Heat Shock Proteins, a Key Modulator of Neuroinflammation in Alzheimer's Disease

Komal Panchal, Vidhi Bhatt, Mahima Raval, and Anand Krishna Tiwari

Abstract

Introduction Heat shock proteins (Hsp) are a key player to maintain protein homeostasis and folding in neurodegenerative diseases (NDDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), etc. Hsp are associated with NDs via induction of proper folding of toxic misfolded protein. AD is the second most common neurodegenerative disease worldwide and is characterized by accumulation of $A\beta_{42}$ plaques and hyperphosphorylated tau that results in cognitive decline, neuronal death and affects brain structure. From the last past decade, several researchers proved that AD is not restricted to the brain, but it also manipulates the immune response and activation of inflammatory cells. AD is the amalgam of neurobiology and Immunology. One of the core pathologies of AD is neuroinflammation which activates the innate immune response followed by activation of microglia (macrophages), a resident immune cell of CNS and astroglia cells. Amyloid plaques and neurofibrillary tangles activate neuroinflammatory components such as microglia which further induce the production of a variety of proinflammatory cytokines, ROS, nitric oxide, eicosanoids, etc. Previous studies have shown that apart from Hsp molecular chaperone function, it also plays a role in neuroinflammation and disease-related signaling mechanisms. In here, we aim to summarize the details of Hsp as a key modulator of neuroinflammation in Alzheimer's Disease.

Methods The authors reviewed most of the relevant papers of Hsp and their role in neuroinflammation in AD.

Results Available data suggest that Hsp plays a protective role in neuroinflammation by acting as an immunomodulator in the central nervous system

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Heat Shock Proteins (2021) 22: 89–145
https://doi.org/10.1007/7515_2020_12

Published Online: 30 August 2020

and is also associated with astrocytes in $A\beta_{42}$ plaques in the brain of AD patients. It has been demonstrated that several signaling pathways are activated by cytokines such as TNF-α, INF-γ, IL-1β, etc. in the brain which exacerbates the AD-related pathologies and overexpression of Hsp decreases the inflammatory cytokines in the brain and decrease the progression and severity of the disease.

Conclusions Hsp are significantly involved in the modulation of neuroinflammation via interacting with inflammation-causing molecules and helps in the prevention of neuroinflammation in AD. It is used as a potential therapeutic target for the prevention of AD-related pathologies. The supplementation of compounds, known as inducers/co-inducers of Hsp in AD might be one of the potential therapeutic targets to treat/prolong the AD related pathologies in future. Moreover, membrane lipid rearrangement and nanoparticle-based therapies are also involved in decreasing the neuroinflammation via increasing the Hsp level at the site of neuroinflammation. Thus, apart from the supplementation of drugs to modulate the Hsp level, the interaction of Hsp with inflammatory cells and their affinity to reduce/inactivate them should be a more focused area in the case of AD and need to be extensively studied to get better therapeutic approach to treat the AD.

Keywords Alzheimer's disease · Astrocytes · $A\beta_{42}$ plaques · Heat Shock Proteins (Hsp) · Microglia · Neuroinflammation · Nuclear factor-kappa B · Pro-inflammatory cytokines · Tau

Abbreviations

17-AAG	17-allylamino-demethoxygeldanamycin
AA	arachidonic acid
AAVs	adeno-associated viruses
ACD	α-crystallin domain
AD	Alzheimer's disease
AP1	activator protein 1
ApoE	apolipoprotein E
APP	amyloid precursor protein
Appl	amyloid precursor protein like
ASK1	apoptosis signal-regulating kinase 1
ATP	adenosine triphosphate
Aβ	amyloid-β
BACE-1	beta-site amyloid precursor protein cleaving enzyme – 1
BAX	Bcl-2-associated X protein
BBB	blood brain barrier
Bcl2	B-cell lymphoma 2
CD	cluster of differentiation
Clp	Casein lytic proteinase
CNS	central nervous system

COX-2	cyclooxygenase-2
CPX	cyclooxygenase – 2
CSF	cerebrospinal fluid
CTF	C-terminal fragment
CTL	cytotoxic T lymphocytes
CTR	c-terminal region
CvHsp	cardiovascular heat shock protein
DAXX	death domain associated protein
DHMN2C	distal hereditary motor neuropathy 2C
DMPK	myotonic dystrophy protein kinase
DNA	deoxyribonucleic acid
DPPC	dipalmitoyl phosphatidyl choline
EEVD	Glu-Glu-Val-Asp (Glu- glutamic acid, Val- Valine, Asp-Aspartic acid)
eIF4E	eukaryotic translation initiation factor
EPF	extracellular protein factor
ER	endoplasmic reticulum
ERGIC	ER-Golgi intermediate compartment
ERK	extracellular-signal regulated kinases
FLT3	FMS-like tyrosine kinase-3
GGA	Geranylgeranyl acetone
GRP78	glucose-regulated protein 78kD
HD	Huntington's disease
HSE	heat shock elements
HSF	heat shock factor
Hsp	heat shock proteins
HTPG	high-temperature protein G
IL	interleukins
INF	interferone
iNOS	inducible nitric oxide synthase
JAK2	Janus kinase
JNK	c-Jun N-terminal kinase
kDa	kilo Dalton
LPS	lipopolysaccharides
MAPK	mitogen-activated protein kinase
MCP-1	macrophage chemo-attractant protein-1
M-CSF	macrophage colony-stimulating factor
MHC	major histocompatibility complex
MIP-1α	macrophage inflammatory peptide
MKBP	myotonic dystrophy kinase binding protein
MN	motor neuron
MS	multiple sclerosis
MtUPR	mitochondrial related unfolding protein response
Myd88	myeloid differentiation factor 88

NDDs	neurodegenerative diseases
NF-kB	nuclear factor-kappa B
NFT	neurofibrillary tangles
NO	nitric oxide
NOD	leucine rich repeat and pyrin containing protein 3 (NLRP3)
NTR	N-terminal region
ODF1	outer dense fiber protein 1
PD	Parkinson's disease
PG	prostaglandins
PI3K	phosphatidylinositol-3-kinase
PP1	protein phosphatase 1
PS	presenilin
RAF	rapidly accelerated fibrosarcoma
RIP	receptor-interacting kinase
ROS	reactive oxygen species
SAPK	stress-activated kinases
sAPP	soluble amyloid precursor protein
sHsp	small heat shock protein
STAT-1	signal transducers and activator of transcription-1
TBI	traumatic brain injury
TCTEL1	T-complex-associated-testis-expressed 1-like 1
TGF	transforming growth factor
TLR	toll like receptor
TNF	tumor necrosis factor
TRAP	tryptophan regulated attenuation protein
WD/EPF domain	WD (Tryptophan-aspartic acid (W-D) dipeptide), epf-domain

1 Introduction

Heat Shock Proteins (Hsp), molecular chaperones play a vital role in maintaining protein homeostasis via proper protein folding, degradation and protein trafficking in cellular stress conditions such as neuroinflammation, autoimmune diseases, environmental stress, brain injury, trauma, ischemia, neurodegenerative disorder, metal ions, ethanol, anoxia, UV exposer, etc. [1–4]. Hsp also plays a key role in multiprotein complexes assembly, sorting/transporting proteins into their respective subcellular compartments, inhibition of cell death and oxidative stress, etc. [5–8]. They are highly conserved proteins that confer their thermotolerance in all organisms [9–11]. Hsp were first discovered in the early 1960s by FM Ritossa. He demonstrated that chromosomal puffs in the salivary gland of the fruit flies were generated in the response of heat shock in *Drosophila busckii* [12].

The Hsp has been categorized as large and small Hsp dependent on their molecular weight [10, 13]. Large ATP has range of 40–110 kDa ATP dependent

Hsp such as Hsp100, 90, 70, 60, 47, 40 and small, ATP independent Hsp (sHsp) categorized as Hsp27, HspB5, Hsp20, Hsp22, etc. [10, 13–15]. Among all, Hsp70 is one of the most studied, conserved and ubiquitously expressed Hsp, present in archaebacteria to human [16, 17]. Hsp are very well known for its role in immunity by presenting antigens to the MHC Class I and class II molecule [7, 18, 19]. They also have anti-cancer properties (mediated by the adaptive and innate immune system) [19, 20].

The regulation of Hsp gene expression in stress condition is mediated by the interaction of heat shock factor (HSF) with heat shock elements (HSEs) in the heat shock protein gene promoter regions in DNA (Fig. 1) [21, 22]. In unstressed condition, HSF is unable to bind DNA and remains in monomeric molecules and are bound to Hsp70 and Hsp90 (repressors of HSF) in the cytoplasm [23–25]. When cellular insults induce cellular stress, Hsp70 and Hsp90 interact with misfolded protein and subsequently, HSF monomers get dissociated form Hsp90 and Hsp70 (Fig. 1) [26, 27]. HSF gets hyperphosphorylated at several serine residues 230, 326, and 419 by the mitogen-activated protein kinase (MAPK) subfamilies such as JNK/SAPK, ERK1, p38 protein kinase, etc. in a ras-dependent manner which promotes its transcriptional activity [26, 28–31]. After phosphorylation HSF forms trimer structure and translocate from cytoplasm to the nucleus and bind at the promoter region of Hsp gene on DNA results in robust increase in various Hsp gene expression such as Hsp70, Hsp60 as well as sHsp27 (Fig. 1) [15, 28, 32, 33].

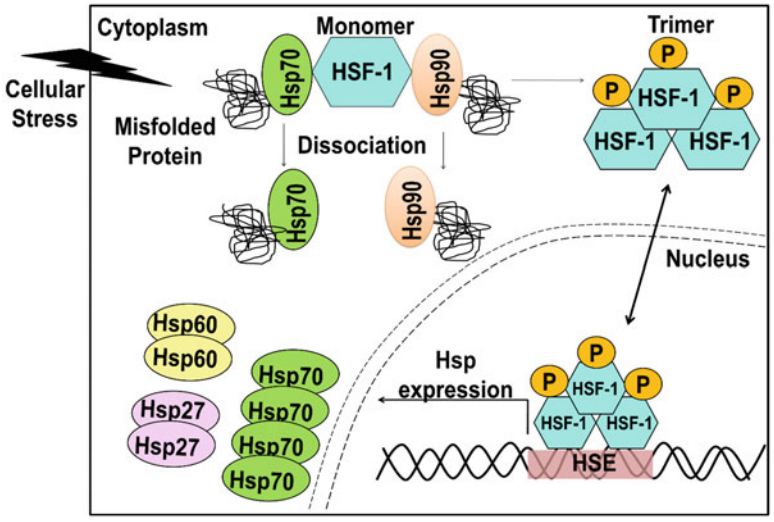

Fig. 1 Heat shock transcription factor 1 (HSF1) activates Hsp expression. The above schematic diagram shows that in normal conditions**,** HSF-1 is in monomeric inactive form in the cytoplasm and Hsp70 and Hsp90 remain bounded with HSF-1 and blocking its transcriptional activity. Under stress conditions, misfolded proteins are formed which binds to Hsp70 and Hsp90 and triggers the detachment of it from the HSF-1. HSF-1 forms a phosphorylated trimer structure in the cytoplasm and translates to the nucleus and binds to specific heat shock elements (HSE) sequences on DNA and activates Hsp such as Hsp70, Hsp60, Hsp27 etc. genes transcription

1.1 Large Heat Shock Proteins (40-110 kDa) [ATP Dependent]

As mentioned above, ATP dependent large Hsp are high molecular weight Hsp ranging from 40 to 110 kDa includes Hsp100, 90, 70, 60, 47, 40 kDa (Table 1).

1.1.1 Hsp40

Hsp40 (DnaJ) has 40 kDa molecular weight and mostly present in the cytosol and endoplasmic reticulum (ER) [41, 42]. It has three types such as type I, type II and type III [141]. All three types of 40 contain J-domain made up of 70 amino acid residues located on N-terminal in Hsp40 types I and II and at any position in the case of type III [37, 40]. The C-terminal domain of type I and type II Hsp40 has a peptide-binding domain [141, 142]. They are bind to the non-native protein and induce protein folding by acting as cochaperones of Hsp70 [141, 143, 144]. Hsp40 and Hsp70 are the members of the DnaJ-like family which make transient complexes with non-native polypeptides results in protein folding, protein assembly, transport and degradation [56, 160, 333]. Hsp40 type I also known as DnaJ (E.coli), Ydj1 (Yeast) and Hdj2 (Human), all these contain middle two Zinc-finger motifs but it is absent in Hsp40 type II such as Sis1 (yeast) and Hdj1 (human) (Table 1) ([34, 35].

1.1.2 Hsp47

Hsp47 (Serpin H1) is 47 kDa molecular weight glycoprotein located in ER as well as cytoplasm [47, 52, 145]. This is a collagen specific chaperon mostly expressed in type I procollagen expressing cells and play a vital role in collagen synthesis [46, 48, 49]. Hsp47 belongs to the serpin family and possesses a serpin loop without serine protease inhibitory activity (Table 1) [145, 146]. It is induced by heat shock and shows the interaction with collagens I, II, III, IV and V [45, 47, 147]. It dissociates from the cis/ER-Golgi intermediate compartment region (ERGIC) after binding with procollagen in the ER. It is bind with procollagen with the help of collagenous repeats (Gly-Xaa-Arg) present on triple-helical procollagen results in inhibition of premature aggregation of procollagen [1, 49, 145, 148]. The previous study demonstrated that knockdown of Hsp47 causes collagen related genetic diseases like osteogenesis imperfect. It is expressed in the case of atherosclerosis involve in the proper folding of procollagen [50, 51, 147].

1.1.3 Hsp60

Hsp60 is a 60 kDa molecular weight containing prototypic molecular chaperone abundantly present in bacterial and eukaryotic cells [16]. It is located in

Table 1 HSP family classification according to their molecular weight and physiological role

Class	Molecular weight (kDa)	Other name/ Organisms	Location	Structure/Characteristics	Biological Function(s)	Interaction with other Hsp	References
Large Heat Shock Proteins (40-100 kDa) [ATP dependent]							
Hsp40	40	**Type I:** DnaJ (*E. coli*), Ydj1 (Yeast), Hdj2 (Human) **Type II:** Sis1 (Yeast), Hdj1 (Human)	Cytoplasm, Endoplasmic Reticulum (ER)	A J-domain made up of 70 amino acids residues on N-terminal in types I and II and at any position in the case of type III	Protein folding, protein assembly, transport and degradation	Hsp70	[34–43]
Hsp47	47	Serpin H1	Cytoplasm, ER, Mitochondria	A serpin loop without serine protease inhibitory activity	Inhibits the aggregation of premature procollagen	–	[44–52]
Hsp60	60	GroEL (*E. coli*)	Nucleus, Cytoplasm, Mitochondria	A ring-shaped heptameric quaternary structure with two stacked heptameric rings	Mitochondrial protein folding and non-folding function such as cell signaling, anti-inflammatory activity	Hsp10	[36, 53–65]
Hsp70	70	Grp78, Hsc70, Ssa1–4, Kar2 (*S. cerevisiae*), DnaK (*E. coli*)	Ubiquitous [Nucleus Cytoplasm, Mitochondria, ER]	640 amino acid residues with N-terminal ATPase domain (44 kDa) and C-terminal domain:18 kDa peptide-binding domainand10kDa part contains the Glu-Glu-Val-Asp (EEVD) regulatory motif	Protein folding, protein assembly and refolding	Hsp40, Hsp100, Hsp60, Hsp90, small heat shock proteins	[2, 36, 66–77]
Hsp90	90	Hsp90A, Hsp90B, TRAP, HtpG (*E. coli*),	Nucleus, Cytoplasm, Mitochondria, ER	A homodimer structure consists of three flexibly linked regions such as an N-terminal ATP-binding domain, a	Protein folding and signal transduction	Tetratricopeptide repeat (TPR) co-chaperone:	[78–87]

(continued)

Table 1 (continued)

Class	Molecular weight (kDa)	Other name/ Organisms	Location	Structure/Characteristics	Biological Function(s)	Interaction with other Hsp	References
		Hsp82 (*S. cerevisiae*)		central domain, and a C-terminal dimerization domain		Hop, Fkbp51 & 2, CHIP, etc. Non-TPR co-chaperones: Aha1, p23, Cdc37, etc.	
Hsp100	100	Casein lytic proteinase (Clp) A ClpB (*E. coli*), ClpX (*Helicobacter pylori*), ClpC (Plant), Hsp78 (*S. cerevisiae*)	Nucleus, Cytoplasm	A large hexameric structures contain a N-terminal domain, two different conserved AAA1 and AAA2 AAA+ ATPase domains and a coiled-coil middle regulatory domain	Resolubilizing aggregated protein	Hsp40, Hsp70, Hsp90	[88–94]
Small Heat Shock Proteins (10–40 kDa) [ATP independent]							
Class I							
Hsp27	22.8	HspB1, Hsp26, Hsp25 (rodents)	Nucleus, Cytosol	A conserved α-crystallin domain near the C-terminus and N-terminus consists of WD/EPF domain	Protein folding, antioxidant activity, anti-apoptotic activity suppress kinases, actin polymerization	Hsp70	[95–101]
HspB5	~20	αB-crystallin	Nucleus, Cytosol	A monomeric structure containing three regions such as α-crystallin domain (ACD) (a conserved central domain), the flanking N-terminal	Protein refolding, protein remodeling of cytoskeletal, anti-apoptotic activity	Hsp70	[43, 102–104]

				region (NTR) and the C-terminal region (CTR)			
Hsp20	~17	α-crystallin, HspB6	Nucleus, Cytosol	A homodimer made up of combined groove at the interface via extending a beta sheet and the shared groove contains two symmetry-related C-terminal extensions with peptide in polyproline II conformation	Protein refolding and inhibit protein aggregation, protection from endotoxin-induced myocardial dysfunction, myocardial ischemia/reperfusion (I/R) injury, platelet aggregation inhibition	HspB8	[38, 105–109]
Hsp22	~20	α-crystallin C, HspB8	Nuclease, Cytosol, Mitochondria	A conservative α-crystallin domain at C-terminaland hydrophobic N-terminal domain	Mitochondrial related Unfolding Protein Response (mtUPR), anti-aging activity, anti-oxidant activity, cell proliferation, carcinogenesis	Hsp60, Hsp70	[100, 110–116]
Class II							
HspB2	~20.3	Myotonic Dystrophy Kinase Binding Protein (MKBP)	Nucleus, Cytoplasm, Mitochondria	A conservative α-crystallin domain at the C-terminal part of the molecule	Maintains muscle structure and function, prevent aggregation of $A\beta_{42}$ plaques	HspB8	[117–124]
HspB3	17	sHsp 27-like protein (HspL27)	Nucleus, Cytoplasm	A monomeric protein lacks a flexible extension of the C-terminal structure	MNs survival, protein refolding and inhibits toxic protein aggregation	HspB2	[119, 123, 125, 126]
HspB4	~20	αA-crystallin CRYAA	Nucleus, Cytoplasm	A90 amino acid long α-crystallin domain" (ACD) flanked by a variable hydrophilic C-terminal domain and hydrophobic N-terminal domain	Proper substrate protein folding, anti-apoptotic activity	HspB5	[127–130]

(continued)

Table 1 (continued)

Class	Molecular weight (kDa)	Other name/ Organisms	Location	Structure/Characteristics	Biological Function(s)	Interaction with other Hsp	References
HspB7	18.6	Cardiovascular HSP (cvHsp)	Nucleus, Cytoplasm	A conserved α-crystallin bordered by variable N- and C-terminal extensions	Tumor suppression in p53 pathway, cardiac morphogenesis, thin filament structural regulation, inhibits polyQ aggregation	HspB1	[131–136]
HspB9	17.5	Cancer/testis antigen 51 (CT51)	Nucleus, Cytoplasm	A conserved α-crystallin flanked by variable N- and C-terminal extensions.	Protein folding, maintains integrity of sperm flagella	–	[102, 137, 138, 140]
HB10	~28	Outer dense fiber protein 1 (ODF1)	Nucleus, Cytoplasm	A conserved α-crystallin flanked by variable N- and C-terminal extensions. C terminal tail like keratins with high content of cystein	Spermatogenesis, structural role in sperm tail	–	[101, 137, 138–140]

mitochondria [36, 64]. It forms a football like crystal structure with an oligomer composed of monomer arranged in two stacked heptameric rings [65, 149]. GroEL is one of the most studied family among all chaperons, *E. coli*. Hsp60 [150, 151]. Hsp60 has a barrel-like structure and can entrap 50 kDa of proteins (Table 1) [62, 152]. Its capacity increases when the co-chaperone GroEL comes into picture which works for closing the structure [62]. This group of proteins shares similarities with other families in terms of the ATP-mediated protein folding mechanism [153, 154]. It is also known as a mitochondrial chaperonin protein because it induces proper folding of nuclear-encoded protein which is imported into the mitochondria with the help of co-chaperonin Hsp10 [53, 56, 63]. Thus, it is important for maintaining mitochondria protein homeostasis [64, 155, 156]. Apart from mitochondria, it is also present in cytosol, nucleus, extracellular space, intracellular vesicles, etc. [54, 55, 57–59]. Hsp60 act as moon lightning protein as it performs multiple functions apart from protein folding, the non-folding functions such as cell-signaling molecule, in the immune system, act as a receptor for several ligands, etc. [60, 61].

1.1.4 Hsp70

This family of heat shock proteins has 70 kDa molecular weight and they are most studied chaperons among all which are involved in the protein folding, protein assembly, protein refolding and interacts with other proteins to achieve proper folding in case of stressed conditions [70, 71, 75]. It has ATP-mediated chaperone activity as it relies on ATP for conformational changes and subsequently proper protein folding [75]. There are 13 members of Hsp70 present in humans i.e. HspA1A, HspA1B, HspA1L, HspA2, HspA3, HspA4, HspA5, HspA5BP1, HspA6, HspA7, HspA8, HspA9B and HspA10 [2, 73, 157, 158]. These Hsp are universally conserved shows high structural similarity [159, 160]. It is made up of 640 amino acid residues with two main domains such as the N-terminal ATPase domain and the C-terminal domain which is divided in two parts such as peptide-binding domain and a Glu-Glu-Val-Asp (EEVD) regulatory motif [66, 68, 76]. The N-terminal ATPase domain binds to ATP and hydrolyzes it while the C-terminal domain binds with the client protein and refold the non-native polypeptides [68, 76]. They are ubiquitously present in the cell such as cytoplasm, nucleus, mitochondria, ER, etc. (Table 1) [67, 69, 73, 77]. Partner proteins such as Hsp40, Hsp100 and nucleotide exchange factors involved in the Hsp70 mechanism [158, 161]. These co-chaperones have J domain made up of long helical hairpin formed by ~70 residues along with a flexible loop and a conserved His-Pro-Asp motif and is required for the ATP hydrolysis by Hsp70 [76, 162]. Hsp70 also exhibits its protein folding and unfolding function by interacting with other chaperones such as Hsp40, Hsp60 chaperonins, Hsp90, small heat shock proteins and Hsp100 AAA+ [36, 72, 74, 77].

1.1.5 Hsp90

Hsp90 belongs to the family of molecular chaperones with 90 kD molecular weight of proteins [86]. Hsp90 family members are encoded by 17 known genes in humans [86, 156]. The Hsp90 family exhibits 4 different classes: Hsp90A (cytosolic), Hsp90B (ER) and TRAP (Tryptophan Regulated Attenuation Protein) (mitochondria) and isoforms are known to localize to the mitochondria, chloroplasts, cytosol, nucleoplasm and ER (Table 1) [163–165]. The structure of Hsp90 contains homodimer and three flexibly linked regions such as a N-terminal ATP-binding domain, a central domain, and a C-terminal dimerization domain [84, 166]. The different members of the family identified by its functions and its subcellular localization. Hsp90A and Hsp90B present in all eukaryotes whereas High-temperature protein G (HTPG), TRAP and Hsp90C occur only in Animalia, Bacteria and Plantae respectively [163]. Hsp90A is duplicated into Hsp90AA and Hsp90AB in vertebrates and Hsp90C duplicated into Hsp90C1 and Hsp90C2 in higher plants [167]. It is an ATP-dependent chaperone that changes its conformation with ATP triggering and binds to unfolded and folded proteins and induce proper protein folding [10, 168]. It has a conserved function in protein folding and signal transduction [79, 169].

1.1.6 Hsp100

Hsp100 protein has a molecular weight of 100 kDa also known as Casein lytic proteinase (Clp) and is located in the cytoplasm and present in bacteria, yeast, plants, humans and animals [91, 170]. The most studied Hsp100 family chaperons are bacterial ClpB and yeast Hsp104 (Table 1) [91, 171]. This family plays a crucial role in resolubilizing aggregated protein with the help of co-chaperones Hsp40, Hsp70 and Hsp90 [91, 172]. Hsp100 chaperones are members of AAA+ ATPases, a super large family of energy-driven conformational “machines” [173]. They form large hexameric structures in the presence of ATP and possess unfoldase activity [92, 174]. The structure of Hsp100 contains a highly mobile N-terminal domain that helps in substrate recruitment, two different conserved AAA1, and 2AAA+ ATPase domains and a coiled-coil middle regulatory domain which forms a belt around the AAA1 tier [94, 175]. In yeast, disaggregates the protein plaques were first studied with Hsp104 chaperons by Lindquist and coworkers [91, 176, 177]. Moreover, the bacterial ClpB is homologous of yeast Hsp104 which reactivates the aggregate proteins with the help of the DnaK/DnaJ/GrpE system [91, 178]. So, these unique properties of Hsp100 make it unique from conventional molecular chaperones that cannot reactivate the protein so efficiently like Hsp100 [91]. Moreover, Hsp110 is located in the cytosol and nucleus and help in the proper folding of proteins folding in stress condition with co-chaperone Hsp70 or Glucose-regulated protein 78 (GRP78) [10, 179].

1.2 Small Heat Shock Proteins (sHsp) [ATP Independent]

Small heat shock proteins (sHsp) are present ubiquitously and are ATP-independent molecular chaperones [124, 180]. They have a molecular weight between 12 and 30 kDa, with a core conserved α-crystallin domain (ACD) flanked by variable N- and C-terminal domains [124, 181, 182]. sHsp have a more confined mode of action than other Hsp such as they have a large binding capacity and can efficiently bind to the non-native proteins from peptides to large-size proteins to prevent their aggregation irreversibly [124]. sHsp perform multiple cellular functions including protein refolding and degradation [183].

Apart from protein folding, sHsp also act as anti-apoptotic, anti-inflammatory, neuroprotective agents [184, 185]. sHsp distributed in the different tissues and specific cell types results in cell survival under stress conditions [186, 187]. There are two classes of sHsp such as class I and class II. Class I sHsp includes Hsp27 (HspB1), αB-crystallin (HspB5), Hsp20 and Hsp22 (α-crystallin C) and class II sHsp includes HspB2, HspB3, αA-crystallin (HspB4), HspB7, HspB9 and HspB10 (Table 1) [186, 188, 189]. Class I sHsp express ubiquitously whereas the Class II sHsp are primarily expressed in myogenic and testicular lineages [190].

1.2.1 Class I sHsp

Class I sHsp includes Hsp27 (HspB1), HspB5 (αB-crystallin), Hsp20 (α-crystallin) and Hsp22 (α-crystallin C) (Table 1).

1.2.2 Hsp27 (HspB1)

Hsp27 has a molecular weight of 22.8 kDa and express ubiquitously but mainly expressed in cardiac, skeletal, smooth muscles (Table 1) [98, 191]. It is a redox-sensitive molecular chaperone and has a homologous highly conserved α-crystallin domain near the C-terminus and N-terminus consists WD/EPF domain ([99, 186, 192]. Activation of Hsp27 activated by phosphorylation in unphosphorylated oligomer which contains Ser-15, Ser-78 and Ser-82 sites for phosphorylation [193, 194]. It induces proper protein folding and inhibits the aggregation of toxic protein in the stress condition [195, 196]. The previous studies have shown that phosphorylation of Hsp27 causes conformation changes and suppress kinases and inhibits the growth of hepatocellular carcinoma [100]. Further, unphosphorylated Hsp27 (HspB1) regulates translation initiation via a direct association with eIF4E in osteoblast [98]. Hsp27 acts as an anti-oxidant agent in oxidative stress conditions by lowering the intracellular ROS level [197–199]. The previous study by Charette et al. [200] has shown that Hsp27 also acts as an anti-apoptotic agent and prevents Fas-FasL mediated apoptosis via binding to Death domain associated protein (DAXX) and prevent the binding of Apoptosis signal regulating kinase 1 (ASK1)

to DAXX ([199, 201]. It also inhibits the mitochondrial-dependent apoptosis by binding to the Bax and cytochrome c [202, 203]. Additionally, it is an actin capping protein and helps in the regulation of actin cytoskeletal by promoting actin polymerization [96, 204, 205].

1.2.3 HspB5 (αB-crystallin)

HspB5 is also known as αB-crystallin and has ~20 kDa molecular weight. It has a monomeric structure containing three regions such as α-crystallin domain (ACD) (a conserved central domain), the flanking N-terminal region (NTR) and the C-terminal region (CTR) (Table 1) [43, 206, 207]. It is mostly expressed in the eye lens but is also present in the brain, skeletal and cardiac muscles [206, 208]. It has chaperonin activity that promotes protein refolding and degradation and also participates in cytoskeletal remodeling in stress conditions as well as during development [43, 101]. It assists ATP dependent Hsp70 chaperone in protein folding and degradation via the ubiquitin-proteasome and autophagic lysosomal pathways [103]. In stress conditions such as oxidative stress, heat shock and ischemia, it regulates the apoptosis in the cells [97, 104]. HspB5 acts as an anti-apoptotic agent, binds to procaspase-3, p53 and Bax which inhibits their translocation to the mitochondria and results in a decrease in apoptosis [97]. Moreover, it also blocks the RAF/MEK/ERK signaling pathway, BAX, Bcl-2 mitochondrial translocation and inhibits caspase-3 maturation in the cells [209, 210].

1.2.4 Hsp20 (α-crystallin)

The Hsp20 also known as α-crystallin, has molecular mass ~ 20 kDa with conserved 100 residues C terminal domain (Table 1) [107, 109, 211]. It is also known as HspB6, a small heat shock protein family that includes 10 members such as HspB1-B10 with 15–30 kDa molecular mass and protects the cell in stress conditions [33, 212]. Hsp20 has a homodimer structure formed by a combined groove at the interface via extending a beta-sheet and the shared groove contains two symmetry-related C-terminal extensions with peptide in polyproline II conformation [107, 213]. It is evolutionarily related to alpha-crystallin, an abundant constituent of eye lenses of vertebrate species and plays a key role in the correction of the refractive index of the lens [3, 129]. Hsp20 is abundantly present in the cytoplasm, mammalian heart, skeletal and various muscle cells [35, 38, 185, 207]. It has a role in protection of heart from endotoxin-induced myocardial dysfunction, myocardial ischemia/reperfusion (I/R) injury via inhibition of Akt, Bax, α-actin, NF-kβ, ASK1, etc. [212, 214, 215]. It also plays a key role in platelet aggregation inhibition and acts as a negative regulator of type 1 protein phosphatase (PP1) (a negative regulator of cardiac function) activity in the heart [38, 106].

1.2.5 Hsp22 (α-crystallin C)

Hsp22 has a molecular weight of ~20 kDa which is involved in the aging process [46, 216]. It contains a conservative alpha-crystallin domain at C-terminal and present in the cytoplasm, nucleus and mitochondria (Table 1) [32, 112, 217–219]. It is also present in the heart, skeletal and smooth muscle and brain along with prostate, lung, and kidney in some extent [110, 220–223]. Apart from aging, it plays a role in cardiac hypertrophy, cell proliferation, apoptosis, and carcinogenesis [146, 224, 225]. In aging, particularly the expression of Hsp22 was increased [216, 226]. In *Drosophila*, it is expressed during the metamorphosis of larvae to pupa development [216, 227]. It is also involved in increasing the lifespan of fly probably via histone deacetylation by Hsp22 [82, 111]. Together, the upregulation of Hsp22 shows a helpful effect in aging and also used as a biomarker for aging which indicates stress and improper homeostasis [216, 228]. The previous study by Tower et al. [229] has shown that Hsp22 decreases the adverse effect of aging via reducing mitochondrial metabolism. In *Drosophila*, it has been reported that Hsp22 alter some gene expressions, protein translation and shows a beneficial effect in maintaining mitochondrial structure and integrity during aging and oxidative stress condition [216, 230, 231]. Hsp22 is also involved in the mitochondrial related unfolding protein response (mtUPR) (a response against protein misfolding in mitochondria) with the help of Hsp60 and mitochondrial Hsp70 [231, 232]. During protein misfolding in mitochondria, Hsp22 decreases the ROS production, increases the lifespan, and enhance mtUPR signaling along with mitochondrial and nuclear signaling [114, 223, 233].

1.2.6 Class II sHsp

Class II sHsp includes HspB2, HspB3, HspB4 (αA-crystallin), HspB7, HspB9 & HspB10 (Table 1).

1.2.7 HspB2

HspB2 is a new member of the sHsp family with ~20.3 molecular weight and also known as Myotonic Dystrophy Kinase Binding Protein (MKBP), expressed mostly in the heart and skeletal muscles [118, 121]. It is present in the nucleus, cytoplasm and mitochondria [118, 122] and contains a conservative alpha-crystallin domain at the C-terminal part of the molecule (Table 1) [123, 124]. It is associated with Myotonic Dystrophy Protein Kinase (DMPK), a serine/threonine-protein kinase and maintains muscle structure and function [120, 234]. The previous study by Prabhu et al. [120] has shown that HspB2 exhibits molecular chaperone activity by inhibiting the aggregation of $A\beta_{42}$.

1.2.8 HspB3

HspB3 (Heat Shock Protein Family B (small) Member 3) is sHsp27 like the smallest sHsp protein with 17 kDa monomeric mass and shows high sequence homology with HspB1 [126, 207]. It lacks a flexible extension of the C-terminal structure (Table 1) [123, 125]. It is localized in the spinal cord, brain cortex and nerves of chicken, mouse and human [119, 235]. HspB3 is linked to neurological and muscular diseases in humans and helps in MNs survival [235, 236]. It shows chaperone-like activity with the help of yeast alcohol dehydrogenase [237]. The mutation of HspB3 associated with distal hereditary motor neuropathy 2C (dHMN2C) [43, 217, 238]. It is associated with HspB2 in the heart. The previous study by [123] has shown that the crystal structure of a tetrameric heterocomplex of HspB2/HspB3 found in muscle cells.

1.2.9 HspB4 (αA-crystallin)

HspB4 has ~20 kDa molecular weight and mainly expressed in eye ocular lens along with spleen and thymus in some amount [130, 239]. It produces from the duplication process of an ancestral α-crystallin gene and exhibits 57% amino acid sequence homology with HspB5 αB crystallin [207, 240]. It has 90 amino acid long α-crystallin domain (ACD) flanked by a variable hydrophilic C-terminal domain and hydrophobic N-terminal domain [129]. It acts as a molecular chaperone, possess anti-apoptotic activity and helps in proper substrate protein folding (Table 1) [128, 130].

1.2.10 HspB7

HspB7 is a member of the sHspB family which heterodimerize with other similar Hsp (Table 1) [97, 134]. It is made up of 170 amino acids with 18.6 kDa molecular mass and mostly expresses in the heart [131, 135] and also known as cardiovascular heat shock protein (cvHsp). It facilitates sarcomeric proteostasis with the help of Filamin C and Titin [134, 136]. It is mainly present in the nucleus, cajal body, cytoplasm, developing and adult heart [131, 132, 136]. Mutation of this gene results in heart failure, renal carcinoma, induction of autophagic pathways etc. [241–243]. The function of this gene includes tumor suppression in the p53 pathway, cardiac morphogenesis along with left-right asymmetry and thin filament structural regulation [133, 135]. The previous study by Wu et al. [244] has shown that HspB7 decreases the polyQ aggregation by its unique N-terminal domain by binding with the HspB1 alpha-crystallin domain.

1.2.11 HspB9 & HspB10

HspB9 & HspB10 are the members of sHsp family B also known as Cancer/testis antigen 51 (CT51) [140, 245]. HspB9 has 17.5 kDa molecular mass and a continuous open reading frame encoding a protein of 159 residues [102, 139]. HspB10 is also known as outer dense fiber protein 1 (ODF1) [138, 139] and has 27 kDa molecular mass with C terminal tail like keratins with high content of cysteine (Table 1) [139, 194]. These two Hsp are the testis-specific expressed sHsp [101, 139]. HspB10 mostly found in sperm tail and also localized in the nucleus, cytoplasm and tumor cells [243, 246]. Both Hsp response to environmental heat stress conditions [139]. HspB10 plays a key structural role in the sperm tail (Table 1) [243, 247]. The previous study has shown that HspB10 interacts with the T-complex-associated-testis-expressed 1-like 1 (TCTEL1) gene in spermatogenesis [139]. HspB9 and B10 expression gradually increases with the age and remain constant after sexual maturity [139]. HspB9 expressed in spermatogonia, spermatocytes, round spermatids and interact with the TCTEL1 gene in spermatogenesis. HspB10 expressed in elongated spermatids [102, 139].

1.3 Neuroinflammation in Alzheimer's Disease

Inflammation is a biological response of body tissue that can be triggered by various factors such as injury, injured cells, pathogen attack, exposure to toxic compounds, etc. [248–250]. Neuroinflammation is the inflammation of central nervous system (CNS) and is characterized by activation of glial cells, release of cytokines chemokines and infiltration of blood cells to the brain parenchyma [251–255]. The neuroinflammation response is induced by microglia, astrocytes, neutrophils, mast cells, macrophages, lymphocytes, etc. (Fig. 2) [256–258]. During neuroinflammation condition, activated microglia, astrocytes, macrophage and lymphocytes releases the inflammatory mediators such as pro-inflammatory cytokines interleukin-1β (IL-1β), IL-6, and Tumor necrosis factor-α (TNF-α), ROS, macrophage chemo-attractant protein-1 (MCP-1), neurotransmitters, pro-inflammatory enzymes such as cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), etc. (Fig. 2) [252, 255].

Further in the CNS, microglia and astrocytes are the two main types of cells involved in the inflammatory response [252, 250]. Microglial cells are a type of macrophage and predominantly found in CNS. Approximately 10% of these cells play a vital role in regeneration, neuronal plasticity, neurogenesis and mounting the immune response in case of injury to the brain [252, 253]. The astrocytes are the abundant glial cells that are crucial for homeostasis of the brain, and help for synaptic plasticity/synapse formation, regulate neurotransmitters and ion balance extracellularly [260, 261].

Neuroinflammation plays an important role in neurodegenerative diseases (NDDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), Multiple

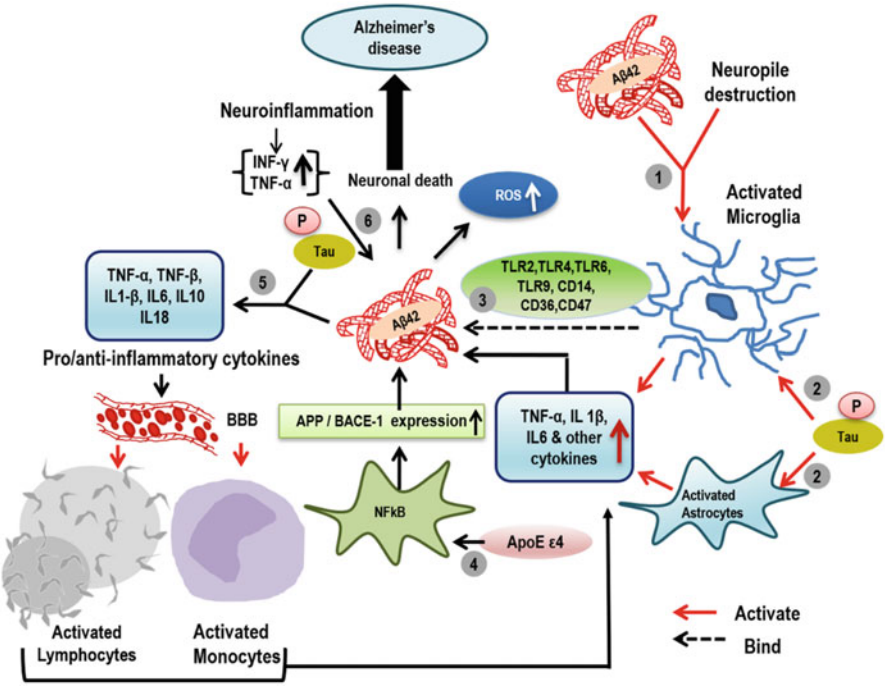

Fig. 2 Neuroinflammation in Alzheimer's disease. Schematic diagram showing various neuroinflammatory mechanisms involved in AD, such as cytokines, TLR receptors and other proteins on amyloid beta (Aβ) production leading to Alzheimer's disease (AD). (1) Neuropil destruction and Aβ aggregates activate the microglial cells which further releases cytokines (IL-1β, IL-6, TNF-α) that promotes an increase in Aβ plaques aggregation. (2) Hyperphosphorylated Tau also activates microglial cells, astrocyte cells and release various cytokines that increase the Aβ plaque formation. (3) Activated microglial also interacts with Aβ peptides using receptors such as- TLR-2, TLR-4, TLR-6, TLR-9, CD-14, CD-36 and CD-47, thus increasing ROS levels. (4) NFκB a transcription factor when activated in the presence of ApoE-ε4, upregulates APP and BACE-1 protein production. This further increases Aβ production in AD. (5) Hyperphosphorylated Tau and Aβ plaques stimulate the release of pro/anti-inflammatory factors such as- TNF-α, TNF-β, IL-1β, IL-6, IL-10, and IL-18. These inflammatory factors cross the blood brain barrier and activate the lymphocytes and monocytes leading to the upregulation of Cytokines (IL-1β, Il-6, TNF-α) and promote Aβ depositions. (6) In the case of neuroinflammation, TNF-α, IFN- γ levels are increased and this leads to Aβ production and eventually AD and neuronal death

sclerosis (MS) and Huntington's disease (HD) [252, 259]. These NDDs are correlated to high levels of pro-inflammatory cytokines [252, 259, 262]. AD is a neurodegenerative disease and the most common cause of mental deterioration in elderly people. It is classified as a type of dementia that was first discovered by Alois Alzheimer in 1907 [263, 264]. Two main neuropathological hallmarks of AD are extracellular peptide aggregates of senile plaques; mainly composed of amyloid-β (Aβ) peptides and formation of intracellular neurofibrillary tangles (NFT) associated with tau protein (microtubule-binding protein) [85, 252, 265–267]. In non-disease condition, amyloid precursor protein (APP) is a transmembrane protein cleaved by

non-amyloidogenic pathway in which it is cleaved by α- and γ- secretases and generates large, soluble, secreted fragments (sAPPα and sAPPγ) along with membrane-associated C-terminal fragments (CTFs) [268, 269]. APP has two isoforms amyloid precursor-like protein 1 (APLP1) and amyloid precursor protein 2 (APLP2) in humans and in flies (*Drosophila melanogaster*) it is present as Appl [266]. In AD, APP is cleaved by the amyloidogenic pathway via β and γ-secretase at the extracellular domain produces two insoluble $A\beta_{42}$ fragments [268, 269]. Amyloid plaques are predominantly found in the basal forebrain and spread to the cortex; which are associated with sensory or motor areas of the brain [270, 271]. Thus, this concludes that $A\beta_{42}$ plaques and NFTs along with microglial activation plays an important role in neuroinflammation in neurodegeneration [252, 272].

Disclosing evidence recommends that inflammatory response contributes to the progression of AD, accelerating the course of the disease [273]. During inflammation process, glial cells like astrocytes and microglia release cytokines such as IL-1β and IL-12 and these are related to the progression of AD pathology (Fig. 2) [262, 274, 275] Aβ plaques and neurofibrillary tangles present in the brain are known to activate inflammatory cells such as astrocytes, microglia and tissue levels of pro and anti-inflammatory mediators like cytokines and chemokines [276]. These inflammatory molecules and mediators are associated with $A\beta_{42}$ plaque aggregation in the brain [273, 276]. This release of mediators activate monocytes and lymphocytes through the blood-brain barrier (BBB, the barrier between blood and brain which are composed of endothelial cells, astrocytic end-feet and pericytes) along with activation of microglia, improve their proliferation and releases more inflammatory factors (Fig. 2) [252, 273, 277]. Activated microglial cells and reactive oxygen species (ROS) contribute to the loss of neurons, apolipoprotein E (ApoE) and nuclear factor-kβ (NF-kβ) as they all are involved in the inflammatory process related to AD (Fig. 2) [278].

Microglia and astrocytes contribute to a pivotal role in the inflammatory response in the AD brain [279]. Microglia interacts with Aβ peptide to produce ROS and other inflammatory mediators such as cytokines and chemokines; these are known to cause damage to the neuronal cells [278, 279]. NFk-B is a well-studied transcription factor and located in the cytoplasm, is responsible for the regulation of cytokine-producing genes [280]. The production of different inflammatory mediators is enhanced when activated NF-kB enters the nucleus. Several molecules can activate NFk-B such as TNFα, Aβ, and secreted *APP* [278, 281]. *APP* and *BACE-1* levels are increased when NF-kB is activated which increases the production of Aβ [224, 278]. Recent studies have demonstrated that in the presence of apolipoprotein E4 (APOE e4) NF-kB levels were increased; also, Aβ peptides increases APOE production via NFk-B dependent pathway [224, 278]. Cytokine production is associated with TNF and by T-lymphocytes and activated microglia [282, 283]. Transforming Growth Factor-β (TGF-β) is an inflammation regulator [274] and is known to have pro-apoptotic and anti-apoptotic effects [283, 284]. In the AD brain, TNF-α has also been shown to have a neuroprotective role. Further, cytokines have a vital role in AD [283, 284]. An interaction of chemokines and cytokines with Aβ was shown recently in an in-vitro study. It showed that Aβ

production and APP processing can be regulated by TNF-α [283, 284]. In the cerebrospinal fluid (CSF) of AD patient's brains; increased TGF-β was correlated with amyloid plaques aggregates. So, in a way cytokine plays a dual role in AD. Another known inflammatory regulator in the case of neuroinflammation is the IL12 and IL-23. Pathway of IL-12/IL-23 attenuates the pathologies of AD [274, 285]. It has been shown that in AD patients IL-12p40 subunit and its receptor activity was decreased due to cognitive deficits, this study also found that in CSF of AD patients IL-12p40 concentration was increased. In a deletion study of AD-related deficits, behavioral deficits in APP/PS1 mice and altered synaptic integrity was shown to be triggered by anti-inflammatory cytokine IL-10 [274, 286]. Chakrabarty et al. [287] have shown that in APP transgenic mouse model, there was an increased amyloid aggregation, synaptic alterations, behavioral deficits and impaired microglial phagocytosis of Aβ when IL-10 levels were up-regulated by using adeno-associated viruses (AAVs) [274, 287].

An important source of cytokines is microglia and astrocytes in AD. Thus, cytokines are the most important aspects of neuroinflammation [253]. The anti-inflammatory and pro-inflammatory processes are started as a result of the response of microglia to the aggregation of $A\beta_{42}$ plaques, chemoattraction and neuronal injury [253, 288]. Immunohistochemistry studies proved that AD trigger neuroinflammatory components in the presence of activated microglia that further express major histocompatibility complex (MHC) and releases the pro-inflammatory mediators such as inflammatory cytokines which are associated with amyloid plaques in AD patient's brain [289, 290]. Microglial cells have an important functions in the brain that tend to protect and support the neurons and neuronal survival [251, 273, 289].

The neuropil destruction process in AD patient's triggers microglial activity as per clinical studies [291, 292]. In an in-vitro study, Aβ peptide generated an inflammatory type response concerning fibrillar Aβ, and they can bind to complement factor-C and activate the complementary pathway in an antibody independent fashion [276]. Genetics and epidemiological studies showed positive signs that inflammatory mechanisms are involved in the AD [293, 294]. Also, these studies point out the linkage of polymorphisms of plaques with pro-inflammatory cytokines i.e., acute-phase proteins [α1-antichymotrypsin], IL-1, IL-6, and TNF-α are risk factors in AD [276, 295, 296]. AD pathogenesis was closely tied to IL-1 in the case of neuroinflammation [297]. Increased expression of IL-1 by microglia was seen in amyloidal plaques' surroundings. Thus IL-1 was associated with AD pathogenesis [277, 297].

In AD patients before neuropil destruction, microglial activation was found to take place in neuropathological and neuroradiological studies [276, 292]. Microglia and astrocytes were related to Aβ aggregation as per mammalian associated studies. Moreover, β-secretase activity was found to be increased due to cytokines in inflammatory conditions, this result was found in correlation with increased Aβ aggregation too [252, 298]. The inflammatory reactions in AD take place with the help of receptors, such as class A scavenger receptor A1, a6β1 integrin, toll-like receptors i.*e* toll-like receptors 2 (TLR2), TLR4, TLR6 and TLR9 and CD14, CD47,

CD36 [210, 299, 300]. Using this mechanism, microglial cells bind to Aβ fibrils and soluble amyloid β (Aβ) oligomers [253, 301].

Inefficient removal of Aβ is identified with AD sporadic cases. Downregulation of Aβ phagocytosis receptors leads to increased levels of cytokine which causes the relative loss of microglial phagocytic capacity [258, 302]. Early response in AD is represented by astroglial atrophy that has further effects on synaptic connections. In synaptic transmission astrocytes predominantly contribute to cognitive defects as per animal model studies [303–305]. Also, cytokines, cytotoxic molecules, nitric oxide and interleukins are released by microglia and astrocytes cells when exposed to Aβ aggregates, thus, increasing the neuroinflammation in the brain [258]. Astrocytes can increase the microglial activity by lipidation and require ApoE60 for the removal of Aβ [258, 306]. Thus, astrocytes play an important role in the degradation of Aβ. While adult astrocytes increase the production of Aβ-degrading proteases like insulin-degrading enzyme, neprilysin, angiotensin-converting enzyme-1 (ACE-1) and endothelin-converting enzyme-2 [258].

In a wider aspect multiple factors such as anti and pro-inflammation, neuronal injury, microglia cells aggregation are associated to cytokine production in presence of Aβ peptides, for example, one such study pointed out the increase in production of pro-inflammatory cytokines (i.e., pro-IL-1α, IL-6, TNF-α), macrophage inflammatory peptide (MIP-1α) and macrophage colony-stimulating factor (M-CSF) due to the exposure of microglia to pre-aggregated $A\beta_{42}$ [258, 307].

1.4 Hsp and Its Biological Role in Neuroinflammation

As mentioned above, Hsp are evolutionarily conserved proteins that expressed in various stress conditions and helps in protein homeostasis by promoting proper protein folding, protein assembly and degradation [134, 308]. Apart from chaperone activity, they play a vital role in neuroinflammation [184, 186, 309, 310]. Heat shock responses (HSR) are triggered due to various cellular stress such as thermal shock, heavy metals, oxidative stress (ROS), etc. [184, 311, 312]. The neuroprotective role of Hsp in the nervous system was first described by [313]. They have shown that in thermal stress conditions, extracellular Hsp migrates from glial cells to neurons in the squid model [190]. Additionally, [314] have also demonstrated Hsp translocation as human glioblastoma cells secrets HspA1 in heat stress condition that is taken up by the human neuroblastoma cells [315]. HspA1 exerts its anti-apoptotic activity in neuroblastoma cells and decreases cell death in neurons [314, 315].

Several studies have demonstrated that apart from chaperone activity, Hsp plays an important role in the prevention of neuroinflammation in various neurodegenerative disease conditions [116, 184]. Hsp are involved in the regulation of neuroinflammation by modulating the expression of pro-inflammatory genes but the detailed study on the role of Hsp in neuroinflammation is still elusive. Hsp has a key role in antigen cross-presentation with its chaperone activity via processing in proteasome and transfer antigenic peptides to MHC class I or class II, followed by

the activation of CD8+ CTL (cytotoxic T lymphocytes) to kill the antigen/virus-infected cells [310, 316, 317]

Furthermore, NF-κB is frequently constitutively activated in neuroinflammatory conditions and activation of NF-kB receptor leads to the production of pro-inflammatory cytokines such as TNF-α, IFN-γ, IL-6 by macrophages which results in neuronal death [242, 318]. The previous study by [319] has shown that Hsp plays a key role in the inhibition of neuroinflammation via inhibiting NF-kB receptor activation [320]. Overexpression of Hsp70 inhibits the NF-kB receptor activation as well as the production of pro-inflammatory molecules such as TNF-α, IFN-γ, IL-6 and prevents neuroinflammation. Hsp70 inhibits NF-kB receptor activation by binding with IKKα and IKKβ, which are required for the NF-κB activation (Fig. 3) [321]. Hsp70 inhibits the IκB kinase (IKK) activation via stabilizing the IκB-α and inhibits the NF-κB activation [322, 323]. Hsp70 inhibits the activity of IκB kinase as well as NF-kB activation and results in decreases TNF-α production and neuroinflammation (Fig. 3) [184, 324–326]. Furthermore, Hsp70 also decreases the NO production stimulated by LPS-activated macrophages [323, 327]. Hsp70 helps in the modulation of neuroinflammation via inhibiting the JNK and NF-κB signaling pathways (Fig. 3) [328, 329]. It suppresses the phosphorylation and activation of JNK as well as IκBα. The inhibition of JNK and IκBα activation by Hsp70 leads to suppress their binding to DNA and also inhibits the production of their transcription factors such as NF-kB, signal transducers and activator of transcription-1 (STAT-1) and activator protein-1 (AP-1) (Fig. 3). The decrease in the expression of pro-inflammatory genes NF-kB, STAT-1 and AP-1 results in decrease neuroinflammation [330–333]. The inflammasomes also plays a key role in neuroinflammation and composed of a receptor and an adaptor through which they activate pro-inflammatory cytokines such as IL-1β or IL-18 [334, 335]. NOD-leucine rich repeat and pyrin containing protein 3 (NLRP3) are most studied inflammasome that activates caspase-1 and produce IL-1β and IL-18 [335–337]. The previous study by Martine et al. [338] have shown that knockdown of Hsp70 increases NLRP3 inflammasome along with the production of pro-inflammatory cytokines such as IL-1β and activates caspase-1 which results in neuroinflammation in mice.

Hsc70 also plays a key role in the prevention of neuroinflammation via inhibiting the activation of NF-kB, and decreases the release of pro-inflammatory molecules, reduces phosphorylation of downstream signaling molecules such as c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinases 1/2 ERK, phosphatidylinositol-3-kinase (PI3K/Akt) (Fig. 3) [116, 323, 339]. JNK, ERK and PI3K play a vital role in the neuroinflammation as JNK and ERK level is increased by the activated astrocytes and microglia [340, 341]. They are involved in the central sensitization especially in chronic pain, induced via glial cell stimulated neuroinflammation so the inactivation of JNK by Hsc70 results in the reduction of neuroinflammation related pathologies (Fig. 3) [323, 341]. Hsc70 also shows the anti-inflammatory effect via decreasing the production of iNOS and COX-2 gene expression and ultimately suppress the neuroinflammation [323].

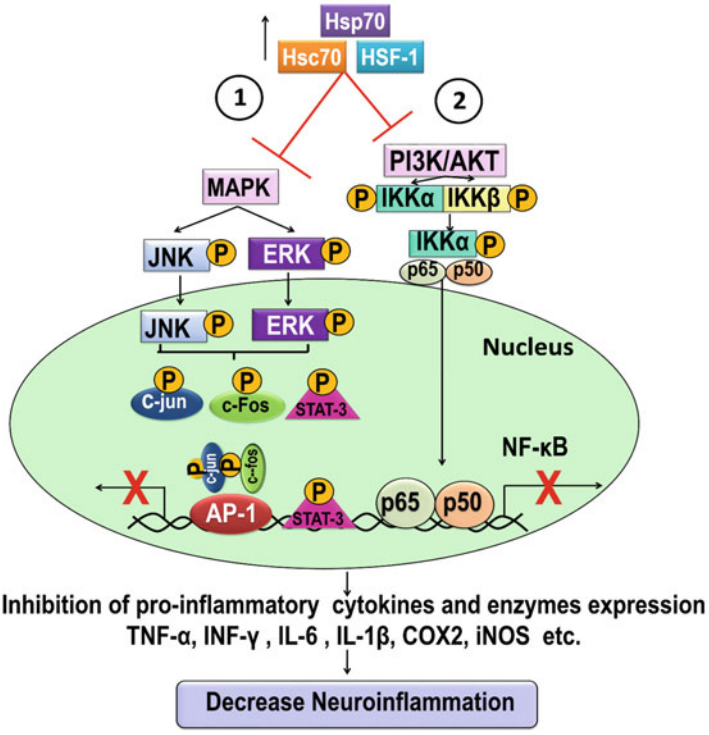

Fig. 3 Hsp role in neuroinflammation. The above schematic diagram shows that Hsp (Hsp70, Hsc70) and HSF-1 inhibit the neuroinflammation via two mechanisms. (1) JNK and ERK pathways are activated in neuroinflammation via MAPK which causes the phosphorylation of JNK and ERK. Activated JNK and ERK translocate into the nucleus and activates the various transcription factors such as c-jun, c-fos and STAT3 via phosphorylation. After phosphorylation, activated transcription factors bind to the pro-inflammatory gene promoter region of DNA and induces the expression of different pro-inflammatory cytokines and enzymes such as TNF-α, INF-γ, IL-6, IL-1β, COX2, iNOS etc. Moreover, (2) PI3K/AKT phosphorylates and activates IKKα and IKKβ. Activated IKKα cleaved by the proteasome and formed p56 and p50 subunits. These subunits are bind to DNA at NF-kB promoter region and increase the expression of NF-kβ which leads to the production of pro-inflammatory cytokines and enzymes such as TNF-α, INF-γ, IL-6, IL-1β, COX2, iNOS etc. and increases the neuroinflammation. Hsp plays a protective role in neuroinflammation via inactivating the JNK, ERK and PI3K/AKT signaling pathways and inhibits the production of TNF-α, INF-γ, IL-6, IL-1β, COX2, iNOS, NF-kB, etc.

The previous study by [342] have demonstrated the anti-inflammatory role of HspA1 in ischemic conditions. They have shown that overexpression of HspA1 leads to a decrease in the activity of NF-κB in the brain via inhibiting the IκB phosphorylation [343]. Overexpression of HspA1 also prevents apoptosis in the case of stroke patients [328]. Intravenous administration of HspB1 significantly decreases the neuroinflammation in the case of ischemic injury and autoimmune demyelination in CNS [344, 345].

It has been demonstrated that the Hsp60 level is significantly increased during stress conditions in the cytosol [346, 347]. Several studies demonstrated that intracellular as well as extracellular Hsp60 is associated with the TLR4 receptor mediates apoptosis in microglia and plays a central role in the generation of neuroimmune responses in the case of NDDs [255, 348]. Thus, Hsp60 can be used as a warning signal in case of neuronal damage caused due to the neuroinflammation, as seen in one such study where the TLR4-MyD88 (myeloid differentiation factor 88) signaling pathway was associated with neuronal damage in microglial cells [255, 325].

Additionally, HSF1 is also involved in the directly regulating the neuroinflammation via inhibiting the production of TNF-α and IL-1β in the response of lipopolysaccharide (LPS)-induced shock in a mouse model [349–351]. The previous study by [116] has shown that overexpression of Hsp70 inhibits the activation of astrocytes, stimulated by α-synuclein in PD. Subsequently, it also decreases the release of pro-inflammatory molecules such as TNF-α and IL-1β by astrocytes. Overexpression of Hsp70 also decreases the pro-inflammatory enzymes such as COX-2 and iNOS level and ultimately suppresses the neuroinflammation [116, 323]. A study by Schettet et al. [352] has demonstrated that the downregulation of HSF1 increases the apoptotic cell death and TNF-α mediated inflammatory signaling pathway.

1.5 Hsp Role in the Modulation of Neuroinflammation in AD

As discussed above, neuroinflammation is one of the prominent features of the different brain-related diseases such as traumatic brain injury, ischemic stroke as well as NDDs i.e. AD, PD, HD [184, 353]. It is characterized by activation of glia and astrocytes cells with the increased level of pro-inflammatory molecules such as cytokines and chemokines, etc. [354, 355]. As mentioned above, the accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles initiate the neuroinflammation and lead to neuronal death [356, 357]. Different Hsp are known as a key modulator of neuroinflammation via preventing the neuroinflammatory response and release of pro-inflammatory molecules such as IL1, IL1β, TNFα, and IL6 [184, 358]. Through this Hsp help in the prevention of neuroinflammation and decreasing the progression of disease condition [359, 360]. The detailed mechanisms, how Hsp modulates the neuroinflammation in AD are still not well understood.

As mentioned above, neuroinflammation in AD is mainly caused by astrocytes and microglial cells [361, 362]. Extracellular HspA1 or HspC1 stimulates microglial cells and enhances their phagocytic activity against Aβ peptides [184, 363]. Nuclear factor-kappaB (NF-kB) level increases in neuroinflammation in the brains of AD patients and plays an important role in inflammation, apoptosis and oxidative stress [364, 365]. The higher level of NF-κB increases the level of BACE1 and the APP gene which results in the accumulation of $A\beta_{42}$ plaques [364, 366]. The previous study by [342] has shown that HspA1 reduced NF-κB activity and exert anti-

inflammatory effect which might play an important role in AD. NF-κB also increases the level of neurodegenerative disease-related pro-inflammatory enzymes iNOS and COX-2 in AD [275, 365]. Hsp70 tends to inhibit the production of iNOS and COX-2 by macrophages and astrocytes in neuroinflammation which might be helpful in decrease the AD-related pathologies [163, 367].

1.6 Therapeutic Strategies Targeting Hsp Anti-inflammatory Role in AD

As mentioned above, Hsp plays an important role in modulation of AD and serve as potential therapeutic targets to treat/improve neuroinflammation in AD [184, 368]. Activation of microglial and astrocyte cells in the brain is one of the prominent pathologies of neuroinflammation in AD [355]. Therefore, targeting the cells along with inhibition of pro-inflammatory cytokines could be a relevant therapy of AD [184, 369]. The immunosuppressive action of Hsp consists of inactivation of antigen-presenting MHC cells, expansion of regulatory T cells and inactivation of NF-kB activity in the diseased condition [370, 371]. In this paper, we have demonstrated the possible therapeutic strategies targeting the modulation of different Hsp levels to decrease the neuroinflammation in AD. Nowadays, increasing the level of endogenous Hsp and delivering extracellular Hsp into the cell is a promising therapeutic strategy to reduce the neuroinflammation related toxicity in AD [372, 373]. Membrane Lipid Therapy is useful to induce the heat shock response and allows the entry of extracellular Hsp into the cell via modulating the membrane fluidity [184, 374].

1.7 Membrane Lipid Therapy

Membrane lipid therapy is one of the promising therapies that target lipid membrane fluidity as well as its structure and influence the lipid organization via principles of structure-function (Structure and function reciprocally dependent on each other like structure of the cell formed according to its function and function of cell is dependent on the structure) results in change in the localization and function transportation of proteins across the lipid bilayer [375, 376]. It is a novel therapeutic approach for drug development that helps in the maintenance of lipid structure and its composition in the membrane [375, 376]. Membrane lipid therapy would also be applicable for Hsp response in neuroinflammation in AD. It might influence the transport of Hsp across the lipid membrane and help in decreasing the neuroinflammation in AD [312, 377]. Through membrane lipid therapy, alteration in the physical properties and microdomain organization of lipid membrane is possible which has a vital role in the activation of heat shock proteins [225, 311]. Hyperfluidization of lipid

membrane helps in the activation of different Hsp which performs various role in the prevention of neuroinflammation in AD by maintaining the normal proteostasis, decreasing pro-inflammatory molecules, activated microglia and astrocytes apoptosis [342, 378, 379]. The previous study by [374] has shown that membrane lipid therapy is also exerting its beneficial effect in normalizing Hsp expression in diseased conditions. The drugs which interact with lipid raft in plasma membranes such as hydroximic acid derivatives, including BGP-15 and BM, play a role as Hsp co-inducers and help in the prolonged activation of HSF1 [374, 380, 381]. These drugs known for their neuroprotective property via increase transcription of Hsp gene and subsequently decreases in neuroinflammation [184, 382, 383]. The previous study by [184] has demonstrated that HSF1 inactivation leads to the uncontrolled inflammatory process and leads to neuroinflammation. Together, BGP-15 and BM might help in the decrease neuroinflammation by increasing HSF1 expression. Further, several studies suggested that different Hsp inducers and co-inducers help in decreasing the neuroinflammation in AD. Few Hsp inducers and co-inducers are described below:

1.8 Hsp Inducers and Co-inducers

1.8.1 Celastrol

Celastrol (tripterine) is a pentacyclic triterpenoid compound that belongs to the family of quinone methides isolated from the root extracts of *Tripterygium wilfordii* (Thunder god vine) and *Celastrusregelii* [384, 385]. Previous studies have shown that celastrol has antioxidant and anti-inflammatory effects. These effects are helpful in the prevention of AD [384, 386]. The anti-inflammatory effect of celastrol is due to suppression of the production of the pro-inflammatory cytokines' TNF-α and IL-1β produced by human monocytes and macrophages which might help in the prevention of AD [384, 387]. Celastrol also acts as a Hsp co inducer as it increases the Hsp32/HO-1 and Hsp70 expression level in AD via activating the HSF1 and HSR (Fig. 4) [388, 389]. Higher expression of Hsp32/HO-1 and Hsp70 shows the anti-inflammatory effect and prevents AD [184, 390–392]. Upregulation of Hsp32/HO-1 and Hsp70 decrease the neuroinflammation by reducing the LPS induced activation of NF-kB signaling cascade and production of TNF-α and INF-γ-induced iNOS expression in rat brain (Fig. 4) [163, 393]. The previous study by [394] has shown that celastrol has the neuroprotective potential through increasing the Hsp level especially Hsp70B in human neurons and showed beneficial effects of celastrol in NDDs including AD. Moreover, celastrol induced expression of Hsp70, Hsp27 and Hsp32 in cerebral cortical cultures of rat and induce Hsp70 expression in the neuronal cell body (Fig. 4) [395, 396]. It shows neuroprotective effect in the case of AD by inhibiting Aβ protein aggregation by in vivo administration of celestrol in a transgenic mouse model of AD [395–398]. The previous

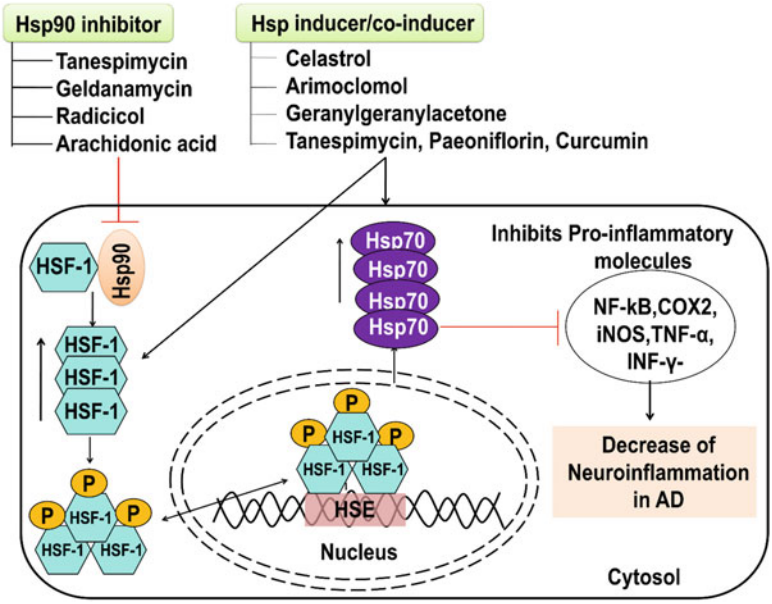

Fig. 4 Therapeutic effects of Hsp inducers/co-inducers and Hsp90 inhibitor in neuroinflammation. Hsp90 inhibitors such as tanespimycin, geldanamycin, Radicicol and Arachidonic acid dissociates Hsp90 from the HSF-1 monomer. Free monomers of HSF-1 phosphorylates and forms trimer which can bind to the HSE region on DNA and induces Hsp70 expression. Secondly, the Hsp inducers/co-inducers such as celastrol, arimoclomol, geranylgeranyl acetone, tanespimycin, paeoniflorin and curcumin increases the expression of HSF-1 and Hsp70. In both cases, an increased Hsp70 level reduces the production of pro-inflammatory molecules such as NF-kB, COX2, iNOS, TNF-α, INF-γ, etc. and ultimately decreases the neuroinflammation in AD

study by [399] has demonstrated that celastrol also act as a Hsp90 inhibitor and shows protective effect in AD by suppressing the accumulation of Aβ-induced cell death and also induces Hsp70 expression along with increases the Blood-Brain Barrier (BBB) penetration [400, 401]

1.8.2 Arimoclomol

Arimoclomol (BRX-220) is a small new chemical compound synthesized by Biorex pharmaceutical company (Hungary) at the end of the last century [204, 205]. The oral administration of this drug easily penetrates the CNS and shows an anti-inflammatory effect [98, 205]. Previous studies have revealed that arimoclomol acts as a co-inducer of Hsp [402, 403] and increases the expression of HSF1 which binds to heat shock elements (HSEs) in the promoter regions of heat shock genes and increases the Hsp level [394, 404] such as Hsp70, Hsp40, and Hsp27and results in decrease of the neuroinflammation in AD [405, 406]. BRX-220 protects

motor neurons from axotomy-induced cell death and causes upregulation of HspC1 and HspA1 in parallel in glial and neuronal cells [370, 411].

1.8.3 Geranylgeranylacetone

Geranylgeranylacetone (GGA) is a non-toxic ulcer drug that induces the expression of Hsp70 [407, 408]. Previous studies have shown that oral administration of GGA significantly decreases the levels of inflammatory cytokines, namely TNF- α, IL-1β and COX-2 in the GGA-treated mice [409, 410] and also improves the cognitive function and other pathological phenotypes in APP/PS1 mice in case of AD. It has been shown that it decreases cerebral ischemic damage in rat brains [410]. The previous study by [411] has shown GGA has cytoprotective and anti-aggregation activities besides the anti-inflammatory effect (Fig. 4). In vivo administration of GGA increases the expression of Hsp70 in neurons and decreases the accumulation of $A\beta_{42}$ plaques in AD. It also exhibits the neuroprotective effect in focal cerebral ischemia by inducing the Hsp expression in the neurons [412]. Oral administration of GGA improved the cognitive defect along with other pathological manifestations in APP23 AD mice [411].

1.8.4 Tanespimycin

Tanespimycin [17-allylamino-demethoxygeldanamycin (17-AAG)] is a water-soluble benzoquinone and antibiotic geldanamycin derivatives which are promising new anticancer drugs [413, 414]. 17-AAG up-regulates the expression l of Hsp70 and Hsp27 in neurons (Fig. 4) [415, 416]. It reduces the expression levels of pro-inflammatory cytokines TNF-α, IL-1β and IL-6 and exhibits the neuroprotective effect in a rat model of Traumatic Brain Injury (TBI) [417]. 17-AAG significantly increases the neuronal survival in the cortex region of the brain following trauma [359, 418]. The previous study by [419] has shown that 17-AAG injection decreasing the accumulation of $A\beta_{42}$ plaques and improve behavior activity by increasing the Hsp70 expression level in the rat.

1.8.5 Paeoniflorin

Paeoniflorin is a monoterpene glycoside which is one of the major elements of an herbal medicine derived from *Paeonia lactiflora* and it can also be isolated from the freshwater fern *Salvinia molesta* [420–422]. It has the potential to induce Hsp via HSF1 activation (Fig. 4) [423, 424]. Cells treated with paeoniflorin showed enhanced phosphorylation and acquisition of the deoxyribonucleic acid-binding ability of heat shock transcription factor 1 (HSF1), as well as enhanced the formation of characteristic HSF1 granules in the nucleus, resulting in the induction of Hsp by the activation of HSF1 [423]. The previous study by [180] has shown paeoniflorin

function in brain protection from cerebral ischemic injury *via* inhibition of apoptosis. Moreover, the intraperitoneal administration of paeoniflorin induces Hsp70 expression in the mouse stomach (Fig. 4) [425].

1.8.6 Curcumin

Curcumin is a biphenolic antioxidant as well as anti-inflammatory molecule present in turmeric, a common seasoning commonly used in Indian food [426, 427]. It plays a tremendous role in cancer, wound repair and inflammatory disorders. Several studies have shown that curcumin as a Hsp co-inducer can induce Hsp such as Hsp27, αB crystallin and Hsp70 expression and help in the prevention of neuroinflammation in AD (Fig. 4) [278, 396, 423, 428, 429]. The previous study by Ma et al. [430] has shown that administration of curcumin in increases Hsp70 expression and decreases the Aβ plaques and tau oligomers accumulation in A-β-infused rats. Moreover, it acts as a homeostatic regulator in inflammatory diseases by association with phagocytic cells like macrophages along with Aβ plaques and induces its clearance in human cells and AD rodent model also [222, 431]. Curcumin decreases the neuroinflammation and hyperphosphorylated Tau toxicity by NF-kB and the Activator Protein 1 (AP1) inhibition [432, 433]. The previous study by Sundaram et al. [434] has demonstrated that curcumin decreases neuroinflammation by inhibiting the p25-induced tau and amyloid-beta pathologies and improve cognitive function in AD p25Tg mice.

The other therapeutic strategy to prevent the neuroinflammation can be treatment by Hsp90 inhibitors is described below:

1.9 Hsp90 Inhibition: Potential Therapeutic Strategy to Modulate Neuroinflammation in AD

Hsp90 interacts with receptor-interacting kinase (RIP) and recruits it to the TNF receptor which activates the NF-kB, a key component of the inflammatory response in AD [435, 436]. The previous studies have shown that overexpression of Hsp such as Hsp27, Hsp70, Hsp60, etc. prevents activation of NF-kB by inducing the degradation of receptor-interacting protein kinase (RIP) and reduce the inflammation [437]. Moreover, Hsp90 directly interacts with HSF1 and inactive it results in a reduction of Hsp levels and neuroinflammation [438]. Hsp90 is also involved in the activation of pro-inflammatory cytokines [439] and increases the neuroinflammation in AD and inhibits the expression of Hsp by binding to HSF1 [440, 441]. Hsp90 inhibitor is one of the prominent therapeutic strategies to cure neuroinflammation in AD [401, 442]. There are several Hsp90 inhibitors available which might be helpful to reduce the neuroinflammation in AD. Some Hsp90 inhibitors are described as below:

1.9.1 Tanespimycin

Tanespimycin (17-AAG) is the first potential Hsp90 inhibitor tested in phase II clinical trials in kidney cancer, thyroid and pancreatic patients [443]. It inhibits the Hsp90 by inhibiting its intrinsic ATPase activity via binding to its N-terminal ATP binding domain [444, 445]. The previous study by Zuo et al. [446] has shown that Hsp90 inhibition by 17-AAG reduced the neuroinflammation via decreasing the level of inflammasome NLRP3, caspase-1 and IL-1β level and increase neurogenesis in mice with Subarachnoid Hemorrhage [447, 448]. Moreover, 17-AAG inhibits Hsp90 association with HSF-1 results in expression of Hsp70 and Hsp40 which decreases the neuroinflammation in AD [449–451] (Fig. 4).

1.9.2 Geldanamycin

Geldanamycin is a 1,4-benzoquinone ansamycin, acts as Hsp90 inhibitor [452, 453]. This is also popular to have antitumor, antibiotic properties and inhibits the expression of Hsp90 by binding at the N-terminal ATP-binding pocket of Hsp90 [454–456]. It also acts as a Hsp co-inducer because it releases the HSF1 and induces the expression of Hsp70 which is known to suppress the pro-inflammatory signals and activate the anti-inflammatory genes (Fig. 4) [108, 451]. The previous study by [457] has demonstrated that geldanamycin inhibits the aggregation of huntingtin protein in both a mammalian and mouse model by increasing the chaperone expression. So, inhibition of Hsp90 by geldanamycin might be useful in the prevention of neuroinflammation in AD [455, 458].

1.9.3 Radicicol

Radicicol is an antifungal macrolactone antibiotic derived from *Diheterospora chlamydosporia* and *Chaetomium chiversii* that inhibits the heat shock protein 90 (Hsp90) and induces the heat shock responses [414, 459, 460]. Radicicol derivatives NXD30001 exhibits higher stability in in-vivo conditions than radicicol and induces the expression of different Hsp such as Hsp70, Hsp60, Hsp40, and Hsp27 via HSF1 activation and helps in decreasing the neuroinflammation in AD [461, 462].

1.9.4 Arachidonic Acid

Arachidonic acid (AA) acts as a potential inhibitor of Hsp90 as well as inducer and co-inducer of Hsp72/Hsp70 [389, 463, 464]. It is a polyunsaturated essential fatty acid present in the plasma membrane of human and animal cells [141, 407]. It is found in human fat cells, liver, brain, and glandular organs [465, 466]. It produces

prostaglandins, thromboxanes, and leukotrienes which can act as mediators in several processes such as immune function, leukocyte chemotaxis, inflammatory cytokine production, etc. [467, 468]. The previous study by [469] has shown that the expression of AA induces HSF1 phosphorylation and results in increased Hsp expression. Moreover, AA product prostaglandins (PGs) are a class of naturally occurring cyclic 20-carbon fatty acids. The type A and J prostaglandins (PGA1, PGA2 and PGJ2), could activate HSF1 and induces Hsp72 in the presence of a reactive, unsaturated carbonyl group in the cyclopentane ring (cyclopenteneone) [37, 470–473]. The previous study suggested that the HSF1/Hsp72 pathway exhibits an endogenous anti-inflammatory role through inhibits the prolonged and higher activation of the inflammatory response [473]. Thus, the supplementation of AA in the early stage of AD reduced the symptoms and toxicity of the disease [474].

Further, the intranasal administration of exogenous recombinant human Hsp70 (eHsp70) administration increases the life and cognitive function in a mouse model of AD [93, 475]. Previous studies have shown that Hsp70 could significantly reduce the production of TNF-α, IL-1β, glial fibrillary acidic protein (GFAP), COX-2 as well as Inos [116, 184]. It also modulates astrocytes induced inflammation [343, 476]. This study indicates that eHsp70 could be a potential therapeutic strategy to decrease the neuroinflammation in AD.

The main challenges are in the effective drug delivery to treat the AD because the BBB restricts drug efficacy. Not many drugs can efficiently cross the BBB and give the 100% results in AD so there are some drugs such as polymeric nanoparticles, liposomes, metallic nanoparticles and cyclodextrins form to achieve most promising drug delivery systems [477]. The BBB serves as a physical barrier that can protect the CNS from exogenous substances and on the other side, the BBB helps in the chemical transportation to the CNS [478–480]. But the traditional AD drugs have low penetration capacity and limited transportation through BBB. Therefore, several types of research are done to overcome this limitation by using nanoscale particles to deliver the drug efficiently through BBB via increasing their penetration capacity [421, 481]. One of the strategies to improve the pharmacokinetic profiles of the drug is liposome-mediated nanoparticle therapy.

1.10 Liposome-Lipophilic Nanoparticles

Liposomes are sphere-shaped colloidal particles containing one or more phospholipid bilayers exposing outside [482, 483]. It has a hydrophilic core inside which is useful to encapsulated hydrophilic drugs and lipophilic particles [484, 485]. The liposome is a potential particle to deliver therapeutic molecules across the BBB by incorporating with cell-penetrating peptides and antibodies [486, 487]. One of the anti-inflammatory drugs is Rivastigmine, an FDA approved drug for AD treatment which reduces the level of T-cells and TNF-α and IFN-γ which are implicated in the pathogenesis of AD but it has 1.5 h half-life and its brain penetration is restricted by tight junctions [488, 489]. Previous studies have shown that the administration of the

rivastigmine by using dipalmitoylphosphatidylcholine (DPPC)/cholesterol liposomes increases the penetration of it into the brain as compared to without liposomes [477]. So, it could be a novel and effective therapeutic strategy to prevent neuroinflammation in AD. The above-mentioned therapeutic strategies could help in the modulation of the neuroinflammation and its related toxicity in AD.

2 Conclusions

Hsp are evolutionarily conserved proteins that play a vital role in maintaining the protein homeostasis through the induction of protein folding, protein assembly and degradation. It also plays a key role in neurodegenerative diseases such as AD, PD, HD, etc. via decreasing the neuroinflammation and promoting neuronal survival. Neuroinflammation in AD is the result of synchronized prolonged activation of astrocytes, microglia, pro-inflammatory cytokines as well as enzymes along with other CNS cells in the brain that induces chronic inflammation which ultimately promotes tissue injury and disease-related toxicities. Thus, the modulation of neuroinflammation via regulating activation inflammation-related cells is one of the effective strategies to treat the AD. As discussed above, large and small Hsp are significantly involved in the modulation of neuroinflammation via interacting with inflammation-causing molecules and helps in the prevention of neuroinflammation in AD. Hsp also interacted with neuroinflammasome and decreases the neuroinflammation in AD. As mentioned above, Hsp play a neuroprotective role by decreasing the neuroinflammation in AD, thus it is used as a potential therapeutic target for the prevention of AD-related pathologies. The supplementation of compounds known as inducers/co-inducers of Hsp and applications in AD might be one of the potential therapeutic targets to treat/prolong AD related pathologies in the future. Moreover, membrane lipid rearrangement and nanoparticle-based therapies are also involved in decreasing the neuroinflammation via increasing the Hsp level at the site of neuroinflammation. Thus, apart from the supplementation of drugs to modulates the Hsp level, the interaction of Hsp with inflammatory cells and their affinity to reduce/inactivate them should be a more focused area in the case of AD. Overall, this chapter highlights the effect of different Hsp in the modulation of neuroinflammation in AD and how Hsp modulating drugs used for the prevention of neuroinflammation in AD.

Acknowledgements The authors are very much thankful to Science and Engineering Research Board (SERB), New Delhi, India (No. EMR/2016/006911/HS), Gujarat Council on Science & Technology (GUJCOST/MRP/2015-16/2680) Gujarat for financial support to AKT and DST-Innovation of Science Pursuit for Inspire Research (INSPIRE), New Delhi for financial support to KP (IF140990).

Disclosure of Interests All authors declare they have no conflict of interest.

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

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

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