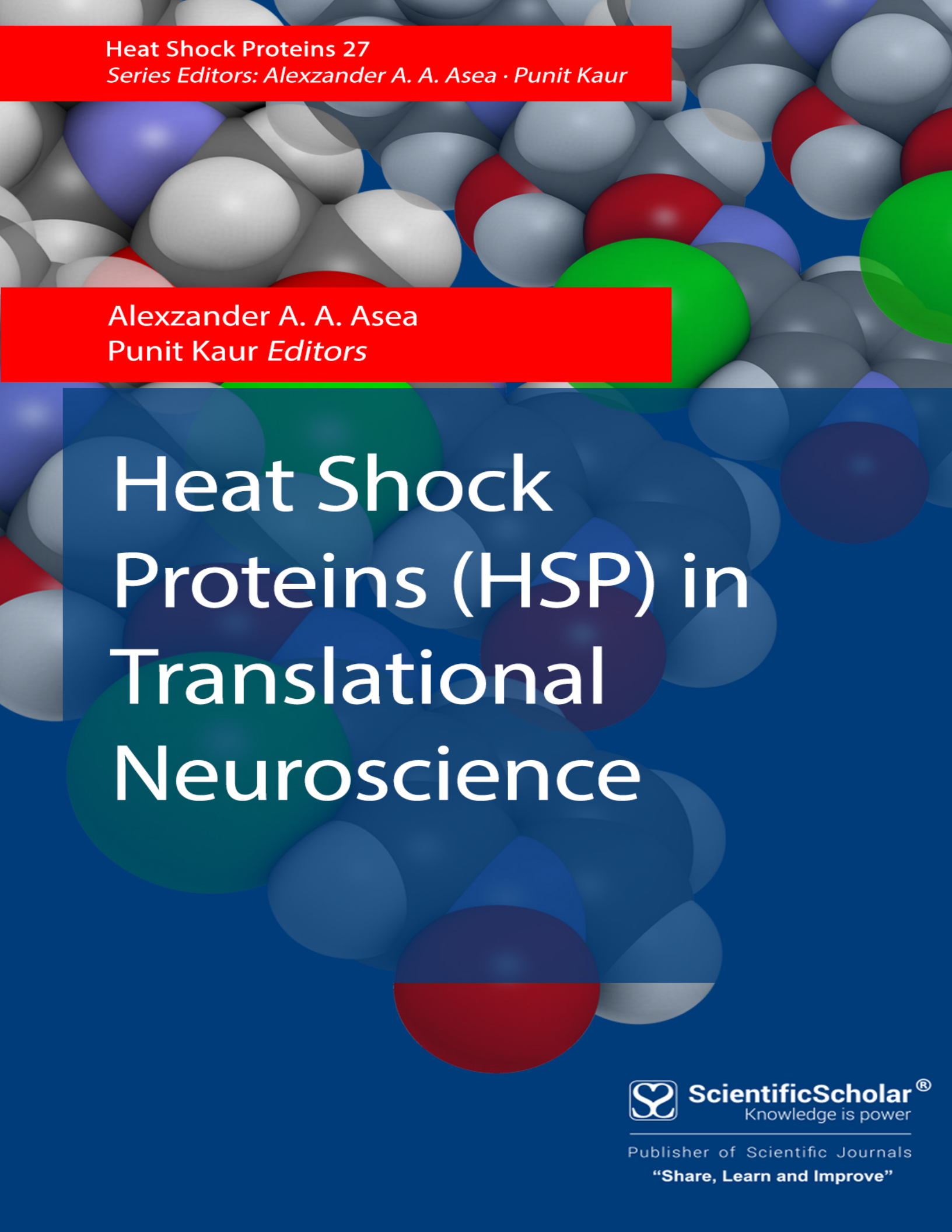
Heat Shock Proteins 27
Series Editors: Alexzander A. A. Asea · Punit Kaur
Alexzander A. A. Asea
Punit Kaur Editors
Heat Shock Proteins (HSP) in Translational Neuroscience
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Heat Shock Proteins (HSP) in Translational Neuroscience

Volume 27

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Heat Shock Proteins (HSP) in Translational Neuroscience

Heat Shock Proteins

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Editors

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Preface

Heat shock proteins (HSP) family members are the principal pathways involved in degradation and clearance of the misfolded protein aggregates. HSP plays a critical role in preventing the misfolding of protein or refolding of partially denatured or misfolded proteins. HSP are also involved in autophagy mechanism and are considered as intracellular lifeguards or guardians of proteome, as well as protein quality control. Importantly, they are constitutively expressed in the nervous system.

The book ***Heat Shock Proteins (HSP) in Translational Neuroscience Volume 27*** is the concise collection of articles focused to develop efficient therapies aimed at combatting various types of neurodegenerative diseases. Using an integrative approach, the contributors provide the most comprehensive review on the role of HSP in signaling pathways relevant to several neurodegenerative diseases. To enhance the knowledge on neurodegenerative diseases, this book reviews on the current progress on our understanding of role of HSP in various neurodegenerative diseases including glioblastoma, neuro-oncology, Alzheimer's and central nervous system.

Key basic and clinical research laboratories from major universities, academic medical hospitals, biotechnology and pharmaceutical laboratories around the world have contributed chapters that review present research activity and importantly project the field into the future. The book is a must read for graduate students. Medical students, basic science researchers and postdoctoral scholars in the fields of Translational Medicine, Clinical Research, Human Physiology, Biotechnology, Natural Products, Cell & Molecular Medicine, Pharmaceutical Scientists and Researchers involved in Drug Discovery.

Alexzander A. A. Asea — Dover, DE and Toledo, OH, USA
Punit Kaur — Toledo, OH, USA

About the Editors

Prof. Dr. Alexzander A. A. Asea is a highly innovative and accomplished world renowned clinical and basic research scientist and visionary executive leader who has exceptional experience spearheading clinical and basic science research, training, education, and commercialization initiatives within top-ranked academic biomedical institutes. Prof. Dr. Asea's initial findings studying the effects of Hsp72 on human monocytes lead to the proposal of a novel paradigm that Hsp72, previously known to be an intracellular molecular chaperone, can be found in the extracellular milieu where it has regulatory effects on immunocompetent cells—a term now called chaperokine. Prof. Asea has authored over 320 scientific publications including peer-reviewed articles, reviews, books, book chapters, editorials, and news headliners in a wide range of biomedical-related disciplines. Prof. Asea is the Editor-in-Chief of the widely successful book series *Heat Shock Proteins* (Scientific Scholar) and is an editorial board member of numerous scientific peerreviewed journals. Prof. Dr. Asea is the President & CEO at NampEVA BioTherapeutics LLC in Dover, USA and Professor at the University of Toledo College of Medicine and Life Sciences in Toledo, USA.

Dr. Punit Kaur is an expert in onco-proteogenomics, with extensive training and experience in quantitative mass spectrometry imaging, protein chemistry, and biomarker discovery. Dr. Kaur's main research focus is on the use of heat-induced nanotechnology in combination with radiotherapy and chemotherapy in the cancer stem cell therapy. Dr. Kaur has published more than 70 scientific articles, book chapters, and reviews, and currently serves as editorial board member for the *European Journal of Cancer Prevention and the Journal of Proteomics and Bioinformatics.* Dr. Kaur is the Associate Editor of the highly successful Heat Shock Proteins book series by Scientific Scholar Publishers. Currently, Dr. Kaur is at the University of Toledo College of Medicine and Life Sciences in Toledo, USA.

Heat Shock Proteins (HSP) in Translational Neuroscience

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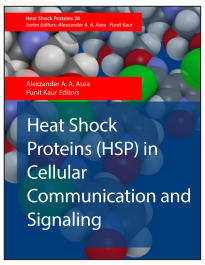

Molecular Mechanisms of Heat Shock Proteins in Distinct Diseases

Nazlican Yürekli, Merve Tutar, Laziz Niyazov, Fatma Sağır, Kübra Açıkalın Coşkun, Mervenur Al, Kezban Uçar Çifçi, Cansu Abay, Asiye Gök Yurttaş, Zehra Okat, and Yusuf Tutar

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ABSTRACT

Heat shock proteins (HSPs) modulate the molecular mechanics of cells and cellular systems. Properly folded proteins are required for cellular processes and organisms use molecular mechanics to keep substrate proteins in their native state. Therefore, cellular compartments employ redundant isoforms of HSP to maintain substrate protein homeostasis and keep them functional. Hence, HSP folder function is critical for cell, HSPs are universally conserved. HSPs play essential roles in cellular signalling and in immune system besides their folder function. To this purpose, the roles of distinct HSP are described in this review to describe their molecular mechanisms in diseases.

Keywords: Cancer · Heat shock proteins · HSP inhibitors · Mutation · Neurodegenerative diseases · Protein folding

ABBREVIATIONS

Aß	amyloid beta
ACD	alpha-crystalline domain
AD	Alzheimer's disease
ADP	adenosine diphosphate
AHA1	activator of Hsp90 ATPase
AIF	apoptosis initiator factor
Akt	A serine/threonine protein kinase
ALS	amyotrophic lateral sclerosis
APAF1	apoptotic protease-activating factor-1
ATP	adenosine triphosphate
Cdc37	cell division cycle 37
Cdk5	cyclin-dependent kinase 5
CHIP	chromatin immunoprecipitation
CMT	Charcot-Marie tooth disease
CTD	carboxyl-terminal domain
DAXX	cytochrome C and/or death domain-associated protein 6
DNAJ	DnaJ-like protein
EGCG	epigallocatechin gallate

ERAD	endoplasmic reticulum-associated degradation
ErbB-2 (Her2)	Erb-B2 receptor tyrosine kinase 2
FKBP51	FK506-binding protein 5
GDA	geldanamycin
HIF	hypoxia-inducible factor
HSE	heat shock elements
HSF	heat shock transcription factors
HSP	heat shock protein family
HTT	Huntingtin
IL-8	interleukin 8
JDP	J-domain proteins
LB	Lewy bodies
LN	Lewy neuritis
LOX-1	lectin-like oxidised low-density lipoprotein receptor-1
LRRK2	leucine-rich repeat kinase 2
MAPK	mitogen-activated protein kinase
MAPKAP	mitogen-activated protein kinase (MAPK)-activated protein kinase
mHTT	mutant HTT
Mif	macrophage migration inhibitory factor
MMP9 and MMP2	matrix metallopeptidase protein 2 and 9
NBD	nucleotide-binding domain
NTD	amino-terminal domain
PD	Parkinson's disease
PDCD	programmed cell death protein
[PIN+]	prion
PINK1	Pten-induced kinase 1
PKC	protein kinase C
PTEN	phosphatase and TENsin homolog deleted on chromosome 10
RAF	rapidly accelerated fibrosarcoma
RAS	rat sarcoma virus
ROS	reactive oxygen species
SBD	substrate-binding domain
sHSP	small heat shock protein
Sis1	HSP40 gene of *Saccharomyces cerevisiae*
SNCA	alpha-synuclein
STAT1-2	signal transducer and activator of transcription 1
TDP-43	TAR DNA-binding protein 43
Tid1	mitochondrial co-chaperone gene
UV	ultraviolet
VPS35	vacuolar protein sorting 35

1 INTRODUCTION

The family of heat shock proteins (HSP) is conserved in all species [1]. HSPs are associated with cell proliferation, differentiation, apoptosis, survival and carcinogenesis [2]. These proteins are called 'HSP' because they were initially identified in *Drosophila melanogaster* as the temperature rises [3]. HSPs are 'stress proteins' because their expressions are activated by stressors such as toxins, heavy metals and viruses [4]. The production of these proteins aids the natural folding of substrate proteins for appropriate biochemical function. Proper function depends on its native structure and HSPs play a crucial role in substrate protein folding, but they have other functions in transportation, signalling pathways, regulation of the immune system and cell survival as well. Furthermore, HSPs are expressed both constitutively and inducible under stress to perform housekeeping activities [5]. HSP isoforms are distinct in each compartment, and redundant versions of HSP exist even within the same compartment. The HSP complex serves a range of functions because each HSP coordinates and cooperates with distinct co-chaperones [6]. In addition, the other heat shock protein family member is the small heat shock protein (sHSP) class, and these proteins are accepted as housekeeping proteins because of their function in cytoskeleton stabilisation and contribute to proteostasis [7]. The expression regulation alters the functional role of the proteins as well; small HSPs are coordinated through heat shock factors for their stress-induced expression, but their constitutive expression is under the regulation of other transcription factors [7]. With their different functions and expression patterns, the HSP families are classified to their own molecular weights, this classification ranges from 8 to 110 kDa [3]. The majority of the HSP are part of the HSP27, HSP40, HSP60, HSP70, HSP90 and large HSP groups [2]. The families show sequence homology across the phylogenetic spectrum, and they are found to be extremely conserved throughout evolution [6].

The presence of the HSP families in all species, as well as their conservation, shows that they play important roles in the cell. Some of them serve as molecular chaperones and play in the maintenance of cellular homeostasis [6–8]. Each family member takes role(s) in the cellular processes such as protein folding and unfolding, multiprotein complex assembly, cell cycle control and stress protection [1]. The proteins that are constitutively expressed in normal conditions have been found to maintain and repair intracellular proteins. The HSPs that are expressed on stress are also affected by a variety of conditions such as cold, ultraviolet (UV) radiation, change of osmolarity, change of pH and tissue remodelling [2]. Under normal physiological conditions, HSPs are in the cytosol of mammalian cells, linked with heat shock transcription factors (HSFs). These HSFs can act as inducible transcriptional regulators [2]. If a stress condition occurs, HSP and HSF dissociate and HSP may bind denatured proteins. Unbound HSF gets phosphorylated by protein kinase C (PKC) or other serine/threonine kinases to be trimerised. After trimerisation, HSFs are transferred to the nucleus and interact with heat shock elements (HSEs) which are localised in HSP genes' promoters. As a result, the expression of HSP increases. Furthermore, a protein that is a constitutive HSE-binding factor is present under no stress conditions to prevent HSF from binding to HSE. HSP moves to the cytosol after being translated, and HSFs follow.

On stress, the expression of HSP increases in the cell, their primary goal is to protect the cell through interactions with proteins. Because of their known protective roles in the cell, some HSPs are also known as molecular chaperones. Molecular chaperones play critical roles in processes such as promoting newly synthesised polypeptide chains of proteins to self-assemble into their native spatial structure, stabilising protein intermediates during intercellular transport and folding and assisting in protein degradation [9]. Normally, functional proteins are found in the cell in their folded native form. However, during certain cellular processes such as protein synthesis and translocation, nascent proteins expose hydrophobic regions and are

not fully folded to their native three-dimensional state. During this process, partially folded substrate proteins may interact with other proteins which result in protein aggregation. Cells programmed to restrict protein aggregation; therefore, unfolded and/or partially folded proteins' non-specific interaction must be prevented through HSP folder activity. As a result, HSPs bind to these unfolded hydrophobic surfaces, promoting folding [10, 11]. HSP diverse roles come from the coordination of different redundant isoforms with co-chaperones. In the human body, there are 13 HSP70 isoforms and 60 HSP40 isoforms. Specific cellular functions are performed by the combination of distinct HSP40s and/or co-chaperones with distinct HSP70s [12]. Its J-domain stimulates HSP70 ATPase activity, and HSP40's C-terminal peptide-binding fragment binds to non-native polypeptides, which are then submitted to HSP70 [12]. HSP40 works to stabilise the interaction between HSP70 and unfolded protein. If this process of protein refolding fails, aggregation may occur, as in the case of poly-glutamine protein, which is commonly found in neurodegenerative disorders [13]. This review highlights the roles of distinct HSP in diseases.

2 THE ROLES OF HUMAN HSP IN DIFFERENT DISEASES

2.1 Heat Shock Protein 27 (HSP27)

Human HSP27 is encoded by the HSPB1 gene in the human genome and is involved in cellular development, muscle cell contraction, protein folding, apoptosis and stress response [14, 15]. It functions as a chaperone in the cell, as other HSP, and interacts with a wide range of proteins [16]. The HSP27 protein is divided into three domains: The amino-terminal domain (NTD), the alpha-crystalline domain (ACD) and the carboxyl-terminal domain (CTD) (Fig. 1) [17]. There is an alpha-crystalline region consisting of 80–100 residues in the middle domain, which is quite well conserved and is responsible for the formation of stable dimers [17]. The less conserved N terminal region, on the other hand, is responsible for ensuring the movement and flexibility of the protein [18]. It is in the cytosol, mainly in the perinuclear spaces. Its synthesis has been increased at various stages of cell differentiation and development [19]. The α-crystalline domain of HSP27 interacts with inter-subunits of other human sHSP. Any change in the genetic code of *HSP27* conserved cysteine inhibits dimer formation, which also prevents multimer (large oligomer) formation. These findings suggest that HSP27's conserved cysteine residue is important for large oligomer formation, which is related to its chaperone activity and ability to interact with a wide range of polypeptides [17]. HSP27 molecular chaperone has 'holdase' activity which means that its working process is independent of ATP [15]. Therefore, HSP may be categorised as folder and holder structures. In the presence of stress, HSP27 exhibits prominent holdase activity, allowing these proteins to interact with misfolded polypeptides [19]. They gain the ability to contribute to the refolding-competent state of misfolded proteins or the degradation of substrate proteins after phosphorylation [20].

Once phosphorylated and activated, it regulates many vital activities in the cell through chaperone oligomerisation [17]. In the absence of stress, they are found in low concentrations within the cell. However, during the presence of increased heat, oxidative stress and all other extracellular stress agents, the P38-MAPK cascade is stimulated demonstrated in Fig. 2 [21]. Following this, activated protein kinase MAPKAP kinases 2 and 3 (MAPKAPK-2-3) are activated, and they phosphorylate serine residues Ser-15, Ser-78 and Ser-82 to activate HSP27 [19]. This activation results in a quick response to stress. HSP27 can also be phosphorylated by the PKC delta isoform [22]. Furthermore, HSP27 plays an important role in controlling smooth muscle contraction through phosphorylation by PKC, most likely by interaction with thin filaments [23]. In the presence of stress, a dramatic increase in phosphorylated HSP27 levels can be observed in a cell within a few minutes, indicating that HSP27 is a stress-inducible protein [24]. These phosphorylated forms build by large oligomers, then form small oligomers which is the active form [18]. These large oligomeric units are heavier than their monomer form, the weight of which can be up to 800 kDa, and usually consist of six tetrameric complexes [25]. The presence of physical and chemical parameters such as temperature, pH, ionic strength and monomer phosphorylation influences the size of this oligomeric unit [26]. When the stress factors are removed, the molecule quickly returns to its previous form of large oligomers and resumes its chaperone activity [27]. In addition, a sudden and rapid increase in expression at critical stages in cell growth and differentiation has also been observed [28]. In the presence of apoptotic agents, HSP27 inhibits the apoptotic pathway in the presence of apoptotic agents, ensuring cell survival [29]. Recent studies have shown that HSP27 controls the apoptotic pathway by interacting with key molecules such as caspase 3 [30].

3 HSP27-RELATED DISEASES

3.1 Anti-Apoptotic Function-Related Diseases – Cancers

Overexpression of HSP27 is observed in many types of cancer and is, therefore, considered to be one of the factors involved in cancer development [25]. HSP27 can suppress controlled cell death not only through intrinsic pathways through the formation of large oligomers but also through extrinsic pathways through the formation of small oligomers. This role requires the interaction of HSP27 forms with cytochrome C and/or death domain-associated protein cytochrome C and/or death domain-associated protein 6 (6 DAXX) (Fig. 3). Aside from its anti-apoptotic or anti-ageing effect in cancer development, it plays a crucial function in metastasis and migration [19]. Overexpression of HSP27 has been demonstrated in various cancer types, such as lung, gastric, prostate and pancreatic cancer [31]. HSP27 expression has been associated with improved treatment response, prognosis and tumour progression [32]. Phosphorylated HSP27 has been linked to a suppressive function in cell proliferation and chemosensitivity, which is essential for cytoskeleton integrity and may aid in cell survival and invasion due to its filament regulation role and anti-apoptotic feature. For example, HSP27 expression and the phosphorylated HSP27 state are thought to be important in gemcitabine resistance in pancreatic cancer [31, 32]. In conclusion, cancer cells are also abundant and they have a significant role in tumour development. HSP27 expression is high and inhibits apoptosis. Low expression of HSP27 is linked to the p53 pathway, which is linked to p21. The high expression of HSP27, on the other hand, leads to the inhibition of senescence by toxic agents and oxidants. HSP27 is not only anti-apoptotic and anti-senescent but it also plays a role in metastasis and cell migration.

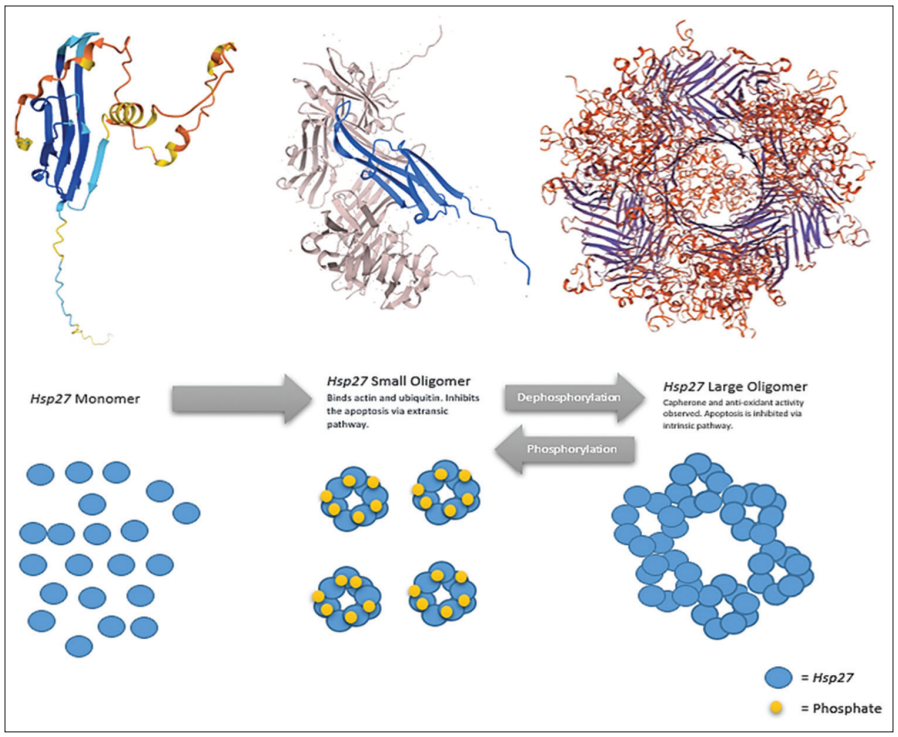

Fig. 1 Monomer, small oligomer and large oligomer structures of heat shock protein 27 (HSP27). phosphorylation of HSP27 results in the disturbing of the oligomer structure of HSP27 (protein structures are modelled by Swiss Model Bioinformatics Tool, HSP27 UniProt ID: P04792)

HSP27's interaction with the actin cytoskeleton explains its role in cell migration. Metalloproteases that are required for HSP27 metastasis, on the other hand, are MMP2 and MMP9 [33].

3.2 Protein Folding Function-Related Diseases – Neurodegenerative Diseases

Protein misfolding and aggregation have been identified as significant clinical hallmarks in various neurodegenerative diseases, including alpha-amyloid misfolding in Alzheimer's and alpha-synuclein misfolding in Parkinson's disease (PD). Aggregation of alpha-synuclein is important in the autophagy pathway and proteasome inhibition, which feeds the rise of alpha-synuclein inclusion within cells. PD occurs when dopaminergic neurons selectively degenerate as a result of the formation of Lewy bodies (LB) composed of sHSP and alpha-synuclein. When HSP27 interacts with alpha-syn fibrils, it decreases their hydrophobicity, which is the primary cause of aggregation and cellular toxicity. However, rapid protein accumulation reduces HSP27 functionality. As a result, HSP27 becomes active at this point [27]. As previously stated, HSP27's primary function is to maintain protein homeostasis [34]. There are two main ways that HSP27 maintains homeostasis within the cell. At the first one, it interacts with the denatured and/or misfolded proteins then prevents the protein aggregation. HSP27 large oligomer complexes have a role in both prevention of misfolded or denatured protein aggregation and interaction with ATP-dependent HSP, misfolded or denatured proteins are denatured. Another way is undergoing the misfolded or denatured proteins to degradation in the protease system [35]. Thus, HSP27 is important for cell protection from protein accumulation of partially denatured or misfolded proteins within the cell [36].

Mutations in HSP27 that render it inactive or bulk amounts of misfolded protein may result in protein aggregation associated with neurodegenerative diseases such as Charcot-Marie-Tooth disease, Alzheimer's disease (AD), PD and various forms of tauopathies. These mutations which are G34R, P39L and E41K in the NTD, L99M, R127W, S135F and R140G in the ACD and T180I, P182S and R188W in CTD in the Hsp27 cause larger size of protein oligomers, alter the function that is seen in small oligomer form of Hsp27 and, thereby, decrease the thermal stability. Even mutant proteins are phosphorylated by MAPKAP kinase 2 like HSP27, HSP27 phosphorylation leads to rapid large oligomer dissociation. However, phosphorylation of the mutants leads to insufficient changes in quaternary structure. Because phosphorylation induces the dissociation of large HSP27 oligomers that play a crucial role in the molecular chaperone feature of HSP90, mutations located in the NTD prevent phosphorylation of the protein and the molecular chaperone activity of HSP27 is depleted. ACD β-strands can interact with β-amyloid proteins and result in stabilisation of the structure of the latter, which ends with preventing their accumulation and/or their proteolytic degradation. Overexpression of HSP27 in a mouse model of AD resulted in improved learning capacities and boosted synaptic neuron excitability in the mouse model due to a decrease in aggregate quantity [37].

Tau is also a possible agent that can cause the formation of aggregates and neurofibrillary tangles within the cells that cause AD. Wild-type tau protein is involved in microtubule stabilisation and can be

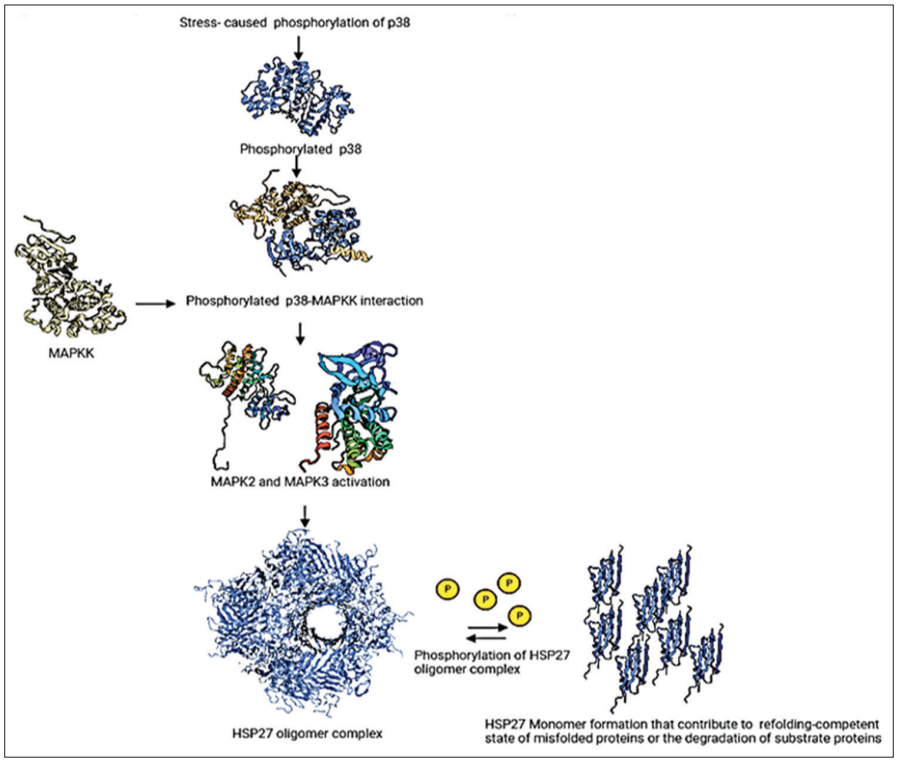

Fig. 2 Stimulation of p38-MAPK cascade results in heat shock protein 27 (HSP27) phosphorylation. HSP27 phosphorylation requires activation of p38-MAPK signalling cascade induced by stress conditions. When HSP27 oligomer structure is phosphorylated, oligomer form disturbed and monomer form of HSP27 is formed that contributes refolding-competent state of misfolded proteins or degradation of substrate proteins

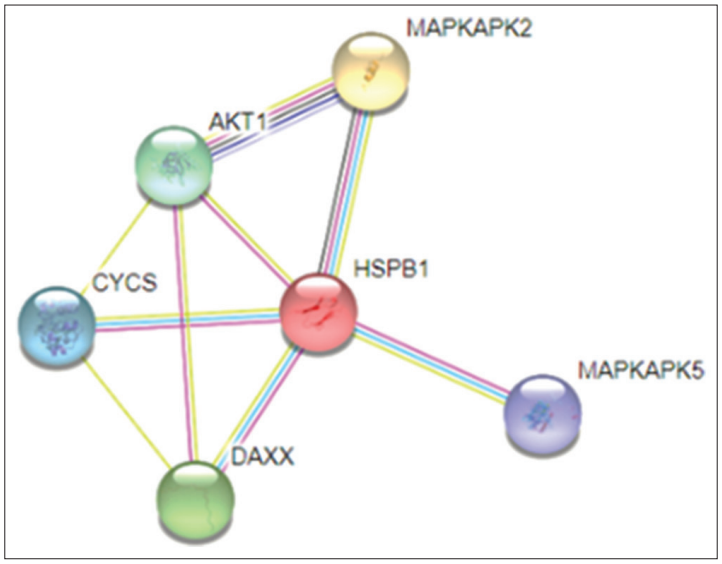

Fig. 3 *HSPB1* gene product interactions shown with STRING database. HSPB1 gene products have interactions with not only mitosis-related proteins including MAPKAPs but also apoptosis-related proteins including DAXX

phosphorylated by a variety of protein kinases. When tau proteins are highly phosphorylated, also known as hyperphosphorylation, their interaction with tubulin is reduced. Moreover, the increasing probability of tau aggregation that ends with inclusion bodies causes the development of various tauopathies. HSP27 interacts with hyperphosphorylated tau proteins and degrades them, therefore decreasing the amount of protein that has the potential for aggregate formation [37].

3.3 *Heat Shock Protein 40 (HSP40)*

Heat shock protein 70 (HSP70s) are molecular chaperones whose primary function is ATPase activity. These proteins play roles in the folding of misfolded non-native polypeptides into their native form, and to do so, they require the collaboration of heat shock protein 40 (HSP40s) in selecting and capturing substrates for them, as well as enhancing their ATPase activity, resulting in a firm substrate binding. HSP40s are also referred to as J-domain proteins (JDPs). JDPs belong to a protein family that includes a diverse set of proteins categorised as Class I, Class II and Class III. Class I JDPs have an N-terminal J-domain, a G/F rich region (30 residues) of glycine and phenylalanine, a cysteine containing zinc-binding motif, two similar barrel domains called CTD1 and CTD2 that contain the client binding cleft and a C-terminal dimerisation domain for substrate binding. In terms of structural lineup, Class II JDPs are like Class I JDPs but lack the zinc-binding motif. Class III JDPs have J-domains but lack the members found in typical Class I or Class II JDPs. The J-domain of Class III JDPs does not have to be located at the protein's N-terminus. HSP40s bind to the substrate through their zinc-binding motif and C-terminal domain (Fig. 4) [39, 40].

Except for Class III, all J-domains (70 residues) of the JDP classes are found on the N-terminus of HSP40. The J-domain of HSP40 interacts with HSP70 by binding to its ATPase domain and stimulating its ATPase activity. In Class I JDPs with zinc-binding motifs before the substrate-binding region and Class II JDPs, the G/F rich regions are located between the N-terminus J-domain and the C-terminus substrate-binding region [41]. HSP70s have an N-terminal nucleotide-binding domain (NBD), also known as an ATPase domain that is connected to a conserved region called the linker region. This region connects NBD to substrate-binding domain β (SBDβ). SBD consists of two sub-domains: SBDβ and SBDα. While SBDβ is formed of 8-stranded β-sheets, SBDα is a C-terminal lid domain that is formed with α helices. The J-domain of the *HSP40* interacts with the HSP70-ATP bound state of the HSP70 in which both SBDs bind to the NBD. J-domain clings to the linker region between these regions after binding with the substrate [42].

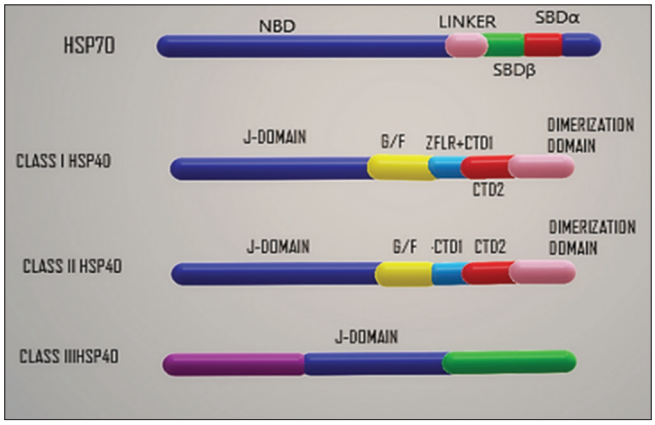

Fig. 4 Demonstration of structural organisation of heat shock protein *(HSP)70* and *HSP40* family members. The black lines in Class I and Class II *HSP40*s represent G/F rich regions. Class II *HSP40*s are lack of zinc-finger motifs and the J-domain of Class III may be in any region on the polypeptide

To achieve this interaction, SBD and NDB create a peptide-binding pocket by two loops and two SBD stands called 3 and 4, and then, SBD forms a lid structure by covering the peptide-binding pocket. These interactions are crucial for allosteric coupling. This peptide-binding pocket encircles the substrate peptide. Once the peptide binds to this region HSP40 and peptide substrate initiates ATP hydrolysis. The folding process occurs in HSP70's ADP-bound state. Then, at the end of the folding process, HSP40s are separated and HSP70s become ATP-bound through NEF (nucleotide exchange factor removes ADP so that a new cycle may start); in this state, HSP70s are fully closed. That is, HSP40 not only converts HSP70 to its open conformation but it also brings substrate to HSP70 [43]. While there are more than 50 variants of *HSP40* encoded in the human genome, the human genome encodes only 11 HSP70s. HSP40 family members can work in coordination and can function in protein aggregation that is independent of being cofactor elements for HSP70s. HSP40s may play essential roles in a variety of pathologies, including some cancer types and neurodegenerative diseases [44].

4 HSP40 AND NEURODEGENERATIVE DISEASES

4.1. *Amyotrophic Lateral Sclerosis (ALS)*

ALS, acknowledged as 'Lou Gehrig's Disease', is also a fatal neurodegenerative disease that causes motor neuron loss in the brain and spinal cord, as well as inclusions containing the RNA/DNA-binding protein TDP-43. TDP-43 proteinopathies are another name for ALS disease. TDP-43 (43 kDa) is a prion-like protein that accumulates in the neurons of ALS patients. TDP-43 inhibits the proteolysis of misfolded proteins in the cytoplasm. Prions are formed when certain soluble cellular proteins transform into insoluble self-seeding aggregates (amyloids). Aggregations are formed by the aggregation of disease-specific soluble proteins and are present in many neurodegenerative illnesses (NFTs), including Alzheimer's, Parkinson's and ALS [45]. Sis1 is a yeast-derived HSP40 chaperone. Overexpression of *Sis1* reduces the toxicity of [PIN+] yeast prion-dependent TDP-43. When prion [PIN+] is present, the overexpression of TDP-43 increases toxicity, but this situation turns the exact opposite in the overexpression of *Sis1*. Like *Sis1*, overexpression of the mammalian homolog of *Sis1* called *DNAJB1*, reduces the toxicity of TDP-43 [46].

4.2 *PD*

Parkinson's disease is the second most common neurodegenerative disease, with neuronal loss in the substantia nigra pars compacta as its hallmark. Striatal dopamine deficiency is caused by the loss of dopaminergic neurons. Intracellular inclusions contain LBs, which are protein aggregates encoded by the alpha-synuclein (*SNCA*) gene, such as alpha-synuclein. PD is the most frequent synucleinopathy among all synucleinopathies [47, 48]. The pathological hallmark of PD is an accumulation of LB aggregates composed of alpha-synucleins. It has been demonstrated that the *Dnaj/HSP40* families reduce alpha-synuclein-mediated toxicity. HSP40/DNAJ proteins, which play roles in clathrin dynamics, have been linked to PD. Some of them are *Dnajc13/Rme-8*, *Dnajc6/Auxilin-1*, *Dnajc12/Jdp1*, *DnajC5/Cspα* and *DnajC10/Erdj5* [49]. The DNAJC family is a subclass of *Dnaj/HSP40*s, and mutations in

this group are thought to be linked to PD. While missense mutations in *Dnajc6* occur in early onset, (c.801-2A>G, p.T 741=) splicing mutations occur in both early onset and juvenile and (p.Q791*, p.Q846*) nonsense mutations also lead to rapid and severe disease progression in juvenile onset. Compound heterozygous mutations (c.203813A>G and c.1468183del) or heterozygous variants (p.L209P, p.R619C, p.M133L, p.F 839Lfs*22) in *Dnajc6* identify early-onset PD in sporadic patients. *Erdj5* is an ER (endoplasmic reticulum)-resident oxidoreductase encoded by *Dnajc10*. ERAD (ER-associated degradation) is machinery in which the misfolded proteins are translocated from the endoplasmic reticulum to cytosol and degraded by the ubiquitin-proteasome system. *Dnajc10* binds to misfolded proteins that are directed to degradation through interaction with ERAD machinery proteins. According to reviews in the Chinese-Han population with 512 patients and control groups, a missense mutation in *Dnajc10* (p.L301I) is thought to be related to a diminished risk of PD [50].

4.3 Cancer and HSP40

During cancer development, HSP40 family proteins perform both anticancer and pro-cancer functions. Tid1 has two alternatively spliced forms: hTid-1 (L) and hTid-1 (R) (S). These variants can interact with HSP70 and regulate its activity. Interactions between these two isoforms and transcription factors (STAT1 and STAT2) can facilitate interactions with other proteins (Hsc70), or these two isoforms can enhance IFN-mediated transcriptional activity directly. This form of Tid1 knockdown with shRNA causes a decrease in the potential migration of cancer cells and by inhibiting IL-8 production, it is understood that this form of Tid1 can also suppress tumour angiogenesis and downregulate IL-8 [51]. Overexpression of *Tid1* in *ErbB-2* (*Her2*) has been found to induce cell death by promoting ubiquitination and degradation of *ErbB-2*. This situation leads to the inhibition of some crucial signalling pathways (e.g., the MAPK pathway) that lie behind programmed cell death [52].

The high level of HLJ1 expression has a negative effect on lung cancer cell proliferation, motility and invasion, as well as cell cycle progression by the Stat1/P21 pathway. In the presence of non-small cell lung cancer (NSCLC), HLJ1 expression can also cause apoptosis through its interaction with caspase-3. Overexpression of DNAJB6, which is only found in malignant melanomas and breast cancers, reduces cancer cell proliferation, motility and invasion in mouse models, primarily by inhibiting the Wnt/catenin signalling pathway. Erdj3 (DNAJB11) is an ER protein that primarily functions in anti-apoptotic activity, and the KSHV K1 protein has anti-apoptotic functions. DNAJ25 acts as a tumour suppressor and increases the apoptotic rate in liver cancer. *DNAJB1* is a DNAJ isoform that inhibits p53-dependent apoptosis by forewarning programmed cell death protein-5 [53]. The high level of HLJ1 expression has a negative effect on lung cancer cell proliferation, motility and invasion, as well as cell cycle progression through the Stat1/P21 pathway. In the case of NSCLC, HLJ1 expression may also cause apoptosis through its interaction with caspase-3. Overexpression of DNAJB6, which is only found in malignant melanomas and breast cancers, reduces cancer cell proliferation, motility and invasion in mouse models, by inhibiting the Wnt/-catenin signalling pathway. Erdj3 (DNAJB11) is an ER protein that primarily functions in anti-apoptotic activity, and KSHV K1 protein has anti-apoptotic functions. DNAJ25 acts as a tumour suppressor and increases the apoptotic rate in liver cancer.

4.4 Heat Shock Protein 60 (HSP60-Cpn60)

Heat Shock Protein 60 (HSP60), so called chaperonin, is a mitochondrial chaperone (also known as Cpn60), it is also present in the extracellular matrix of the cell membrane and the peripheral circulation [54]. In prokaryotes, HSP60 plays a crucial function in assisting the folding of immature proteins into their native state. Its chaperone activity necessitates collaboration with HSP10 (also found in mitochondria, Cpn10), which functions as a cap [55]. HSP60 chaperone proteins, like HSP70, recognise proteins that cannot be folded correctly or have had their native structure altered, such as the expansion of hydrophobic faces to the protein's outer surface. Because exposed hydrophobic residues of the proteins have the potential to become the source of an aggregation. *HSP60* has a crucial role in their elimination or refolding. The unfolded or misfolded proteins that fall between these rings formed by *HSP60* can be folded properly, without interfering with other unfolded proteins [56]. The primary function of HSP60 proteins is to separate unfolded or misfolded proteins from other proteins, thereby preventing misfolded protein accumulation. Even though these actions are critical in preventing protein aggregation, their primary function is to quarantine the polypeptides. As a result, these proteins are unable to interact with other molecules in the cell [57]. HSP60 plays a critical role in initiation of apoptosis. Furthermore, HSP60, both cytosolic and mitochondrial, is involved in both pro-apoptotic and pro-survival pathways. During carcinogenesis, Hsp60 levels in various organs gradually increase or decrease depending on the function of HSP60 in the cell. As a result, it can be used as a prognostic or diagnostic marker in certain types of malignancies. HSP60 overexpression promotes cell proliferation, inhibits senescence, confers resistance to stress-induced apoptosis and causes neoplastic transformation in tumour cells. HSP60, on the other hand, has a pro-apoptotic effect and promotes apoptosis by cleaving and activating caspase 3, starting with mitochondrial release and accumulation in the cytosol and ending with pro-caspase 3 activations. In contrast, *HSP60* also inhibits p53 action by stabilising the antiapoptotic protein survivin, inducing cell growth [58].

5 STRUCTURE OF *HSP60*

The HSP60 complex's structure is made up of 14 different subunits. They form two rings, each of which consists of seven subunits. HSP60 and its companion HSP10 are found in the mitochondria of humans, where they form the protein folding mechanism. These *HSP10* and *HSP60* form a stable double-ring complex (Fig. 5) [56]. HSP60 binds unfolded proteins in an ATP-dependent manner and catalyses their folding. HSP10 acts as a cap at the mouth of the heptameric rings, opening and closing the core cavity and controlling HSP60 monomer interactions and ATP hydrolysis. HSP60 monomers include three structural domains: The apical intermediate domain, the equatorial apical domain and the ATP turnover domain. The intermediate domain links the apical and equatorial domains, and the equatorial domain facilitates interactions between two heptameric rings, single subunits in a ring and chaperonins [56].

6 *HSP60* AND DISEASES

Hsp60 is induced by various types of stress conditions such as heat shock, oxidative stress and DNA damage. HSP60 plays both

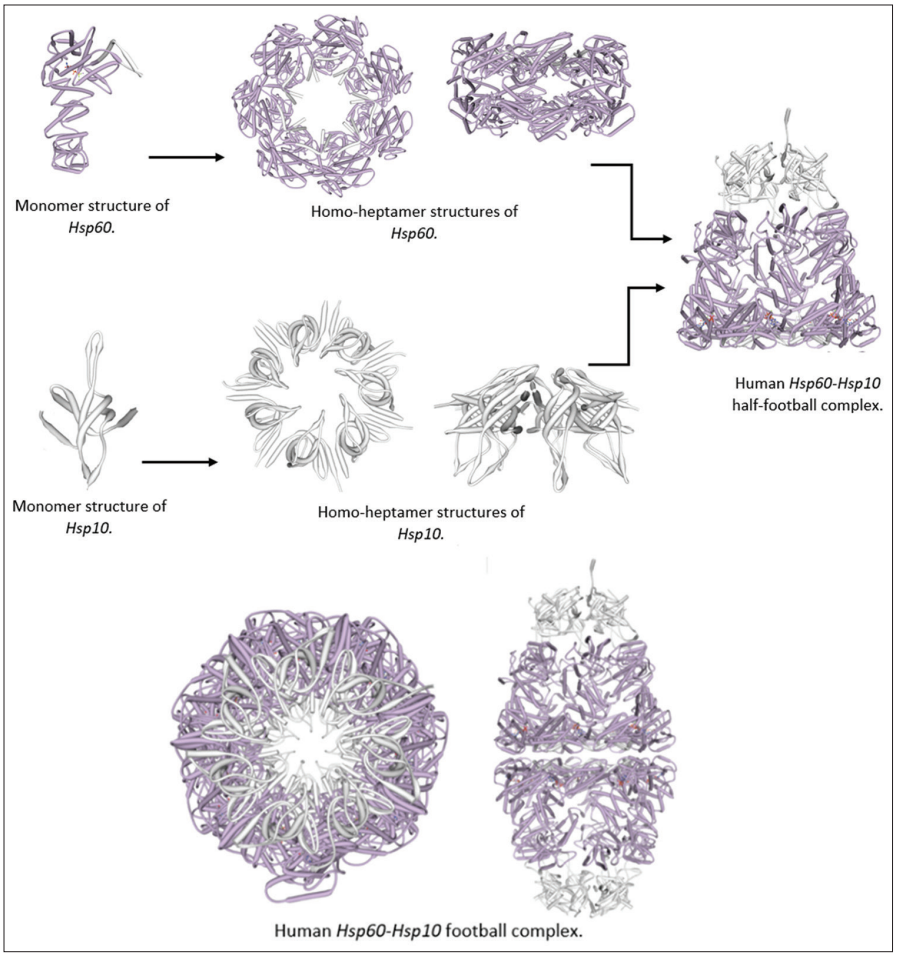

Fig. 5 Structural components and the formation steps of the heat shock protein *(HSP)60-HSP10* complex. HSP10 and HSP60 are expressed separately and joined within the cytoplasm to form HSP70. Seven proteins of HSP60 and HSP10 joined within their each other to form homo-heptamer structures of HSP60 and HSP10 and two of each one of them come together to create the HSP70 structure. All structures are modelled by SwissModel, amino acid sequence information of proteins was received from Uniprot Database (HSP10 Uniprot ID: P38910, HSP60 Uniprot ID: P10809)

pro-survival and pro-death roles according to the tissue, cell type and apoptosis inducers. These features make Hsp60 essential in the mechanism of a variety of diseases. It has been shown that Hsp60 increases in malignant cell cytosol and plasma membrane. Furthermore, HSP60 binds pro-caspase 3 in cancer cells such as Jurkat and HeLa cell lines [59]. It has also been implicated in the mechanism of cell ageing. In the case of the replicative senescence process of healthy human skin fibroblast cells, HSP60 increases, then a special complex with MOK, a mitogen-activated protein kinase superfamily protein, is involved in signal transduction to the nucleus [60].

HSP60 has been associated with autoimmune diseases such as multiple sclerosis and myasthenia gravis. By attaching to an adipocyte receptor, HSP60 regulates adipocyte pro-inflammatory capability, contributing to obesity-related inflammatory illness that leads to diabetes [60]. Crohn's disease and other chronic inflammatory diseases have also been linked to the presence of chaperonin. Prior research has thoroughly investigated the role of *HSP60* in ageing and their research on human fibroblast senescent replication requires the presence of *HSP60* [61]. In addition to cellular protein folding, HSP60 is essential for the correct folding of other mitochondrial proteins and enzymes. HSP60 is not only essential for cellular protein folding but also crucial for the correct folding of other mitochondrial proteins and enzymes. Extracellular HSP60 has been linked to the induction of microglia-mediated neuroinflammation as well as a longer delay in HSP60 production in damaged brain areas through binding to LOX-1 (lectin-like oxidised low-density lipoprotein receptor-1) [62]. Such a deficit might be a prevalent source of mitochondrial malfunction, which is noteworthy since AD has been defined as an illness exacerbated by oxidative stress and/or mitochondrial failure characterised by protein conformation abnormalities [63].

7 *HSP70*

HSP70 is involved in protein folding, transport and regulation, as well as preventing protein aggregation. HSP70 binds newly synthesised proteins as well as partially folded hydrophobic

substrate polypeptides, directing them to their final native state. The biological activity of the HSP70 family, like that of HSP90, is based on ATP hydrolysis and ADP/ATP exchange, which is directed by co-chaperone proteins. HSP70 coordinates with HSP90 and submits pre-folded substrate proteins to HSP90. HSP70 processes a substrate by seven residues at a time and this pre-folded structure facilitates HSP90 folding. HSP70 exists in several distinct but redundant forms. HSP70 isoforms are classified as constitutive or inducible. Further, each cellular organelle has more than 1 isoform. HSP70 coordinates with HSP40 and displays a variety of functions. Human has 13 HSP70 and HSP40 isoforms, thus, the number of combinations is huge and provides an estimate of the degree of distinct coordination and functions. HSP70 family members have structural similarities. HSP70 has an NBD that binds to ATP as well as SBD that binds linear peptides and exposed parts of folded proteins. A flexible structure known as a linker connects NBD and SBD. This linker transports the energy of ATP hydrolysis to SBD [64].

8 *HSP70-INDUCED* FOLDING MECHANISM

HSP70's highly flexible NBD lid domain allows it to open and close the nucleotide-binding cavity, allowing nucleotide binding and release. In this case, ATP is hydrolysed and a signal is sent to the SBD. This signal keeps the substrate protein in the NBD cavity and closes the lid. The incoming signal from the formation of ADP causes the lid to close. The folding process begins when the lid closes over SBD with a rotational movement. SBD's cavity is a hydrophobic domain, and hydrophobic interactions between the substrate and the domain transport the substrate to its native state conformation. When new ATP binds to NBD, the lid opens and the substrate is released, and HSP70 is ready to enter the new cycle. *HSP40* coordinates to *HSP70* through its J domain. HSP70 is hydrolysed by ATP because of the binding. HSP40 submits substrates to HSP70, which facilitates and speeds up substrate folding for HSP70. Proper orientation and sometimes dissolving aggregated substrate protein make HSP40 coordination effective in folding [64–66]. HSP70 not only participates in substrate protein folding but it also plays important roles in oncogenesis, neurodegenerative and autoimmune diseases, viral infections and ageing by regulating cell cycle, differentiation and apoptosis-related tasks [64–66].

9 *HSP70* AND CANCER

Cancer cells are constantly subjected to internal and external stresses, such as cytokine attack, hypoxia due to insufficient blood supply, increased free radicals through high metabolic activity and misfolded protein accumulation by decreased genetic stability. Ciocca and colleagues discovered that HSP70 expression levels increased excessively in breast cancer about 20 years ago, and this finding was later extended to colon, liver, prostate, oesophageal and cervical cancers [67]. These findings establish HSP70 as a biomarker for determining tumour stage, metastasis and prognosis. HSP70 has been shown to have prognostic significance in many human cancers and to be an independent factor from other prognostic factors. These studies have significantly increased the number of studies on the role of HSP70 in cancer, paving the way for understanding cancer aetiologies and identifying new drug design approaches [67–70].

Cancer cell metabolism is higher and HSP70 provides cancer cells with survival mechanisms by preventing apoptosis. HSP70, on the other hand, plays a negative role in cancer suppression, most likely through distinct isoforms. The protein is known for its immunomodulatory properties. High HSP70 expression for example, is linked to a good prognosis in squamous cell carcinoma, and there is a significant positive association between HSP70 and lymphocytic infiltration, which signals a strong anti-tumour immune response and is a favourable prognostic indicator. The immunomodulatory effect of HSP70 is associated with the structure's extracellular function, which is considered an immune stimulant. Extracellular HSP70 can activate the natural immune system and can be used as an adjuvant for tumour antigens in the development of anticancer vaccines. As a result, in tumour types, where HSP70 expression and prognosis are inversely related, a greater immune response to HSP70 tumour antigen complexes develops [71, 72]. HSP70 plays a direct role in the apoptotic pathway and protects cancer cells from cell death. HSP70 binds to the N-terminal c-junk of kinase 1, blocking its functions and the signals that initiate apoptosis before reaching the mitochondria. HSP70 inhibits Bax protein translocation in mitochondria, preventing the release of cytochrome-c and AIF. This shows that HSP70 directly binds to Apaf1, preventing the formation of an apoptosome. HSP70 protects the cell from further apoptosis by inhibiting caspase 3 activation and blocking caspase-independent pathways. HSP70 is used as an early hepatocellular cancer marker in liver cancer, whereas in cervical cancer, the level of HSP70 in the tissue is associated with tumour size and proliferation.

HSP70 is also detected in the blastemal and epithelial components of nephroblastomas, which are cancers of the urinary system, and its level rises following chemotherapy. Inhibiting the activation of HSP70, HSP90 and HSP27 is lethal to tumour cells but has no effect on healthy cells. HSP70 expression reduction has been proven to destroy cancer cells in cell culture and xenograft tumour models in mice. As a result of HSP70 reduction induced by the cell cycle inhibitors p16 and p21, many cancer cell lines undergo rapid and early senescence. Higher levels of HSP70-1 and HSP70-2 expression result in lower levels of p53. This situation raised the level of p21, which causes senescence with the help of Ras, Her2, Pten and Raf [68–73].

10 *HSP70* AND AD

Alzheimer's disease is a neurological illness that results in reduced function and the loss of neurons. Amnesia and dementia symptoms can be detected at a higher level, but late onset delays diagnosis and complicates treatment. AD has been linked to abnormal Aß polypeptide activity. Extracellular peptide accumulation impairs cell function and synaptic transmission, eventually inducing cell death. Moreover, the excessive secretion of tau proteins, neuroinflammation and mutations that affect the respiration mechanism or cause oxidative stresses in mitochondria can also be considered among the causes of this disease. HSP70 proteins have been linked to Aß polypeptide accumulation protection. To reduce Aß formation, HSP70 binds the APP protein, which is the precursor protein of Aß polypeptide. HSP70 proteins contribute to cell toxicity reduction by decreasing Aß protein oligomerisation. Extracellular HSP70 proteins have been shown in the laboratory to promote tau protein phagocytosis through microglial activation. HSP70 proteins protect against the deposition of Aß and tau proteins. Highly phosphorylated

tau proteins are detected by *HSP70* proteins. With the help of CHIP ubiquitin ligase, HSP70 binds to phosphorylated tau proteins and marks them for proteasomal degradation. The determination of protective roles against AD has led to HSP70 targeted drug studies. The synthetic YC-1 molecule and sulphoraphane are examples of the *HSP70* targeting molecules. By overexpressing HSP70, the YC-1 molecule reduces the toxic effects of amyloid proteins. It is determined that the sulphoraphane molecule influences Aß and tau proteins by increasing the amount of CHIP and *HSP70* proteins [73–75].

11 HEAT SHOCK PROTEIN 90 (HSP90)

HSP90 is a unique, greatly preserved molecular chaperone that has a pivotal role in the folding of proteins in a three-dimensional structure. HSP90 family members account for 1–2% of total cellular proteins found in eukaryotic cells' cytosol, nucleus and organelles. The amount of these proteins can increase as the cells are subjected to heat, oxidative stress and chemicals [76]. HSP90, a preserved molecular chaperone, is critical for the maintenance and activation of clients throughout the cell. HSP90 clients include Huntingtin, tau, transcription factors, alpha-synuclein, steroid hormone receptors, kinases and E3 ubiquitin ligases [77]. Importantly, these proteins regulate protein folding and deterioration, cell proliferation, cellular trafficking, chromatin remodelling, distinction and other cellular processes [78]. Two isoforms of HSP90, extracellular and intracellular types, exist. These isoforms of the HSP90 family are HSP90α and HSP90β are located inside the nucleus and cytosol [79]. One notable dissimilarity is that the form dimerises α quickly unlike the β form which dimerises much more slowly. Considering cellular operation, *Hsp90β* plays roles in cell cycle regulation, growth promotion and cancer cell intrusion. On the other hand, *Hsp90β* is linked to premature embryonic development, cellular transformation, signal transduction and long-term cellular adjustment [80].

There are three domains of this chaperone; ATP-binding domain or N-terminal domain (~ 35 KDa), ATP hydrolysis regulating domain or middle domain (~ 40 KDa) and dimerisation domain or C-terminal domain (~ 12 KDa), as illustrated in Fig. 6 [81]. HSP90's N-terminal domain has an ATP-binding site (Bergerat fold) that can be occupied by drugs such as geldanamycin (GA) and tanespimycin as well as nucleotides. The catalytic loop and binding sites for client proteins such as Akt (serine/threonine kinase), nitric oxide synthase, cyclin-dependent kinase 4 and co-chaperones like Aha1 (activator of HSP90 ATPase activity 1) are in the ATP hydrolysis regulating domain [82]. Client protein and small compounds (e.g., nucleotides, cisplatin and novobiocin) binding and HSP90 dimerisation occurs in the C-terminal domain [83]. Furthermore, co-chaperones in this domain help proteins fold properly into three-dimensional structures [84]. The functional activity of proteins in the cell depends on proper protein folding to create a three-dimensional formation. Otherwise, the formation of protein aggregates as well as protein misfolding occur, and these aggregates cause cellular metabolic abnormalities. Protein aggregates are known to exist in more than 30 different human diseases. Therefore, HSP90 has been related to several important disorders, including cerebral and cardiovascular diseases (ischaemia and reperfusion), neurodegenerative diseases, autoimmune diseases and cancer [85] However, the role of HSP90 and its co-chaperones in these conditions, particularly PD, AD, cancer and HD, is highlighted in this section.

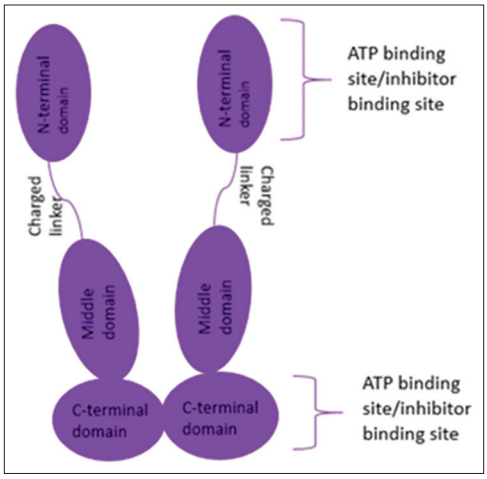

Fig. 6 Structure of heat shock protein (Hsp) 90 dimer. Three main domains form the protein: its N-terminal domain bind ATP, which is critical for its chaperone function. A charged linker separates the middle domain from the N-terminal domain. The middle domain is responsible for binding of client proteins and cochaperone and ATPase activation. The C-terminal domain allows the binding of small molecules and cochaperone, as well as two monomers [81]

12 HSP90 AND AD

The agglomeration of amyloid (A) in senile plaques and the creation of intracellular neurofibrillary tangles characterise AD, one of the principal NFTs. Tau is a protein found in NFTs that are associated with microtubules. Even though tau's physiological function is unknown, pathologic events in the brain cause it to become hyperphosphorylated, making it susceptible to misfolding and separation from microtubules [87]. The primary cause of cognitive decline, according to a study on a mouse model of tauopathy, is aberrant tau phosphorylation. Tau phosphorylation and dephosphorylation may be regulated by HSP90 and its co-chaperones [88]. The HSP90 co-chaperone cell division cycle 37 (Cdc37), which interacts with tau in the human brain, has been found to modulate tau phosphorylation. The stability of tau kinases such as cyclin-dependent kinase 5 and Akt was found to be affected by Cdc37 knockdown in HeLa cells. Furthermore, although Cdc37 overexpression keeps tau levels in these cells steady, Cdc37 suppression causes tau to become unstable. As a result, it was observed that as one gets older, their Cdc37 levels increase, impacting tau phosphorylation and hence the protein's toxicity and stability [89]. FK506-binding protein 5 is an HSP90 co-chaperone that has been shown to be considerably upregulated in aged and AD brains by Blair et al. [90]. Furthermore, in an Alzheimer's disease mice model, *Aha1* increases tau aggregation and insoluble tau build-up. When *Aha1* is inhibited, the accumulation of tau in cultured cells is reduced. In addition, in a mouse model, overexpression of *Aha1* causes neuronal death and cognitive impairments [78].

13 HSP90 AND PD

Patients with PD lose dopaminergic neurons in the substantia nigra as well as toxic alpha-synuclein aggregates forming in LB.

Although PD is mostly sporadic, some cases are caused by heritable factors, such as mutations in the genes encoding synuclein, parkin and protein deglycase/disease Parkinson's protein 7, Pten-induced kinase 1, leucine-rich repeat kinase 2 (Lrrk2) and vacuolar protein sorting 35, are all proteins that have been linked to PD [91]. The *Snca* (alpha-synuclein gene) is responsible for the production of alpha-synuclein, which is a major component of LB and Lewy neurites (LNs). The SNCA gene duplications, triplications or point mutations have been linked to sporadic and autosomal dominant PD. HSP90 was found to colocalise with alpha-synuclein in LB, LN and glial cell inclusions. HSP90 and insoluble alpha-synuclein levels have been found to be higher in PD individuals' brains [92]. Furthermore, in yeast, *Hsp90 (Hsp82)* deletion resulted in toxicity and an increase in reactive oxygen species accumulation [93]. In an *in vitro* study, it was discovered that when HSP90-ATP is present, alpha-synuclein oligomers cannot form. Because they are swiftly converted into fibrils. However, there was only a modest conversion from oligomer to fibril form in the absence of ATP. As a result, several co-chaperones, such as P23 or STT1/HOP, have been proposed to impede the HSP90-ATP cycle, increasing the creation of soluble oligomers, while *Aha1* activation may promote the formation of amyloid fibrils [94]. A study showed a complex between HSP90 and *Lrrk2* kinase in *vivo* when HSP90 was inhibited, the connection with *Lrrk2* was disrupted and caused its proteasomal degradation [95]. In microglial cell lines, several inhibitors have been utilised to target the connection between HSP90 and Cdc37, which are crucial for Lrrk2 stability. As a result of this therapy, the HSP90-Cdc37 complex with Lrrk2 kinase was disrupted and Lrrk2 instability and clearance were observed [96].

14 HSP90 AND HUNTINGTON DISEASES (HD)

Exon 1 of the Huntingtin (*Htt*) gene, which causes HD, contains CAG trinucleotide repeats. These CAG repeats form a polyQ tract during protein synthesis. By generating aggregation and inclusion bodies, this PolyQ tract induces neuronal toxicity and degeneration [97]. It has been shown that HSP90 binds to the N-terminus of HTT. In collaboration with Usp19 (ubiquitin-specific protease 19), HSP90 can also influence the aggregation of polyglutamine-expanded ataxin-3 and HTT [98]. Other studies have investigated the physical interaction between HSP90 and wild-type or mutant *Htt* (mHTT). When HSP90 is inhibited, the link between these proteins is broken, and the ubiquitin-proteasome system cleaves HTT. According to the findings, direct suppression of HSP90 is required for mHTT degradation. A study [99] backs up these findings, suggesting that HSP90 inhibitors may reduce the amount of mHTT in neuroblastoma SH-SY5Y cells.

15 HSP90 AND CANCER

HSP90 has a role in cell growth and survival, differentiation, signalling pathways, cellular stress response and apoptosis [100]. According to a study, malignant cells have 2–10-fold greater expression levels than normal cells. HSP90 has been used to identify a variety of cancers since its discovery, including bladder, ovarian, breast, oesophageal, endometrial, colorectal, bone and prostate cancer. Because of their high expression of HSP90, cancer cells can withstand harsh conditions such as low pH, UV light exposure, hypoxia, nutrition and chemicals [101]. HSP90 is found in multi-chaperone complexes in cancer cells that regulate client protein expression, whereas normal cells have an uncoupled inactive form. As a result, in cancer cells, HSP90 and its client proteins can evade apoptosis and immunological destruction. Self-sufficiency in growth signalling, antigrowth signal insensitivity, energy metabolism reprogramming, tissue invasion and metastasis are some of their other features. Cancer cells also express mutant oncoproteins, which contribute to the growth, proliferation and survival of neoplastic cells [102]. Client proteins of the HSP90 include many oncoproteins, such as AKT, BCR-ABL and HIF 1. As a result, HSP90 has been identified as a key molecule of oncogene addiction and cancer survival [103]. HER2 overexpression is related to aggressive tumours, poor prognosis, low response and resistance to chemotherapy in breast cancer followed by HSP70/HSP90 overexpression. HSF1 is a major regulator of heat shock response (HSR) associated with HSP90 and is activated due to the overexpression of HER2 shown in a mouse model of HER2-driven breast cancer. HSF1 activation stabilises tumour promoting HSP90 clients such as Mif (macrophage migration inhibitory factor), Akt and Hsf1. This causes tumour growth in HER2-positive breast cancer [104, 105].

16 HSP AS POTENTIAL DRUG TARGETS

HSPs are molecular chaperones that ensure proper folding and activation of client proteins to keep the cell's protein homeostasis. One distinguishing feature of HSP is their ability to become overexpressed when under stress [106, 107]. HSPs are being studied for their role in the development and advancement of a variety of conditions and diseases, including cancer [109, 110], neurodegeneration [111, 112] and infection [113]. For example, cancer cells were shown to express 2–10 times more HSP90 levels compared to regular cells. Many client proteins are signal transducers, which are required for tumour cell generation, survival and proliferation [114]. Moreover, the HSP90's client proteins belong to three classes which are serine-threonine or tyrosine kinases, steroid hormone receptors as well as proteins with unrelated functions and they have a role in signalling pathways related to tumour progression pathways [115]. Another feature of HSP90 is the importance of protein post-translational maturation and disposition. Its N-terminal domain includes a typical Bergerat fold, which is a structurally unique ATP-binding domain. Topographical alterations to HSP90 are induced by binding and hydrolysis of ATP that grants the HSP90 binding to its client proteins that aid them to fold to the active form. HSP90 inhibitor binds to the ATP domain and prevents the exchange of ADP for ATP by the HSP90 protein. This leads to client proteins experiencing ubiquitination, misfolding and degeneration thanks to the proteasome pathway [116]. As previously stated, scientists work hard to identify therapies for HSP because many diseases are caused by disruptions in protein homeostasis. Among the known HSP, HSP90 and HSP70 have grown in popularity and are best known for their potential in drug discovery [108]. For more than a quarter-century, the advancement of HSP90 inhibitors has primarily focused on the development of drug compounds that disrupt molecular chaperone function through competing binding to the N-terminal ATP-binding sites [117, 118]. HSP90 inhibitors can be classified into four groups based on their chemical structures. These are (i) natural

products and their derivatives, (ii) purine-based, (iii) benzamide and (iv) resorcinol-containing compounds. The remainder of this section provides more information on the five different HSP90 inhibitors that have advanced to clinical trials [119].

17 NATURAL PRODUCTS AND THEIR DERIVATIVES

GDA is the first HSP90 inhibitor which was derived from *Streptomyces hygroscopicus* and is a 1,4-benzoquinone ansamycin antibiotic (Fig. 7). GDA was described as a ligand of HSP90 by the Whitesell Group in the early 1990s that bind to the N-terminal ATP-binding site. Once bonded to GDA, the molecular chaperone's ATPase activity is interrupted which leads to client protein degeneration and an impact on several cellular processes [120]. Specifically, GDA possesses a reactive quinone which brings superoxide radical inducing cell death [122]. Aside from GDA, another natural product, radicicol, was isolated from the fungus *Monosporium border* and has a similar binding activity to GDA [121]. Unfortunately, due to metabolic instability, poor solubility and high liver toxicity, GDA is not used in clinical settings [123]. 17-AAG, a GA analogue, maintains its powerful anticancer exercise while reducing hepatotoxicity and increasing bioavailability (Fig. 7) [115]. Furthermore, the initial GA derivative to enter clinical trials for multiple human cancer types is 17-AAG [124]. 17-AAG inhibits ATP binding by binding to the HSP90's ATP-binding region. This prevents the development of the HSP90 multichaperone complex and promotes the degeneration of client proteins by the ubiquitin-proteasome pathway [115]. The inhibition of a multichaperone complex with greater binding affinity regardless of HSP90 expression is an advantage of 17-AAG over GA. 17-AAG is selective for cancer cells and leads to tumour growth inhibition [125]. Although 17-AAG has advantages over GDA and may be considered acceptable pharmacologically, its high hepatotoxicity and low water solubility may limit its clinic use [115]. These constraints can be overcome using nanomaterials-based drug delivery carriers. Such carriers have the potential to extend the firmness of anticancer drugs and preserve their chemotherapeutic responses, furnish encapsulation and expel chemical drugs that are low soluble within the storage, have targeted transfer to the tumour site, leading to decreased chemical waste, have single-dose drug delivery and minimise systemic toxicity and ill effects to regular tissues [126].

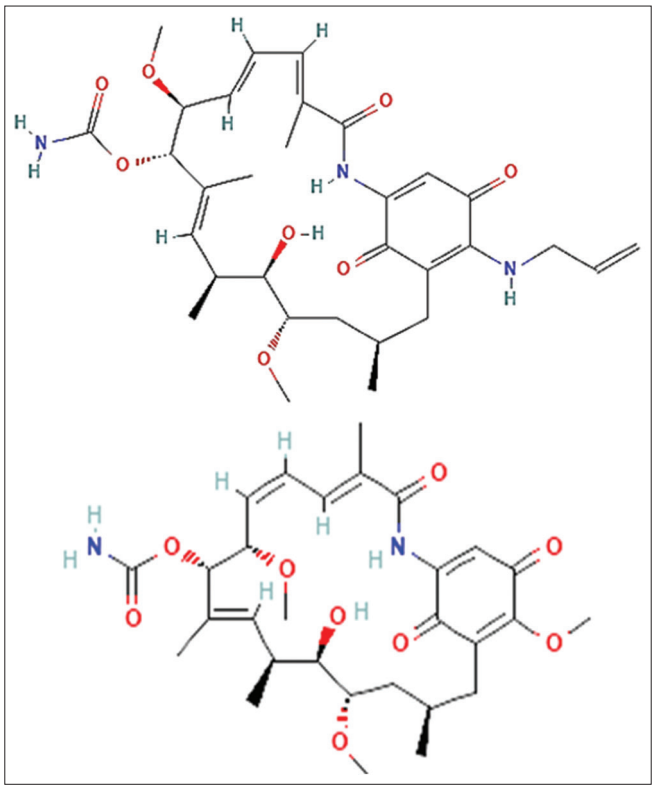

Fig. 7 Structure of (a and b) 17-AAG (PubChem CID: 6440175) and GDA (PubChem CID: 5288382). 17-AAG and GDA molecules are used as inhibitors of heat shock protein

18 PURINE-BASED INHIBITORS

Chiosis and colleagues [127] created the first synthetic purine scaffold inhibitor, PU3 [9-butyl-8(3,4,5-trimethoxybenzyl)-9H-purin-6-ylamine], which can promote protein degradation. To combat the poorer water solubility of the 9-benzyl series, a 2'-pyridyl group was used instead of the phenyl ring [128]. Another HSP90 inhibitor that is soluble in biological fluids is BIIB021, a 3',5'-dimethyl-4'-methoxy-2'-pyridyl derivative [116]. It is a small-molecule inhibitor that is completely synthetic and has the potential to be used as a selective antitumour agent. It has been shown to curb the growth of several types of cancerous cells such as MCF-7, N87 and BT474 at nanomolar concentrations. Moreover, *in vitro* experiments have shown the efficacy of BIIB021in promoting cell cycle arrest, apoptosis and inducing tumour cell autophagy. It has also been observed to cause oncogenic protein degeneration, to disrupt signalling transduction, to reinforce NK cell-mediated cytotoxicity, to act as a complement to radiotherapy, to defeat the resistance of multiple drugs and to have synergistic effects with other drugs. BIIB021 is active in serum, PBMCs and tumour tissue is well absorbed and can result in observational reactions in refractory gastrointestinal stromal tumour (GIST) patients [129, 130]. Combination therapy may also be based on another effective treatment strategy. Several *in vitro* studies have demonstrated the potency of jointly using the HSP90 inhibitor with several other drugs (e.g., FLT3 inhibitor, bortezomib, Ara-C, histone deacetylase inhibitor and imatinib). To illustrate, in Phase I/II trial, 17-AAG + bortezomib was absorbed sufficiently by the patients and 27% of them with relapsed or refractory myeloma resulted in an observational reaction. Hence, it is safe to conclude that BIIB021 is a unique agent in the treatment of cancer and has been shown to treat blood malignancies by targeting HSP90 [131].

19 RESORCINOL CONTAINING INHIBITORS

Another class of *HSP90* inhibitors contains resorcinol. AUY922, also known as luminespib, is an HSP90 inhibitor that effectively inhibits tumour cell division by blocking chaperone functions [132]. HER2-positive breast cancer studies indicated that AUY922 inhibits cell growth and proliferation by significantly reducing PI3-kinase and MAP kinases [133]. AT13387 (2,4-dihydroxy-5-isopropyl-phenyl)-[5-(4-methyl-piperazine-1-ylmethyl)-1,3-dihydro-isoindol-2-yl] thanone, l-lactic acid salt), another resorcinol-containing HSP90

inhibitor, was discovered in the UK. It is a non-GA-containing inhibitor that is less toxic and easier to use than 17-AAG [134]. AT13387 is currently being tested in Phase I and II clinical trials with patients suffering from refractory GIST, ALK-positive lung cancer and prostate carcinomas [135, 136].

20 C-TERMINAL INHIBITORS

Inhibitors bind the nucleotide-binding site at the C-terminus. There are currently no FDA-approved classical HSP90 inhibitors on the market. One of the reasons is the stimulation of the HSR, which is a well-known side effect of this class of inhibitors and has already been demonstrated for GA. The used model for the HSR mechanism involves the binding of N-terminal HSP90 inhibitors discharging heat shock factor-1 (Hsf-1). The transcription factor gets phosphorylated, trimerises and moves to the nucleus, resulting in overexpression of multiple HSP which include HSP70, HSP40 and HSP27. Since HSR supports survival, it can hurt the efficacy of anti-cancer therapy [137].

21 NOVOBIOCIN

The finding of the C-terminal ATP-binding site is closely related to the evaluation of novobiocin as an HSP90 inhibitor. The coumarin antibiotic was discovered to interfere with nucleotide-binding in bacterial gyrase B, but no binding to the NTD was found in HSP90. The pull-down assays suggest that GA has a different binding mode. In other studies, researchers discovered another ATP-binding site in the CTD that is only accessible when the N-terminal ATP-binding site is occupied. Moreover, the C-terminal-binding site can bind purine and pyrimidine nucleotides whereas the NTD is quite specific for adenine [138]. To the best of our knowledge, there is no inhibitor that binds to this site now. Nevertheless, through molecular modelling, there are several ways to estimate the C-terminal ATP-binding site. Next, we will mention HSP90 inhibitors that bind to the C-terminal ATP-binding site [139]. Novobiocin causes depletion of HSP90 clients such as Raf-1 and Her-2, like GA but requires much higher concentrations compared to N-terminal inhibitors. Another confirmation of interference of HSP90 -Hsc70, HSP90-P23 and HSP90-Cdc37 complexes was completed by co-immunoprecipitation assays [140]. Novobiocin was also the first discovered agent that inhibits HSP90 without promoting HSR and/or ocular toxicity. Another compound labelled as RTA 901 underwent a Phase I clinical trial and was administered on non-cancer patients (https://clinicaltrials.gov, identifier: NCT02666963). The agent was disclosed to be derived from novobiocin, but the full structure has not been released as of now [138, 139].

22 EPIGALLOCATECHIN GALLATE (EGCG)

Green tea contains active polyphenolic compounds such as EGCG. Many HSP90 client proteins, including telomerase, many kinases and the aryl hydrocarbon receptor, are thought to be inhibited by EGCG (AhR). Growth factors including epidermal and vascular endothelial growth factors, as well as transcription factors such as Ap-1 and NF-B, are all regulated by EGCG. According to affinity purification of HSP90 fragments, EGCG binds to the protein's C-terminus, specifically amino acids 538–729. This demonstrates that binding occurs at the C-terminus of the ATP-binding site. Unlike previously identified N-terminal HSP90 inhibitors, EGCG does not appear to prevent HSP90 from forming hetero protein complexes. Studies have examined the possibility of EGCG binding competing with novobiocin or cisplatin binding [140].

23 CISPLATIN

Cisplatin is a platinum-based chemotherapeutic drug that is used to treat cancers of the testicles, ovary, bladder and small cell lung. One of the significant properties of cisplatin is its ability to prevent rapidly dividing cells from duplicating DNA during mitosis by coordinating to DNA bases, resulting in cross-linked DNA [141, 142]. Binding to the HSP90 C-terminus and interfering with cisplatin nucleotide binding was also demonstrated by Sreedhar and colleagues [143]. According to Rosenhagen, physiological outcomes could be used as indicators of cisplatin-HSP90 interaction. The hyperactive HSP90-androgen receptor (AR) in prostate cancer is cured with cisplatin through HSP90 inhibition. Similarly, HSP90 inhibitors can overcome cisplatin resistance, which can hinder its therapeutic efficiency and can form under numerous mechanisms [144, 145], in cells that are transfected with the HSP90-dependent protein kinase v-src [144]. These mechanisms include reduced intracellular drug proliferation, improved cellular detoxification by glutathione and metallothionein, altered DNA repair and apoptosis limitation [140, 145]. *In vivo* genomic screening can help to clarify the mechanisms of cisplatin toxicity and acquired resistance [143]. Another appealing strategy to attack cancer is to target HSP70. Scientists have developed HSP90 inhibitors and some are undergoing clinical trials. However, drugs that inhibit HSP70 are less common. HSF1 transcription factor regulates the *HSP70* transcription when activated under stress stimulation [146]. HSF1 inhibition has the potential to curb the expression of HSP70 because Hsf1 activation causes HSP70 expression [146]. HSF1 activation can be inhibited by agents such as quercetin, diterpene triperoxide and triptolide. While these compounds, along with benzopyrene, inhibit the expression of HSP70, they have no effect on the other HSP [147]. Another type of HSP70-targeting drug is AIF-derived peptides [148]. These peptides have AIF sections (150aa–228aa) that are essential for HSP70 binding but do not have AIF's pro-apoptotic activity. ADD70 (AIF-derived decoy for HSP70), for example, has been demonstrated to diminish tumour growth in mice with colon cancers and melanomas (B16F10) and soften these malignancies to cisplatin. It also boosts tumour-infiltrating cytotoxic CD8 + T-cells in syngeneic mice, unlike immunodeficient mice, and has anti-tumour effects [149]. HSP70 interacts with a small molecule termed HS-72, causing misfolded protein aggregation and disrupting lysosome membrane stability, promoting autophagic cell death [150]. PES interacts with HSP70s C-terminal and suppresses its expression [151], but it also triggers the caspase-dependent apoptotic pathway in B-CCL cells [152]. Even though the mechanism is unknown and must be investigated more, HSP70 can be targeted using HSP90 inhibitors that remove the ATP from HSP70 [153]. VER-155008, an adenosine-derived molecule, decreases chaperone action by targeting the HSP70/hsc70 ATPase domain [154]. Compounds including azure C, methylene blue and myricetin may inhibit human HSP70, although additional research is needed [155].

In cancer cells, MKT-077, a cationic rhodacyanine dye, influences ABD-HSP70. MKT-077, which operates by translocating to mitochondria and inhibiting mitochondrial HSP70, is currently undergoing Phase I clinical trials as a cancer treatment [156]. The interaction between MKT-077 and HSP70 does not appear to occur,

but more research is needed [157]. Furthermore, NSC 630668, a dihydropyridine, MAL3-101, a second-generation molecule and MAL2-11B, a polyomavirus inhibitor, all have the potential to be employed as anticancer medicines [158, 159]. HSP70 and its co-chaperones interact with several synthetic substances, which work against them. Pyrimidotriazinediones is a new type of such medication that interacts with Hop/HSP70 and is harmful to WST-1 cells [160]. HSP70-chaperone activity is also inhibited by medicines that target Huntingtin-interacting protein 1 [161], which causes neurodegeneration. HSP90/HSP70 inhibitors increase apoptosis in cancer cells, as previously indicated, and some of them are currently in clinical trials [149]. Unfortunately, patients had higher HSP70 expression levels, which reduce the effectiveness of HSP70 inhibitors by lowering the likelihood of cell death. Chemotherapy medications stimulate TGF signalling and increase HSP70 expression [162]. HSP70 suppression by siRNA makes cancer cells vulnerable to tanespimycin (17-N-allylamino-17-demethoxygeldanamycin, 17-AAG) [163], whereas HSP70 and HSC70 knockdown cause HSP90 client protein degradation and death in HCT116 cells [164]. Furthermore, in HCT116 colon cancer cells, a cocktail of an adenosine-derived inhibitor of HSP70, VER-155008 and 17-AAG causes apoptosis [154]. In addition, 17-AAGs anti-cancer activity is increased when HSP70 is hindered [149]. HSP70 and HSP90 inhibitors increased HSP70 cell surface expression when paired with histone deacetylase inhibitors, according to a study on haematological cancer cells [165]. Suppressive myeloid immune cells are triggered when extracellular HSP70 is present [166]. This needs testing for synergistic effects of HSP70 and HSP90 inhibitors. Finally, both chelerythrine, a benzophenanthridine alkaloid that is a selective inhibitor of PKC, and staurosporine, a non-specific PKC inhibitor, have been demonstrated to suppress HSP70 expression [167].

24 CONCLUSIONS

HSPs are protein that has various roles inner and outer of cell including protein folding, unfolding, cell cycle and other signalling pathways. HSP can be grouped according to their molecular weight. Each group has their specific mechanisms of action. Increased levels of HSF and HSP have been linked to early detection, prediction of prognostic marker for a variety of diseases including neurodegenerative diseases and cancer due to its multifunctional roles. According to their roles, activity of the HSP is changed. For example, they become highly active in cancer but insufficient in neurodegenerative disease. Many significant advances in the field of HSP inhibitors have recently been made. In relation to pre-clinical and clinical studies, some HSP-based inhibitors and vaccine therapies are quite effective and promising in the treatment of cancer.

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REFERENCES

1. Li Z, Srivastava P (2004) Heat-shock proteins. Curr Protoc Immunol 58(1).
2. Aswad A, Liu T (2021) Targeting heat shock protein 90 for anti-cancer drug development. Adv Cancer Res 152:179–204.
3. Koh Y, Lim CM (2008) Role of changes in body temperature in acute lung injury. Mech Ventil:51–60.
4. Ponomarenko M, Stepanenko I, Kolchanov N (2013) Heat shock proteins. In: Brenner's Encyclopedia of Genetics. Netherlands: Elsevier Inc. p.402–405.
5. Ulrich Z, Kaufmann SH (1999) Role of heat shock proteins in protection from and pathogenesis of infectious diseases. Clin Microbiol Rev 12(1):19–39.
6. Elliott T (1998) Stress proteins. In: Encyclopedia of Immunology. p.2228–2232.
7. Morrow G, Tanguay RM (2012) Small heat shock protein expression and functions during development. Int J Biochem Cell Biol 44(10):1613–1621.
8. Daugaard M, Rohde M, Jäättelä M (2007) The heat shock protein 70 family: highly homologous proteins with overlapping and distinct functions. FEBS Lett 581(19):3702–3710.
9. Hongmao S (2016) Structure-based ligand design I. In: A Practical Guide to Rational Drug Design. Netherlands: Elsevier. p.15–60.
10. Becker J, Craig EA (1994) Heat-shock proteins as molecular chaperones. Eur J Biochem 219:11–23.
11. Yeh SL, Hou YC (2014) Glutamine and antioxidant potential in diabetes. In: Diabetes Oxidative Stress and Dietary Antioxidants. Netherlands: Elsevier. p.121–128.
12. Li J, Qian X, Sha B (2009) Heat shock protein 40: structural studies and their functional implications. Protein Pept Lett 16(6):606–612.
13. Rao R, Fiskus W, Ganguly S, Kambhampati S, Bhalla KN (2012) HDAC inhibitors and chaperone function. Adv Cancer Res 116:239–262.
14. Guay J, Lambert H, Gingras-Breton G, Lavoie JN, Huot J, Landry J (1997) Regulation of actin filament dynamics by p38 map kinase-mediated phosphorylation of heat shock protein 27. J Cell Sci 110(Pt 3):357–368.
15. Arrigo AP (2011) Structure-functions of HSPB1 (HSP27). Methods Mol Biol 787:105–119.
16. Jmor F, Kalirai H, Taktak A, Damato B, Coupland SE (2012) HSP-27 protein expression in uveal melanoma: correlation with predicted survival. Acta Ophthalmol 90(6):534–539.
17. Alderson TR, Roche J, Gastall HY, Dias DM, Pritišanac I, Ying J et al. (2019) Local unfolding of the HSP27 monomer regulates chaperone activity. Nat Commun 10(1):1068.
18. McDonald ET, Bortolus M, Koteiche HA, Mchaourab HS (2012) Sequence, structure, and dynamic determinants of HSP27 (HSPB1) equilibrium dissociation are encoded by the N-terminal domain. Biochemistry 51(6):1257–1268.
19. Kostenko S, Moens U (2009) Heat shock protein 27 phosphorylation: kinases, phosphatases, functions and

pathology. Cell Mol Life Sci 66(20):3289–3307.
20. Rahsepar AA, Mirzaee A, Moodi F, Moohebati M, Tavallaie S, Eshraghi A et al. (2012) Anti-heat shock protein 27 titers and oxidative stress levels are elevated in patients with valvular heart disease. Angiology 63(8):609–616.
21. Somborac-Bačura A, Rumora L, Novak R, Rašić D, Dumić J, Čepelak I et al. (2018) Differential expression of heat shock proteins and activation of mitogen-activated protein kinases in A549 alveolar epithelial cells exposed to cigarette smoke extract. Exp Physiol 103(12):1666–1678.
22. Sun X, Ou Z, Xie M, Kang R, Fan Y, Niu X, Wang H et al. (2015) HSPB1 as a novel regulator of ferroptotic cancer cell death. Oncogene 34(45):5617–5625.
23. Bitar KN (2002) HSP27 phosphorylation and interaction with actin-myosin in smooth muscle contraction. Am J Physiol Gastrointest Liver Physiol 282(5):G894–G903.
24. Fujita R, Ounzain S, Wang AC, Heads RJ, Budhram-Mahadeo VS (2011) HSP-27 induction requires POU4F2/Brn-3b TF in doxorubicin-treated breast cancer cells, whereas phosphorylation alters its cellular localisation following drug treatment. Cell Stress Chaperones 16(4):427–439.
25. Wang S, Zhang X, Wang H, Wang Y, Chen P, Wang L (2020) Heat shock protein 27 enhances SUMOylation of heat shock protein b8 to accelerate the progression of breast cancer. Am J Pathol 190(12):2464–2477.
26. Lelj-Garolla B, Mauk AG (2012) Roles of the N-and C-terminal sequences in HSP27 self-association and chaperone activity. Protein Sci 21(1):122–133.
27. Muranova LK, Ryzhavskaya AS, Sudnitsyna MV, Shatov VM, Gusev NB (2019) Small heat shock proteins and human neurodegenerative diseases. Biochemistry (Mosc) 84(11):1256–1267.
28. Majd S, Power JH, Grantham HJ (2015) Neuronal response in Alzheimer's and Parkinson's disease: the effect of toxic proteins on intracellular pathways. BMC Neurosci 16:69.
29. O'Reilly AM, Currie RW, Clarke DB (2010) HSPB1 (HSP 27) expression and neuroprotection in the retina. Mol Neurobiol 42(2):124–132.
30. Grotegut P, Hoerdemann PJ, Reinehr S, Gupta N, Dick HB, Joachim SC (2021) Heat shock protein 27 injection leads to caspase activation in the visual pathway and retinal T-cell response. Int J Mol Sci 22(2):513.
31. Okuno M, Adachi S, Kozawa O, Shimizu M, Yasuda I (2016) The clinical significance of phosphorylated heat shock protein 27 (HSPB1) in pancreatic cancer. Int J Mol Sci 17(1):137.
32. Kuramitsu Y, Wang Y, Taba K, Suenaga S, Ryozawa S, Kaino S, Sakaida I et al. (2012) Heat-shock protein 27 plays the key role in gemcitabine-resistance of pancreatic cancer cells. Anticancer Res 32(6):2295–2299.
33. Choi SK, Kam H, Kim KY, Park SI, Lee YS (2019) Targeting heat shock protein 27 in cancer: a druggable target for cancer treatment? Cancers (Basel) 11(8):1195.
34. Guay J, Lambert H, Gingras-Breton G, Lavoie JN, Huot J, Landry J (1997) Regulation of actin filament dynamics by p38 map kinase-mediated phosphorylation of heat shock protein 27. J Cell Sci 110(Pt 3):357–368.
35. Yang C, Wang H, Zhu D, Hong CS, Dmitriev P, Zhang C et al. (2015) Mutant glucocerebrosidase in Gaucher disease recruits HSP27 to the HSP90 chaperone complex for proteasomal degradation. Proc Natl Acad Sci U S A 112(4):1137–1142.
36. Miranda HV, Chegão A, Oliveira MS, Gomes BF, Enguita FJ, Outeiro TF (2020) HSP27 reduces glycation-induced toxicity and aggregation of alpha-synuclein. FASEB J 34(5):6718–6728.
37. Mandelkow EM, Mandelkow E (2012) Biochemistry and cell biology of tau protein in neurofibrillary degeneration. Cold Spring Harb Perspect Med 2(7):a006247.
38. Faust O, Abayev-Avraham M, Wentink AS, Maurer M, Nillegoda NB, London N et al. (2020) HSP40 proteins use class-specific regulation to drive HSP70 functional diversity. Nature 587(7834):489–494.
39. Tiwari S, Kumar V, Jayaraj GG, Maiti S, Mapa K (2013) Unique structural modulation of a non-native substrate by cochaperone DnaJ. Biochemistry 52(6):1011–1018.
40. Yu HY, Ziegelhoffer T, Craig EA (2015) Functionality of Class A and Class B J-protein co-chaperones with HSP70. FEBS Lett 589(19 Pt B):2825–2830.
41. Li J, Qian X, Sha B (2009) Heat shock protein 40: structural studies and their functional implications. Protein Pept Lett 16(6):606–612.
42. Kampinga HH, Andreasson C, Barducci A, Cheetham ME, Cyr D, Emanuelsson C et al. (2019) Function, evolution, and structure of J-domain proteins. Cell Stress Chaperones 24(1):7–15.
43. Liu Q, Liang C, Zhou L (2020) Structural and functional analysis of the HSP70/HSP40 chaperone system. Protein Sci 29(2):378–390.
44. Jiang Y, Rossi P, Kalodimos CG (2019) Structural basis for client recognition and activity of HSP40 chaperones. Science 365(6459):1313–1319.
45. Park SK, Hong JY, Arslan F, Kanneganti V, Patel B, Tietsort A et al. (2017) Overexpression of the essential Sis1 chaperone reduces TDP-43 effects on toxicity and proteolysis. PLoS Genet 13(5):e1006805.
46. Park SK, Arslan F, Kanneganti V, Barmada SJ, Purushothaman P, Verma SC et al. (2018) Overexpression of a conserved HSP40 chaperone reduces toxicity of several neurodegenerative disease proteins. Prion 12(1):16–22.
47. Blauwendraat C, Nalls MA, Singleton AB (2020) The genetic architecture of Parkinson's disease. Lancet Neurol 19(2):170–178.
48. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J et al. (2017) Parkinson disease. Nat Rev Dis Primers 3:17013.
49. Hasegawa T, Yoshida S, Sugeno N, Kobayashi J, Aoki M (2018) DnaJ/HSP40 family and parkinson's disease. Front Neurosci 11:743.
50. Roosen DA, Blauwendraat C, Cookson MR, Lewis PA (2019) DNAJC proteins and pathways to parkinsonism. FEBS J 286(16):3080–3094.
51. Mitra A, Shevde LA, Samant RS (2009) Multi-faceted role of HSP40 in cancer. Clin Exp Metastasis 26(6):559–567.
52. Sterrenberg JN, Blatch GL, Edkins AL (2011) Human DNAJ in cancer and stem cells. Cancer Lett 312(2):129–142.
53. Wu J, Liu T, Rios Z, Mei Q, Lin X, Cao S (2017) Heat shock proteins and cancer. Trends Pharmacol Sci 38(3):226–256.
54. Yun CW, Kim HJ, Lim JH, Lee SH (2019) Heat shock proteins: agents of cancer development and therapeutic targets in anti-

cancer therapy. Cells 9(1):60.
55. Cappello F, Gammazza AM, Piccionello AP, Campanella C, Pace A, de Macario EC et al. (2014) HSP60 chaperonopathies and chaperonotherapy: targets and agents. Expert Opin Ther Targets 18(2):185–208.
56. Liu Y, Zhang X (2018) Heat shock protein reports on proteome stress. Biotechnol J 13(4).
57. Wu J, Liu T, Rios Z, Mei Q, Lin X, Cao S (2017) Heat shock proteins and cancer. Trends Pharmacol Sci 38(3):226–256.
58. Kumar S, O'Malley J, Chaudhary AK, Inigo JR, Yadav N, Kumar R et al. (2019) HSP60 and IL-8 axis promotes apoptosis resistance in cancer. Br J Cancer 121(11):934–943.
59. Samali A, Cai J, Zhivotovsky B, Jones DP, Orrenius S (1999) Presence of a pre-apoptotic complex of pro-caspase-3, HSP60 and HSP10 in the mitochondrial fraction of jurkat cells. EMBO J 18(8):2040–2048.
60. Miyata Y, Ikawa Y, Shibuya M, Nishida E (2001) Specific association of a set of molecular chaperones including HSP90 and Cdc37 with MOK, a member of the mitogen-activated protein kinase superfamily. J Biol Chem 276(24):21841–21848.
61. Juwono J, Martinus RD (2016) Does HSP60 provide a link between mitochondrial stress and inflammation in diabetes mellitus? J Diabetes Res 2016:8017571.
62. Zhang D, Sun L, Zhu H, Wang L, Wu W, Xie J et al. (2012) Microglial LOX-1 reacts with extracellular HSP60 to bridge neuroinflammation and neurotoxicity. Neurochem Int 61(7):1021–1035.
63. Nemirovsky A, Fisher Y, Baron R, Cohen IR, Monsonego A (2011) Amyloid beta-HSP60 peptide conjugate vaccine treats a mouse model of Alzheimer's disease. Vaccine 29(23):4043–4050.
64. Tutar L, Tutar Y (2010) Heat shock proteins; an overview. Curr Pharm Biotechnol 11(2):216–222.
65. Shan Q, Ma F, Wei J, Li H, Ma H, Sun P (2020) Physiological functions of heat shock proteins. Curr Protein Pept Sci 21(8):751–760.
66. Bertelsen EB, Chang L, Gestwicki JE, Zuiderweg ER (2009) Solution conformation of wild-type E. coli HSP70 (DnaK) chaperone complexed with ADP and substrate. Proc Natl Acad Sci U S A 106(21):8471–8476.
67. Ciocca DR, Calderwood SK (2005) Heat shock proteins in cancer: diagnostic, prognostic, predictive, and treatment implications. Cell Stress Chaperones 10(2):86–103.
68. Tutar Y (2007) Therapeutic use of heat shock protein 70. Recent Pat DNA Gene Seq 1(2):125–127.
69. Tutar Y (2011) HSP70 in oncology. Recent Pat DNA Gene Seq 5(3):214–218.
70. Tutar L, Özgür A, Tutar E, Coşkun KA, Tutar Y (2014) Heat shock response agents and the diseases. Front Protein Pept Sci 1:139.
71. Lee HW, Lee EH, Kim SH, Roh MS, Jung SB, Choi YC (2013) Heat shock protein 70 (HSP70) expression is associated with poor prognosis in intestinal type gastric cancer. Virchows Arch 463(4):489–495.
72. Cai MB, Wang XP, Zhang JX, Han HQ, Liu CC, Bei JX et al. (2012) Expression of heat shock protein 70 in nasopharyngeal carcinomas: different expression patterns correlate with distinct clinical prognosis. J Transl Med 10:96.
73. Sherman MY, Gabai VL (2015) HSP70 in cancer: back to the future. Oncogene 34(32):4153–41561.
74. Gupta A, Bansal A, Hashimoto-Torii K (2020) HSP70 and HSP90 in neurodegenerative diseases. Neurosci Lett 716:134678.
75. Turturici G, Sconzo G, Geraci F (2011) HSP70 and its molecular role in nervous system diseases. Biochem Res Int 2011:618127.
76. Picard D (2002) Heat-shock protein 90, a chaperone for folding and regulation. Cell Mol Life Sci 59(10):1640–1648.
77. Shelton LB, Koren J 3rd, Blair LJ (2017) Imbalances in the HSP90 chaperone machinery: implications for tauopathies. Front Neurosci 11:724.
78. Jackson SE (2013) HSP90: structure and function. Top Curr Chem 328:155–240.
79. Bohush A, Bieganowski P, Filipek A (2019) HSP90 and its co-chaperones in neurodegenerative diseases. Int J Mol Sci 20(20):4976.
80. Sreedhar AS, Kalmár E, Csermely P, Shen YF (2004) HSP90 isoforms: functions, expression and clinical importance. FEBS Lett 562(1–3):11–15.
81. Jafari A, Rezaei-Tavirani M, Farhadihosseinabadi B, Taranejoo S, Zali H (2020) HSP90 and Co-chaperones: impact on tumor progression and prospects for molecular-targeted cancer therapy. Cancer Invest 38(5):310–328.
82. Street TO, Lavery LA, Agard DA (2011) Substrate binding drives large-scale conformational changes in the HSP90 molecular chaperone. Mol Cell 42(1):96–105.
83. Söti C, Rácz A, Csermely P (2002) A Nucleotide-dependent molecular switch controls ATP binding at the C-terminal domain of HSP90. N-terminal nucleotide binding unmasks a C-terminal binding pocket. J Biol Chem 277(9):7066–7075.
84. Scheufler C, Brinker A, Bourenkov G, Pegoraro S, Moroder L, Bartunik H et al. (2000) Structure of TPR domain-peptide complexes: critical elements in the assembly of the HSP70-HSP90 multichaperone machine. Cell 101(2):199–210.
85. Cuanalo-Contreras K, Mukherjee A, Soto C (2013) Role of protein misfolding and proteostasis deficiency in protein misfolding diseases and aging. Int J Cell Biol 2013:638083.
86. Moser C, Lang SA, Stoeltzing O (2009) Heat-shock protein 90 (HSP90) as a molecular target for therapy of gastrointestinal cancer. Anticancer Res 29(6):2031–2042.
87. Selkoe DJ, Schenk D (2002) Alzheimer's disease: molecular understanding predicts amyloid-based therapeutics. Annu Rev Pharmacol Toxicol 43:545–584.
88. Tanemura K, Murayama M, Akagi T, Hashikawa T, Tominaga T, Ichikawa M et al. Neurodegeneration with tau accumulation in a transgenic mouse expressing V337M human tau. J Neurosci 22(1):133–141.
89. Alonso AD, Cohen LS, Corbo C, Morozova V, ElIdrissi A, Phillips G et al. (2018) Hyperphosphorylation of Tau associates with changes in its function beyond microtubule stability. Front Cell Neurosci 12:338.
90. Jinwal UK, Trotter JH, Abisambra JF, Koren J 3rd, Lawson LY, Vestal GD et al. (2011) The HSP90 kinase co-chaperone Cdc37 regulates tau stability and phosphorylation dynamics. J Biol Chem 286(19):16976–16983.
91. Blair LJ, Nordhues BA, Hill SE, Scaglione KM, O'Leary JC 3rd,

Fontaine SN et al. Accelerated neurodegeneration through chaperone-mediated oligomerization of tau. J Clin Invest 123(10):4158–4169.
92. Hernandez DG, Reed X, Singleton AB (2016) Genetics in Parkinson disease: Mendelian versus non-mendelian inheritance. J Neurochem 139 Suppl 1(Suppl 1):59–74.
93. Tan EK, Chandran VR, Fook-Chong S, Shen H, Yew K, Teoh ML et al. (2005) Alpha-synuclein mRNA expression in sporadic Parkinson's disease. Mov Disord 20(5):620–623.
94. Liang J, Clark-Dixon C, Wang S, Flower TR, Williams-Hart T, Zweig R et al. (2008) Novel suppressors of alpha-synuclein toxicity identified using yeast. Hum Mol Genet 17(23):3784–3795.
95. Falsone SF, Kungl AJ, Rek A, Cappai R, Zangger K (2009) The molecular chaperone HSP90 modulates intermediate steps of amyloid assembly of the Parkinson-related protein alpha-synuclein. J Biol Chem 284(45):31190–31199.
96. Wang L, Xie C, Greggio E, Parisiadou L, Shim H, Sun L et al. (2008) The chaperone activity of heat shock protein 90 is critical for maintaining the stability of leucine-rich repeat kinase 2. J Neurosci 28(13):3384–3391.
97. Narayan M, Zhang J, Braswell K, Gibson C, Zitnyar A, Lee DC et al. (2015) Withaferin a regulates LRRK2 levels by interfering with the HSP90-Cdc37 chaperone complex. Curr Aging Sci 8(3):259–265.
98. Gusella JF, MacDonald ME (2006) Huntington's disease: seeing the pathogenic process through a genetic lens. Trends Biochem Sci 31(9):533–540.
99. Baldo B, Weiss A, Parker CN, Bibel M, Paganetti P, Kaupmann K (2012) A screen for enhancers of clearance identifies huntingtin as a heat shock protein 90 (HSP90) client protein. J Biol Chem 287(2):1406–1414.
100. Orozco-Díaz R, Sánchez-Álvarez A, Hernández-Hernández JM, Tapia-Ramírez J (2019) The interaction between RE1-silencing transcription factor (REST) and heat shock protein 90 as new therapeutic target against Huntington's disease. PLoS One 14(7):e0220393.
101. Wu J, Liu T, Rios Z, Mei Q, Lin X, Cao S (2017) Heat shock proteins and cancer. Trends Pharmacol Sci 38(3):226–256.
102. Ciocca DR, Calderwood SK (2005) Heat shock proteins in cancer: diagnostic, prognostic, predictive, and treatment implications. Cell Stress Chaperones 10(2):86–103.
103. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144(5):646–674.
104. Whitesell L, Lindquist SL (2005) HSP90 and the chaperoning of cancer. Nat Rev Cancer 5(10):761–772.
105. Schulz R, Streller F, Scheel AH, Rüschoff J, Reinert MC, Dobbelstein M et al. (2014) HER2/ErbB2 activates HSF1 and thereby controls HSP90 clients including MIF in HER2-overexpressing breast cancer. Cell Death Dis 5(1):e980.
106. Kim YE, Hipp MS, Bracher A, Hayer-Hartl M, Hartl FU (2013) Molecular chaperone functions in protein folding and proteostasis. Annu Rev Biochem 82:323–355.
107. Hartl FU, Bracher A, Hayer-Hartl M (2011) Molecular chaperones in protein folding and proteostasis. Nature 475(7356):324–332.
108. Shrestha L, Bolaender A, Patel HJ, Taldone T (2016) Heat shock protein (HSP) drug discovery and development: targeting heat shock proteins in disease. Curr Top Med Chem 16(25):2753–2764.
109. Miyata Y, Nakamoto H, Neckers L (2013) The therapeutic target HSP90 and cancer hallmarks. Curr Pharm Des 19(3):347–365.
110. Mahalingam D, Swords R, Carew JS, Nawrocki ST, Bhalla K, Giles FJ (2009) Targeting HSP90 for cancer therapy. Br J Cancer 100(10):1523–1529.
111. Paul S, Mahanta S (2014) Association of heat-shock proteins in various neurodegenerative disorders: is it a master key to open the therapeutic door? Mol Cell Biochem 386(1–2):45–61.
112. Adachi H, Katsuno M, Waza M, Minamiyama M, Tanaka F, Sobue G (2009) Heat shock proteins in neurodegenerative diseases: pathogenic roles and therapeutic implications. Int J Hyperthermia 25(8):647–654.
113. Rochani AK, Singh M, Tatu U (2013) Heat shock protein 90 inhibitors as broad spectrum anti-infectives. Curr Pharm Des 19(3):377–386.
114. Whitesell L, Lindquist SL (2005) HSP90 and the chaperoning of cancer. Nat Rev Cancer 5(10):761–772.
115. Piper PW, Millson SH (2012) Spotlight on the microbes that produce heat shock protein 90-targeting antibiotics. Open Biol 2(12):120138.
116. He W, Hu H (2018) BIIB021, an HSP90 inhibitor: a promising therapeutic strategy for blood malignancies (Review). Oncol Rep 40(1):3–15.
117. Csermely P, Schnaider T, Soti C, Prohászka Z, Nardai G (1998) The 90-kDa molecular chaperone family: structure, function, and clinical applications. A comprehensive review. Pharmacol Ther 79(2):129–168.
118. Soga S, Akinaga S, Shiotsu Y (2013) HSP90 inhibitors as anti-cancer agents, from basic discoveries to clinical development. Curr Pharm Des 19(3):366–376.
119. Sanchez J, Carter TR, Cohen MS, Blagg BS (2020) Old and new approaches to target the HSP90 chaperone. Curr Cancer Drug Targets 20(4):253–270.
120. Gorska M, Popowska U, Sielicka-Dudzin A, Kuban-Jankowska A, Sawczuk W, Knap N et al. (2012) Geldanamycin and its derivatives as HSP90 inhibitors. Front Biosci (Landmark Ed) 17:2269–2277.
121. Sanchez J, Carter TR, Cohen MS, Blagg BS (2020) Old and new approaches to target the HSP90 chaperone. Curr Cancer Drug Targets 20(4):253–270.
122. Samuni Y, Ishii H, Hyodo F, Samuni U, Krishna MC, Goldstein S et al. (2010) Reactive oxygen species mediate hepatotoxicity induced by the HSP90 inhibitor geldanamycin and its analogs. Free Radic Biol Med 48(11):1559–1563.
123. Hostein I, Robertson D, DiStefano F, Workman P, Clarke PA (2001) Inhibition of signal transduction by the HSP90 inhibitor 17-allylamino-17-demethoxygeldanamycin results in cytostasis and apoptosis. Cancer Res 61(10):4003–4009.
124. Zolghadr AR, Boroomand S (2017) Spontaneous assembly of HSP90 inhibitors at water/octanol interface: a molecular dynamics simulation study. Chem Phys Lett 669:130–136.
125. Li L, Wang L, You QD, Xu XL (2020) Heat shock protein 90 inhibitors: an update on achievements, challenges, and future directions. J Med Chem 63(5):1798–1822.
126. Usmani SZ, Bona R, Li Z (2009) 17 AAG for HSP90 inhibition in cancer--from bench to bedside. Curr Mol Med 9(5):654–664.

127. Chiosis G, Timaul MN, Lucas B, Munster PN, Zheng FF, Sepp-Lorenzino L et al. (2001) A small molecule designed to bind to the adenine nucleotide pocket of HSP90 causes Her2 degradation and the growth arrest and differentiation of breast cancer cells. Chem Biol 8(3):289–299.
128. Taldone T, Chiosis G (2009) Purine-scaffold HSP90 inhibitors. Curr Top Med Chem 9(15):1436–1446.
129. Dickson MA, Okuno SH, Keohan ML, Maki RG, D'Adamo DR, Akhurst TJ et al. (2013) Phase II study of the HSP90-inhibitor BIIB021 in gastrointestinal stromal tumors. Ann Oncol 24(1):252–257.
130. Saif MW, Takimoto C, Mita M, Banerji U, Lamanna N, Castro J et al. (2014) A phase 1, dose-escalation, pharmacokinetic and pharmacodynamic study of BIIB021 administered orally in patients with advanced solid tumors. Clin Cancer Res 20(2):445–455.
131. Richardson PG, Chanan-Khan AA, Lonial S, Krishnan AY, Carroll MP, Alsina M et al. (2011) Tanespimycin and bortezomib combination treatment in patients with relapsed or relapsed and refractory multiple myeloma: results of a phase 1/2 study. Br J Haematol 153(6):729–740.
132. Okamoto J, Mikami I, Tominaga Y, Kuchenbecker KM, Lin YC, Bravo DT et al. Inhibition of HSP90 leads to cell cycle arrest and apoptosis in human malignant pleural mesothelioma. J Thorac Oncol 3(10):1089–1095.
133. Chen Y, Wang X, Cao C, Wang X, Liang S, Peng C et al. (2017) Inhibition of HSP90 sensitizes a novel Raf/ERK dual inhibitor CY-9d in triple-negative breast cancer cells. Oncotarget 8(61):104193–104205.
134. Woodhead AJ, Angove H, Carr MG, Chessari G, Congreve M, Coyle JE et al. (2010) Discovery of (2,4-dihydroxy-5-isopropylphenyl)-[5-(4-methylpiperazin-1-ylmethyl)-1,3- dihydroisoindol-2-yl]methanone (AT13387), a novel inhibitor of the molecular chaperone HSP90 by fragment based drug design. J Med Chem 53(16):5956–5969.
135. Kang MH, Reynolds CP, Houghton PJ, Alexander D, Morton CL, Kolb EA et al. (2012) Initial testing (Stage 1) of AT13387, an HSP90 inhibitor, by the pediatric preclinical testing program. Pediatr Blood Cancer 59(1):185–188.
136. Shapiro GI, Kwak E, Dezube BJ, Yule M, Ayrton J, Lyons J et al. (2015) First-in-human phase I dose escalation study of a second-generation non-ansamycin HSP90 inhibitor, AT13387, in patients with advanced solid tumors. Clin Cancer Res 21(1):87–97.
137. Bickel D, Gohlke H (2019) C-terminal modulators of heat shock protein of 90 kDa (HSP90): state of development and modes of action. Bioorg Med Chem 27(21):115080.
138. Chen Y, Wang X, Cao C, Wang X, Liang S, Peng C et al. (2017) Inhibition of HSP90 sensitizes a novel Raf/ERK dual inhibitor CY-9d in triple-negative breast cancer cells. Oncotarget 8(61):104193–104205.
139. Kang MH, Reynolds CP, Houghton PJ, Alexander D, Morton CL, Kolb EA et al. (2012) Initial testing (Stage 1) of AT13387, an HSP90 inhibitor, by the pediatric preclinical testing program. Pediatr Blood Cancer 59(1):185–188.
140. Donnelly A, Blagg BS (2008) Novobiocin and additional inhibitors of the HSP90 C-terminal nucleotide-binding pocket. Curr Med Chem 15(26):2702–2717.
141. Galanski M (2006) Recent developments in the field of anticancer platinum complexes. Recent Pat Anticancer Drug Discov 1(2):285–295.
142. Goodisman J, Hagrman D, Tacka KA, Souid AK (2006) Analysis of cytotoxicities of platinum compounds. Cancer Chemother Pharmacol 57(2):257–267.
143. Frankenberg-Schwager M, Kirchermeier D, Greif G, Baer K, Becker M, Frankenberg D (2005) Cisplatin-mediated DNA double-strand breaks in replicating but not in quiescent cells of the yeast *Saccharomyces cerevisiae*. Toxicology 212(2–3):175–184.
144. Sreedhar AS, Soti C, Csermely P (2004) Inhibition of HSP90: a new strategy for inhibiting protein kinases. Biochim Biophys Acta 1697(1–2):233–242.
145. Rosenhagen MC, Sōti C, Schmidt U, Wochnik GM, Hartl FU, Holsboer F et al. (2003) The heat shock protein 90-targeting drug cisplatin selectively inhibits steroid receptor activation. Mol Endocrinol 17(10):1991–2001.
146. Kumar S, Tomar MS, Acharya A (2013) HSF1-mediated regulation of tumor cell apoptosis: a novel target for cancer therapeutics. Future Oncol 9(10):1573–1586.
147. Kumar S, Stokes J 3rd, Singh UP, Gunn KS, Acharya A, Manne U et al. (2016) Targeting HSP70: a possible therapy for cancer. Cancer Lett 374(1):156–166.
148. Correction: peptides and aptamers targeting HSP70: a novel approach for anticancer chemotherapy. Cancer Res 75(5):902. Erratum for: Cancer Res. 2011;71(2):484–495. Deminov, Oleg [corrected to Demidov, Oleg N].
149. Schmitt E, Maingret L, Puig PE, Rerole AL, Ghiringhelli F, Hammann A et al. (2006) Heat shock protein 70 neutralization exerts potent antitumor effects in animal models of colon cancer and melanoma. Cancer Res 66(8):4191–4197.
150. Leu JI, Pimkina J, Frank A, Murphy ME, George DL (2009) A small molecule inhibitor of inducible heat shock protein 70. Mol Cell 36(1):15–27.
151. Huang C, Wang J, Chen Z, Wang Y, Zhang W (2013) 2-phenylethynesulfonamide prevents induction of pro-inflammatory factors and attenuates LPS-induced liver injury by targeting NHE1-HSP70 complex in mice. PLoS One 8(6):e67582.
152. Steele AJ, Prentice AG, Hoffbrand AV, Yogashangary BC, Hart SM, Lowdell MW et al. (2019) 2-Phenylacetylenesulfonamide (PAS) induces p53-independent apoptotic killing of B-chronic lymphocytic leukemia (CLL) cells. Blood 114(6):1217–1225.
153. Williamson DS, Borgognoni J, Clay A, Daniels Z, Dokurno P, Drysdale MJ et al. (2009) Novel adenosine-derived inhibitors of 70 kDa heat shock protein, discovered through structure-based design. J Med Chem 52(6):1510–1513.
154. Massey AJ, Williamson DS, Browne H, Murray JB, Dokurno P, Shaw T et al. A novel, small molecule inhibitor of Hsc70/HSP70 potentiates HSP90 inhibitor induced apoptosis in HCT116 colon carcinoma cells. Cancer Chemother Pharmacol 66(3):535–545.
155. Jinwal UK, Miyata Y, Koren J 3rd, Jones JR, Trotter JH, Chang L et al. (2009) Chemical manipulation of HSP70 ATPase activity regulates tau stability. J Neurosci 29(39):12079–12088.
156. Koya K, Li Y, Wang H, Ukai T, Tatsuta N, Kawakami M et al. (1996) MKT-077, a novel rhodacyanine dye in clinical

trials, exhibits anticarcinoma activity in preclinical studies based on selective mitochondrial accumulation. Cancer Res 56(3):538–543.
157. Deocaris CC, Widodo N, Shrestha BG, Kaur K, Ohtaka M, Yamasaki K et al. Mortalin sensitizes human cancer cells to MKT-077-induced senescence. Cancer Lett 252(2):259–269.
158. Evans CG, Wisén S, Gestwicki JE (2006) Heat shock proteins 70 and 90 inhibit early stages of amyloid beta-(1-42) aggregation *in vitro*. J Biol Chem 281(44):33182–33191.
159. Wright CM, Seguin SP, Fewell SW, Zhang H, Ishwad C, Vats A et al. (2009) Inhibition of simian virus 40 replication by targeting the molecular chaperone function and ATPase activity of T antigen. Virus Res 141(1):71–80.
160. Yi F, Regan L (2008) A novel class of small molecule inhibitors of HSP90. ACS Chem Biol 3(10):645–654.
161. Roodveldt C, Bertoncini CW, Andersson A, van der Goot AT, Hsu ST, Fernández-Montesinos R et al. (2009) Chaperone proteostasis in Parkinson's disease: stabilization of the HSP70/alpha-synuclein complex by Hip. EMBO J 28(23):3758–3770.
162. Yun CH, Yoon SY, Nguyen TT, Cho HY, Kim TH, Kim ST et al. (2010) Geldanamycin inhibits TGF-beta signaling through induction of HSP70. Arch Biochem Biophys 495(1):8–13.
163. Powers MV, Clarke PA, Workman P (2009) Death by chaperone: HSP90, HSP70, or both? Cell Cycle 8(4):518–526.
164. Powers MV, Clarke PA, Workman P (2008) Dual targeting of HSC70 and HSP72 inhibits HSP90 function and induces tumor-specific apoptosis. Cancer Cell 14(3):250–262.
165. Jensen H, Andresen L, Hansen KA, Skov S (2009) Cell-surface expression of HSP70 on hematopoietic cancer cells after inhibition of HDAC activity. J Leukoc Biol 86(4):923–932.
166. Chalmin F, Ladoire S, Mignot G, Vincent J, Bruchard M, Remy-Martin JP et al. (2010) Membrane-associated HSP72 from tumor-derived exosomes mediates STAT3-dependent immunosuppressive function of mouse and human myeloid-derived suppressor cells. J Clin Invest 120(2):457–4571.
167. Kumar S, Deepak P, Kumar S, Gautam PK, Acharya A (2013) A benzophenanthridine alkaloid, chelerythrine induces apoptosis *in vitro* in a Dalton's lymphoma. J Cancer Res Ther 9(4):693–700.
168. Yang S, Xiao H, Cao L (2021) Recent advances in heat shock proteins in cancer diagnosis, prognosis, metabolism and treatment. Biomed Pharmacother 142:112074.