




Molecular Chaperones as Therapeutic Target: Hallmark of Neurodegenerative Disorders

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Abstract

Misfolded and aggregated proteins build up in neurodegenerative illnesses, which causes neuronal dysfunction and ultimately neuronal death. In the last few years, there has been a significant upsurge in the level of interest towards the function of molecular chaperones in the control of misfolding and aggregation. The crucial molecular chaperones implicated in neurodegenerative illnesses are covered in this review article, along with a variety of their different methods of action. By aiding in protein folding, avoiding misfolding, and enabling protein breakdown, molecular chaperones serve critical roles in preserving protein homeostasis. By aiding in protein folding, avoiding misfolding, and enabling protein breakdown, molecular chaperones have integral roles in preserving regulation of protein balance. It has been demonstrated that aging, a significant risk factor for neurological disorders, affects how molecular chaperones function. The aggregation of misfolded proteins and the development of neurodegeneration may be facilitated by the aging-related reduction in chaperone activity. Molecular chaperones have also been linked to the pathophysiology of several instances of neuron withering illnesses, enumerating as Parkinson's disease, Huntington's disease, and Alzheimer's disease. Molecular chaperones have become potential therapy targets concerning with the prevention and therapeutic approach for brain disorders due to their crucial function in protein homeostasis and their connection to neurodegenerative illnesses. Protein homeostasis can be restored, and illness progression can be slowed down by methods that increase chaperone function or modify their expression. This review emphasizes the importance of molecular chaperones in the context of neuron withering disorders and their potential as therapeutic targets for brain disorders.

Keywords Neurodegeneration · Molecular chaperones · Heat shock protein · Ubiquitin-substrate conjugate

Highlights

- Neurodegenerative disorders result due to misfolded and aggregated proteins which accumulate and lead to neuronal dysfunction and ultimately neuronal death.
- By avoiding misfolding, aiding in protein folding, and enabling protein breakdown, molecular chaperones serve critical roles in preserving protein homeostasis.
- Molecular chaperones have also been linked to the pathophysiology of several neurological disorders including Parkinson's disease, Huntington's disease, and Alzheimer's disease.
- Molecular chaperones have become potential therapy targets concerning with the prevention and therapeutic approach for neuronal disorders.
- Effective therapies will likely involve modulating multiple components of the protein and it serves as the initial defense against misfolded proteins and an exciting prospect for therapeutic intervention.

Extended author information available on the last page of the article

Introduction

Protein is a biochemical that plays an active role in almost all biological processes. Every protein is first synthesized by the process called translation in a form of chain consisting beads of amino acids. To become active functionally, the chain structure of protein must be eventually folded into a three-dimensional structure on the basis of the information on the sequence of amino acids. It is observed that proteins are capable of folding into their functional three-dimensional conformation *in vitro* without any external aid. But, *in vivo*, numerous proteins are involved in protein folding called molecular chaperones (MCs) [1]. The primal function of molecular chaperones is preventing misfolding and aggregation of protein. However, when proteins undergo stressful conditions including factors like oxidative stress, high temperature, and inflammation, they are

susceptible to forming structures that are not native to their functional structure. This leads to protein misfolding, which results in aggregate which can have a cytotoxic element to it [2–4]. Therefore, irregular folding or proper removal of potentially deadly forms of proteins is a common feature of many disorders, including neurological diseases like Prion's disease, Parkinson's disease, Huntington's disease, and Alzheimer's disease [5]. Several of these brain diseases initiate with abnormalities in the function of synapse, which causes neurodegenerative networks to malfunction [6]. Other studies have also shown that cytotoxic aggregates are capable of exiting cells and entering the neighboring cells, causing prion-like spreading of disease [7]. Recent research has unveiled the presence of chaperones within the extracellular space, suggesting their capacity for neuroprotection [8, 9]. Some studies conducted recently have suggested that molecular chaperones are capable of suppressing neurodegeneration, when utilized as a therapeutic target. The subject of this review would be to summarize the important molecular chaperones involved in neurodegenerative disease, different aspects of misfolding and aggregation and involvement of molecular chaperones in its prevention, how molecular chaperones help in neuroprotection, effect of aging on molecular chaperone function, involvement of molecular chaperones in pathogenesis of different neurodegenerative disease, and finally, how molecular chaperones can be a potential target in preventing brain diseases.

Molecular Chaperones

After transcription, many of the formed polypeptides are capable of assembling themselves into their native functional three-dimensional structure while there are others that require a special type of protein called molecular chaperones. Molecular chaperones are a family of unrelated protein that help and facilitate the proper assembly of polypeptide chain according to the information encoded in the polypeptide chain in vivo without themselves getting incorporated in the final structure [10]. Even if the concept of “Molecular chaperone” was first used to provide a comprehensive explanation of the function of nucleoplasmin, which is a protein within in the nucleus in the building of chromatin [11], our major understanding of the role of molecular chaperone in the folding of proteins and overall regulation of protein balance came after researchers were conducted on heat shock protein 70 (Hsp70s) and the chaperonins when it was proposed, based the ability of Hsp70s to induct heat, that it helps in repair or degradation of polypeptide chain that gets damaged under stress [12]. Molecular chaperones, the majority of which are heat shock proteins (Hsp), have been grouped into nine primary families based on their function, shown in Table 1 [13]. Only the chaperone families Hsps,

Table 1 The chaperone families along with number of chaperones and co-chaperones in the family

| Family of chaperone | Number of chaperones | Number of co-chaperones |
|---------------------|----------------------|-------------------------|
| HSP 40 | 0 | 49 |
| HSP 90 | 5 | 41 |
| HSP 70 | 17 | 10 |
| HSP 60 | 14 | 1 |
| sHsps | 10 | 0 |

Hsp60, Hsp70, Hsps90, and Hsp100, which have the greatest influence on human aging and neurodegenerative illnesses, will be of interest to us. The chaperone families along with number of chaperones and co-chaperones in the family is summarized in Table 1.

The Hsp90 System

The members of the Hsp90 family, characterized by heat shock proteins with a molecule weight of 90 kDa, operate in conjunction with the Hsp70/Hsp40 chaperone system. These proteins play a vital role in regulating the alteration of protein structure and cellular signaling. Despite extensive research, a comprehensive understanding of the precise workings of Hsp90 remains elusive. When there is no environmental stress, Hsp90 appears to form connections with a specific set of substrates, primarily associated with medical contexts. These include numerous proteins involved in transmission of signals, including receptors for steroid hormones, kinases associated with proto-oncogenes (like Src or Raf), and cell cycle (such as Cdk4) regulators [14, 15]. A C-terminal dimerization domain, an N-terminal ATPase domain, and a linker domain are present on each subunit of the homodimer Hsp90 [16]. Hsp90 seems to recognize its substrates in a setup similar to the natural state. The Hsp70-dependent mechanism that results in substrate loading is facilitated through p60/Hop (Hsp-organizing protein), a protein that directly engages with both Hsp70 and Hsp90 [17, 18]. Hsp90 goes through controlled repeated sequences of ATP binding and enzymatic breakdown, with the goal of eventually releasing the inherent form of the protein [19, 20]. In the presence of stressful circumstances, Hsp90 decreases the respective substrate specificity and takes on a broader warehousing function for unfolded protein molecules, and can subsequently undergo re-folding with the assistance of extra chaperones [21]. Hsp90 is integrated within a chaperone consortium system that is very sophisticated. According to the bound substrate protein, different cofactors may be needed for it to function. Many of these co-factors compete for interaction with the EEVD peptide motif situated at Hsp90's C-terminus and contain TPR-clamp domains [18].

Two examples of cofactors with additional enzymatic activity are the enzymes that carry out peptidylprolyl isomerization (like immunophilins and cyclophilins) and serine/threonine phosphatase 5 [22]. Recent research has demonstrated that hemoglobin-stabilizing protein (AHSP) preferentially inhibits aggregation of α -hemoglobin, allowing β -chain and α -chain to assemble stoichiometrically for the formation of functional hemoglobin A (HbA) [23].

The Hsp70 System

The molecular chaperone family known as Hsp70 makes up the vast majority of them. Hsp70s are found within the cytoplasm associated with bacterial organisms, archaea, and also in eukaryotic organisms including their endoplasmic reticulum (ER), chloroplasts, mitochondria, and nuclei. In a number of post-translational activities, Hsp70 interacts with growing chains during de novo protein folding and prevents protein aggregation [24], which includes targeting of protein, translocation through plasma membrane, and apoptosis [25–27]. Under stressful circumstances, such as heat stress, the representation of particular Hsp70 family members are strongly activated. Various cofactors work through Hsp70 via adjusting its ATP-binding capacity and directing its role to particular cellular arrangements in order to adapt to these various roles. An N-terminal ATPase domain and a C-terminal peptide binding domain are the two main functional domains of Hsp70 chaperones [28, 29]. Hsp70 recognizes characteristics that are typically present in non-native proteins, such as accessible polypeptide backbone with hydrophobic amino acid side chains exposed [30]. The primary bacterial Hsp70 homolog DnaK provides the most comprehensive understanding of the cycle of substrate binding, release regulated by ATP that underlies all Hsp70 activities. DnaK quickly binds and releases substrate when it is ATP-bound. The chaperone-substrate complex is stabilized as a result of the conversion of ATP to ADP. The co-factors GrpE and DnaJ control DnaK's cycling between the ADP- and ATP-bound states [31]. Peptide capture and retention are made easier by DnaJ's stimulation of DnaK's ATPase activity. In order to offer unfolded polypeptides to DnaK, DnaJ, which can also recognize hydrophobic peptides, may be used [32]. The release of substrate and dissociation of ADP from DnaK by the nucleotide exchange GrpE factor signifies the completion of the DnaK cycle reaction cycle.

Eukaryotes do not have any homologs of GrpE, in contrast to Hsp70 chaperones, which appear to frequently collaborate with DnaJ-proteins (known as Hsp40 in eukaryotes). However, it has been discovered that the protein Bag-1 functions in the eukaryotic cytosol in the role of a nucleotide-exchange factor and a particular modulator of Hsp70 [33, 34]. It has been discovered that a variety of additional Hsp70 co-chaperones regulate the various Hsp70 activities

throughout particular cellular processes in eukaryotes. For instance, some cofactors with Bag domains, such BAG-6 or BAG-1, also include an extra domain resembling ubiquitin, which allows them to work with CHIP in a functional way [35]. The chaperone action of Hsp70 and Hsp90 is inhibited by CHIP, a co-chaperone that contains the tetratricopeptide repeat (TPRclamp), the mechanism of which is not known yet. Furthermore, Hsp70- and Hsp90-bound substrates are in vivo promoted by CHIP to undergo ubiquitination and proteasomal degradation [36, 37]. The Hsp70 system like Bag-1 and CHIP has vital role in protein folding. This process is assisted by molecular chaperones and protein degradation, two of the main systems that maintain protein homeostasis in cytoplasm of cell [38].

The Hsp60 System

The 60-kDa mitochondrial chaperone Hsp60, commonly known as chaperonins, and GroEL, its prokaryotic homolog, share a high degree of conservation and are both members of this family [39, 40]. Since its formation, Hsp60 mainly remains active in the mitochondria, but under certain cellular stressors, it can move to the cytoplasm [41, 42]. The Hsp60 is made up of that form bond to form a complex of two heptameric rings, and these rings are stacked one upon another [43]. This special structure formed due to the stacking of two rings results in formation of a huge cavity in the middle in which the folding of proteins occurs through hydrophobic bonding [41]. Hsp10 chaperonin supports Hsp60 in folding by functioning as a dome-like cover over the ATP-active form. The inner cavity enlarges as a result, encouraging protein folding [42]. Together with other chaperones, Hsp60 and Hsp70 help unfolded proteins fold. Little is understood about the role of Hsp60 proteins in the reconfiguration of pathological misfolded proteins in the context of neurodegenerative conditions. Other evidences showed that α -synuclein has connection with Parkinson's disease mutant interacts with Hsp60 [44].

The Small Heat Shock Protein System

In situations where cells are exposed to free radicals and extreme temperatures, a group of chaperones referred to as the small heat shock proteins (sHsps) having size of 12–35 kDa suffers damage [45]. HspB1 through HspB11 are the only 11 sHsps that have been found to date, and they are structurally and functionally quite similar [46]. sHsps form massive multimeric structures and have a conserved α crystallin domain at their C-terminus, which is roughly 90 amino acids long [47]. The majority of these heat shock proteins have been discovered in the nervous system [48]. While only operating in the multimeric state and lacking any substrate specificity, sHsps shows a remarkable liking

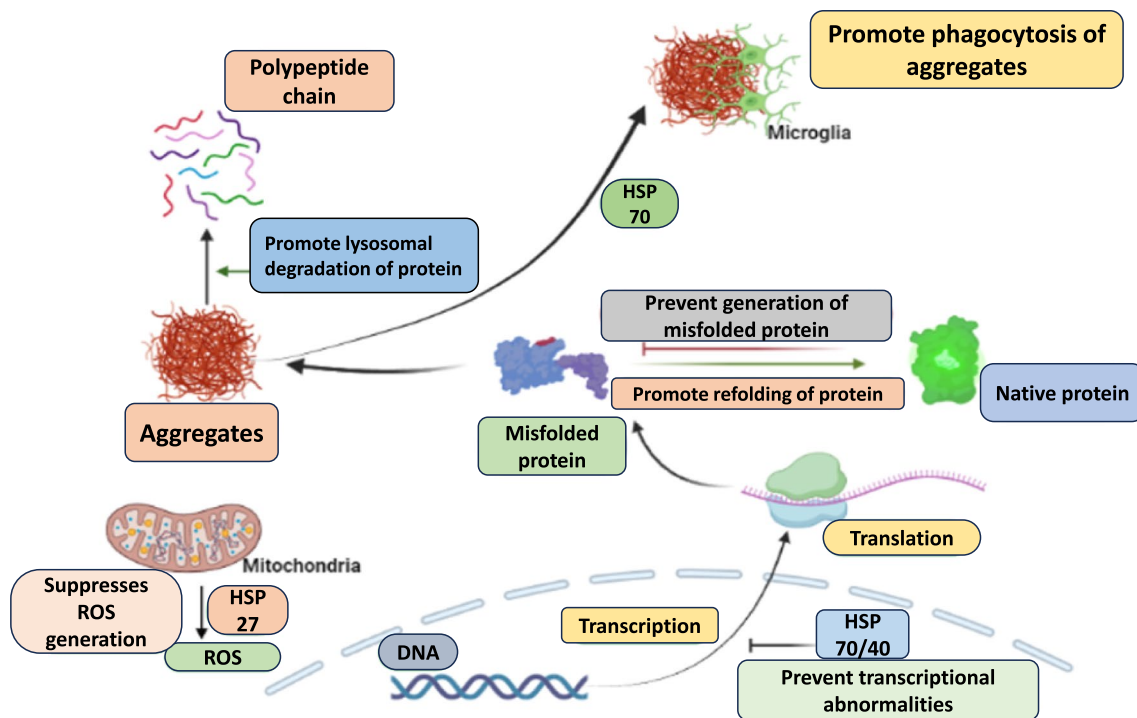


Fig. 1 Function of molecular chaperones in protein homeostasis

for partially folded intermediates [49]. It has been proven that the small Hsp protects the exposed hydrophobic surface of partially unfolded polypeptides, maintaining their solubility. In recent studies, researchers have found that sHsps destabilizes the aggregates, allowing the chaperones Hsp70/Hsp40 and hsp104 to mediate their solubilization and refolding [50, 51].

The Hsp104 System

Both the eukaryotic homolog and its bacterial ClpB, Hsp104, are crucial components associated with the heat-shock reaction and possess the extraordinary ability to rescue stressed proteins from a state of aggregation [52]. Hsp104 and ClpB belong to the extensive AAA+ superfamily. The energy needed to facilitate protein unfolding, disaggregation, and disassembly is produced by the ATP hydrolysis mediated by the AAA+ domain, which is the characteristic feature of this family [53]. The Hsp100 family is made up of members that are heat-inducible proteins and that have similar roles in assisting organisms in surviving under extremely stressful circumstances [54]. Hsp104 is Hsp100 family member of motor proteins known as AAA+ (ATPase's connected with several cellular processes), which help organisms withstand and adapt to environmental pressure [55]. Adenine nucleotides act as a molecular stabilizer for the homo-hexameric Hsp104 [56]. Each Hsp104 monomer has two AAA-1 and AAA-2 ATP-binding domains, two additional domains, and

a domain at its N-terminus that facilitates physical contact with Hsp70 aggregates [57]. When protein balance is disturbed, proteins get accumulated which are removed by Hsp104. In humans, this aggregation has a connection with neurodegenerative diseases like PD. It is important to note that humans lack a cytoplasmic homolog of Hsp104. By cooperating with Hsp70 and its co-chaperone Hsp40, scientists have discovered that Hsp104 boosts the generation of refolded proteins and expedites the protein aggregation resolution [58] (Fig. 1).

Misfolding and Aggregation of Protein: a Concise Summary

Misfolding of Proteins

Over an extended period, researchers thought that a polypeptide could take on a range of potential configurations, and the majority of smaller proteins were able to fold to one native configuration under the correct conditions in a matter of a few milliseconds [59]. To be physiologically and functionally active, a protein must be in its natural form. Uversky, however, demonstrated that a large number of so-called intrinsically disorganized or naturally unfolded proteins do not have a steady tertiary structure while being biologically active [60]. These proteins do not have a clear and distinct 3D structure, but they do have a tendency to fold into unusual

shapes with unusual biological activities. These proteins may misfold either naturally or as a result of various circumstances. Numerous protein conformation disorders, such as neurodegenerative disorders, are thought to start with the protein misfolding, which are called intrinsically disordered proteins (IDP) [61]. We should stress that when considering the subject of protein folding and misfolding, a funnel metaphor is usually used to portray it. This idea shows the energy environment folding and aggregating of protein [62]. The freest energy is found in unfolded proteins, which can also take on many 3D geometries. The range of sustained thermodynamic states for polypeptides in a healthy condition, however, is far smaller than it is for their normal active function [63]. The number of conformations in which a polypeptide can be in decreases when it starts to fold. Since the majority of proteins in cells are made up of N100 amino acids, they have a higher propensity to experience rapid lipophilic collapse into globular structure. These proteins have a propensity to fold intermediates with higher chances of escaping into non-native states before reaching their native state [64]. Due to their exposed hydrophobic areas, these partially folded proteins can occasionally cluster easily. This can lead to harmful byproducts being produced inside the cell, which may play a factor in some disorders associated with abnormal protein misfolding. Aggregation, however, can also result in amorphous aggregates that have non-toxic implications [65].

Protein Aggregation

Wetlaufer proposed a nucleation condensation growth model in 1973, which describes how proteins aggregate [66]. Three distinct phases may be seen in this model: a delay period, initial growth phase, and a concluding plateau phase. As a start, we are used to thinking that this concept emphasizes a progressive change of phase from natural to misfolded monomer, which subsequently initiates to combine into larger entities known as nucleation sites (nuclei). Only if the nucleus develops local connections during the latency phase can the aggregation reaction take place [67]. After nucleation, the nuclei enlarge, which results in a quickening of growth or elongation phase. The extremities of bigger aggregates known as protofibrils are supplemented with misfolded monomers and/or oligomers during this phase, and the protofibrils combine to form fibrils. At the end of the elongation phase, these insoluble, strongly hydrogen-bonded fibrils, also known as amyloids, result in the formation of plaque-like formations [68]. Recent research, however, demonstrates that the lag phase and exponential phase also include a variety of microscopic processes in addition to the nucleus formation and fibril formation responses [69]. It is now clear that, contrary to what we previously believed, the lag phase comprises of several simultaneous processes beginning with the primary nuclei that emerge from the solution of monomers during the

lag phase. As a result, the lag-time denotes the amount of time needed for the reaction's initial nuclei to expand and multiply into an aggregate concentration that can be easily identified. The majority of the time, this proliferation occurs by secondary nucleation, in which fibrils may act as a surface with catalytic properties to encourage the growth of new aggregates [69]. These fibrils could also divide or fragment to generate new elongation ends. The four events—that include primary level nucleation, elongation, secondary level nucleation, and fragmentation—thus frequently take place during the lag phase in many systems, with at least two of the four reactions taking place during this phase. These same processes, albeit at slightly different rates, occur during each of the three stages of the process of large aggregation due to the concentration and rate constants of reactive entities at each point of time [70]. Interaction observed among different entities can be attributed to the inclination of masking the hydrophobic surfaces of misfolded proteins to escape the hydrophilic intracellular environment through forming small nuclei and engaging in mutual interactions within their core [71]. The conformational stability of α -helices is compromised during nucleation-condensation growth and the process of aggregate/fibril creation, leading to the emergence of potentially harmful aggregate structures [72]. Research findings have provided evidence that the factor responsible for maturing bacterial hydrogenase HypF exhibits its highest toxicity in the form of small aggregates generated in the lag phase or in the stage prior to fibrillar aggregate formation that emerge at the onset of the growth phase. When these aggregates are introduced into the culture medium, they have been observed to substantially diminish the viability of cultured cells. Conversely, the fully developed fibrils of the identical proteins, which develop towards the conclusion of the development phase, demonstrate a lack of significant harmful effects [71, 72].

Protein aggregation is enhanced by a number of factors that have been found. One such aspect is the increase in the quantity of improperly folded proteins within cells, which causes aggregates to develop [73]. Moreover, studies have shown that modifications in the environment within the cell, including variations in pH, temperature, and the presence of different metal ions, have the potential to trigger protein misfolding and subsequent clustering into harmful forms. These environmental changes can arise from a range of sources, mutations either somatic or genetic, and post-translational modifications, exposure to metabolic or oxidative stress, or even inherent oxidative or metabolic processes [74].

Molecular Chaperones as Neuroprotector

The protein quality control system (PQC), a well-built mechanism in the cell, assists in maintaining protein homeostasis, verifies that proteins are folded in their

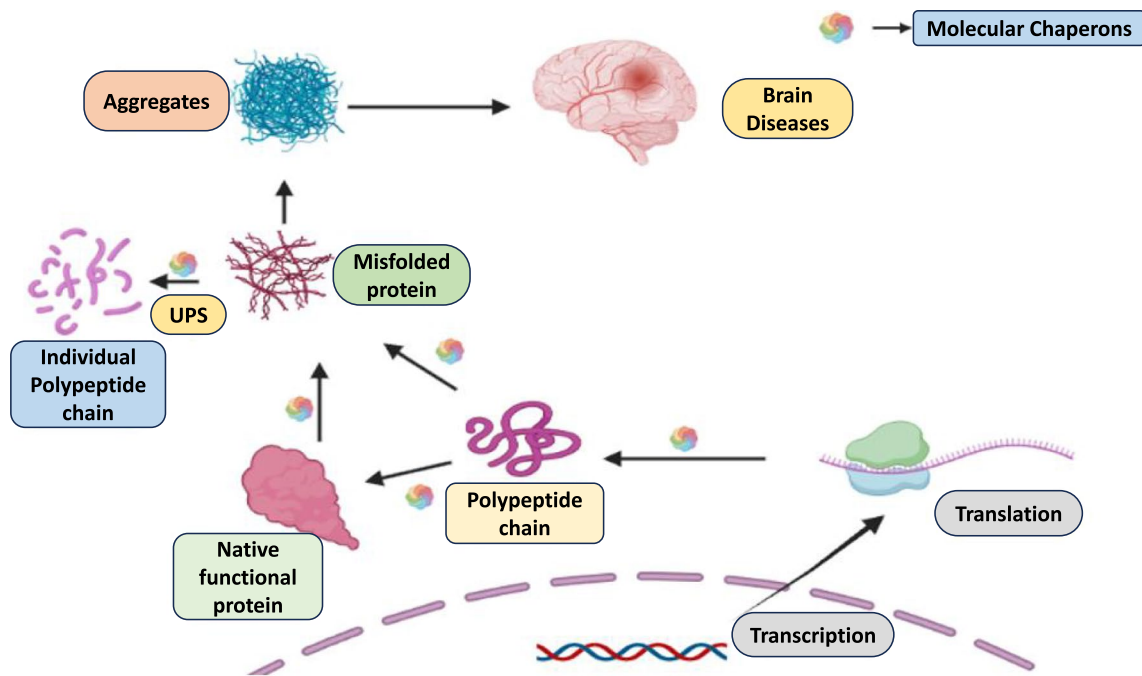


Fig. 2 Role of molecular chaperone in neuroprotection. Molecular chaperones play a vital role in maintaining regulation of protein by assisting the refolding of misfolded or unfolded proteins. In an event when the substrate proteins are unable to configure properly, chap-

erones guide them towards proteolytic pathways. Misfolded proteins that are soluble typically broken down through the UPS (ubiquitin-proteasome degradation system). However, the unchecked misfolded protein tends to form protein aggregates which leads to brain diseases

natural conformation, and aids in the destruction of proteins that undergone misfolding when necessary [75]. Following the synthesis of polypeptides, they undergo a crucial folding process to acquire their functional shape. Nevertheless, certain proteins, particularly those categorized as intrinsically disordered or natively unfolded, have the propensity to undergo spontaneous misfolding when subjected to stress conditions. This misfolding event can subsequently result in protein conformation disorders, disrupting their normal structure and function [76, 77]. The accumulation of unfolded proteins is a common occurrence that can lead to cellular damage. The PQC system serves as a protective mechanism against such damage resulting from the buildup of misfolded proteins. This pathway involves various components, including molecular chaperones, the proteolytic system (such as the system for degradation involving ubiquitin-proteasome), and the process of autophagy. Molecular chaperones play a vital role in assisting unfolded or improperly folded proteins in attaining their correct shape. They are considered the primary line of protection against neurodegenerative disease caused by protein misfolding due to their essential role in maintaining protein structure. Defects in the functioning of molecular chaperones can lead to the hazardous accumulation of unfolded or misfolded proteins and subsequent toxicity [78] (Fig. 2).

Role of Molecular Chaperone in UPS

The ubiquitin-proteasome degradation system (UPS) has a vital function in eliminating both unfolded and misfolded proteins [79]. This process relies on the coordinated action of several enzymes, including E3, E1, and E2, which mediate the interaction between target receptor and the ubiquitin. The UPS initiates with enzyme E1 establishing a thioester bond through ATP-dependent means with the glycine at C-terminal of ubiquitin, activating it [80, 81]. Activated ubiquitin molecules are then transferred to the linking enzyme E2, which subsequently transfers them to the lysine residue of protein substrates through the action of the ubiquitin ligase E3. The E3 enzyme establishes bond involving is-peptide linkage between the ubiquitin's glycine and the protein substrate lysine. Molecular chaperones are essential in this process as they assist in recognizing unfolded or misfolded proteins, which the E3 ubiquitin ligase alone cannot efficiently identify. The recognition of the ubiquitin-substrate conjugate is facilitated by RPN13 and RPN10, located within the subunits of proteasomes having 19S cap. Specific ubiquitin proteases, such as UCHL5, USP14, and RPN11, enable the recycling of ubiquitin by deubiquitinating the ubiquitin chains [82–84]. Subsequently, hydrolysis of ATP at the 19S cap subunits of proteasomes transforms the substrate protein into a polypeptide, which is further

degraded by the 20S subunit. This degradation leads to the production of small peptides composed of approximately 9–12 amino acids [85]. These peptides can be utilized for the new protein synthesis or displayed on the cell membrane to undergo immunosurveillance. In this way, the proteasome acts as the structural foundation for recognizing proteins targeted that are degraded by ubiquitin chains [86]

In the UPS, several Ub ligases including UBR2, UBR1, E6AP, encoded by the San1, UBE3A gene, and Hul5 collaborate with molecular chaperones such as the c-terminus of HSP70 interacting protein (CHIP) and parkin [87–89]. TPR (tetratricopeptide repeat) proteins act as cochaperones with CHIP, which is a Ub ligase part of U-box dependent, to regulate the chaperone activities of HSC70 and transform HSP70 into a degradation machinery for endoplasmic reticulum (ER) quality control [90, 91]. Additionally, CHIP triggers ubiquitylation, leading to the proteasomal degradation of receptors associated with HSP90 [92]. Consequently, CHIP is considered an E3 enzyme in the protein quality control (PQC) system, specifically targeting substrate proteins bound by chaperones HSP70 and HSP90 for ubiquitylation [93]. The E2 enzyme UBCH5 collaborates with CHIP to exhibit E3 ligase activity, facilitating proteasomal degradation. Ub ligase E3 subsequently recognizes and ubiquitinates misfolded protein [94]. The transport of ubiquitinated substrates is then facilitated by CHIP's interaction with the subunit RPN10 of the proteasome particles of 19S cap. As a result, mutant superoxide dismutase (SOD) 1 in ALS and hyperphosphorylated tau in AD are two examples of substrate proteins that CHIP indirectly recognize [95]. Another co-chaperone from the sHsps family known as Bcl-2 associated athanogene 1 (BAG-1) aids in the function of CHIP. The C-terminal region of BAG-1 engages in interactions with the domain of Hsp70 that is ATPase, facilitating the release of substrates bound to Hsp70. On the other hand, the N-terminal portion of BAG-1 contains a UBL (Ub-like) domain that cooperates with ubiquitin protein degradation protein system the proteasome. CHIP and BAG-1 work together to direct proteins that are misfolded towards the degradation [96–98]. HSP70/HSP40 hence aids in the refolding of protein substrates in brain disorders.

Effect of Aging on Molecular Chaperone Function

Throughout its lifespan, a stable protein undergoes diverse posttranslational modifications. These modifications encompass several processes such as methionine oxidation, and protein glycation, as well as the deamidation of asparaginyl and glutaminyl residues. As a consequence of these modifications, isopeptide linkages are formed, which play a major role in altering the function and structure of the protein

[99–101]. In comparison of glutamine synthase, bovine serum albumin, and various K⁺ channels, it was shown that proteins' susceptibilities to oxidative damage vary. This finding suggests that folding and tertiary quaternary structure may play a role in this variation [102, 103]. Early research has suggested that the inactivation of enzymes such as isocitrate lyase and phosphoglycerate kinase due to aging may be linked to the accumulation of a heat-sensitive, non-native conformation. In a study on refolding, it was observed that the augmented helical content of aged aldolase was maintained even after the refolding process, indicating that post-translational modifications occurring throughout the protein's lifespan were primarily responsible for inducing the conformational changes [104, 105]. Proteins that have an extended lifespan experience the accumulation of various posttranslational modifications. While intracellular proteins typically undergo rapid turnover under normal conditions, certain tissues, such as the brain, heart, and liver, exhibit a threefold increase in the carbonyl content of aging proteins, reflecting oxidative damage. Furthermore, proteins present extracellularly like collagen have longer lifetimes, and as proteotoxic damage accumulates in these proteins, it leads to elevated tissue stiffness and impaired cell-to-cell communication [106, 107]. The proteasome, aided by various chaperones, is primarily responsible for protein degradation. However, aging results in a reduced ability to adapt to changing conditions, which leads to an increased occurrence of proteotoxicity within cells. The capacity of chaperones to identify deteriorated proteins and the function of the primary cytoplasmic proteolytic machinery, the proteasome, are both diminished by aging. Additionally, certain oxidized and crosslinked proteins are less susceptible to degradation and, in fact, can be potent inhibitors of the proteasome. These factors collectively contribute to a significant buildup of post-translationally modified and misfolded proteins [108–110]. As organisms age, the accumulation of misfolded proteins necessitates an elevated amount of chaperones to deter protein aggregation and support degradation. This could potentially be the underlying cause of the high levels of certain chaperones, including Hsp22 and Hsp70, found in some aging species. The adaptive response of aging kidneys, in particular, is characterized by a marked increase in the amount of chaperone proteins, with the collagen-specific chaperone Hsp47 being particularly prominent. This is likely due to the heightened fibrosis associated with aging kidneys, which requires additional amounts of Hsp47 to be produced [111]. A substantial body of evidence indicates that the ability to induce different chaperones becomes compromised in aged organisms, as detailed in Table 2. Notably, in older rats, the production of Hsp70 through heat exposure is reduced, but intriguingly, exercise can elicit a significant increase in Hsp70 levels in these same animals. Furthermore, the distinct changes observed in the

induction mechanisms of numerous chaperones during aging gain further support from the discoveries made by Fleming and colleagues, who discovered a significantly modified heat shock protein induction pattern observed in elderly fruit flies compared to their younger counterparts [117, 118]. The differences observed in chaperone induction between aged animals and human subjects dismiss the notion of a universal disruption in the transcriptional mechanism of molecular chaperones. Surprisingly, the heat shock factor (HSF1) level, the transcription factor accountable for the activation of the majority of chaperones, remains mostly consistent throughout the aging journey. However, there is a significant reduction in the binding and activation of HSF1 to the element of heat shock, which represents in aged animals, its DNA-binding site within the promoter region of molecular chaperones is affected. This suggests that the age-related reduction in chaperone induction is not solely attributed to alterations in HSF1 levels, but rather to impair HSF1 binding and activation at the heat shock element [119, 120]. The precise mechanism underlying the defective activation remains unknown. However, in recent times, a number of heat shock factor-binding proteins have been uncovered that regulate the heat shock response, and they may potentially represent the molecular basis for the divergent impairments of chaperone induction observed during aging [121]. There is a scarcity of studies specifically investigating the functional changes occurring in molecular chaperones during the aging process, as compared to the abundance of research on their quantity or induction. Nevertheless, there have been observations indicating a significant decline in the role of alpha crystallin as a chaperone in aged human lenses. This implies that, with age, there may be a functional impairment in the molecular chaperones to efficiently aid in protein folding and hinder protein aggregation, highlighting the need for further exploration in this area [122]. Among the proteins found in the lens, crystallins possess one of the longest lifespans in the human body, rendering them highly susceptible to various forms of proteotoxic damage. Hence, the reduced activity of crystallins in aged lenses is not surprising. This prompts an intriguing question regarding whether impaired activity of other chaperones might exacerbate the detrimental effects resulting from their decreased induction in aging organisms. Another noteworthy example of functional

changes in chaperones observed in older individuals involves Hsp90, which plays a protective role against the decline in proteasome activity associated with aging. However, with advancing age, the association between Hsp90 and the proteasome diminishes, potentially rendering the proteasome more vulnerable to stress-induced damage in aging organisms. This decline in the Hsp90-proteasome interaction highlights a potential mechanism through which the aging process can impact the proteasomal system and its ability to effectively degrade and remove damaged proteins. Moreover, more investigations are warranted to explore the consequences of impaired chaperone function and their interplay in the context of aging-related proteostasis [108] (Fig. 3).

Involvement of Molecular Chaperone in Human Brain Disease

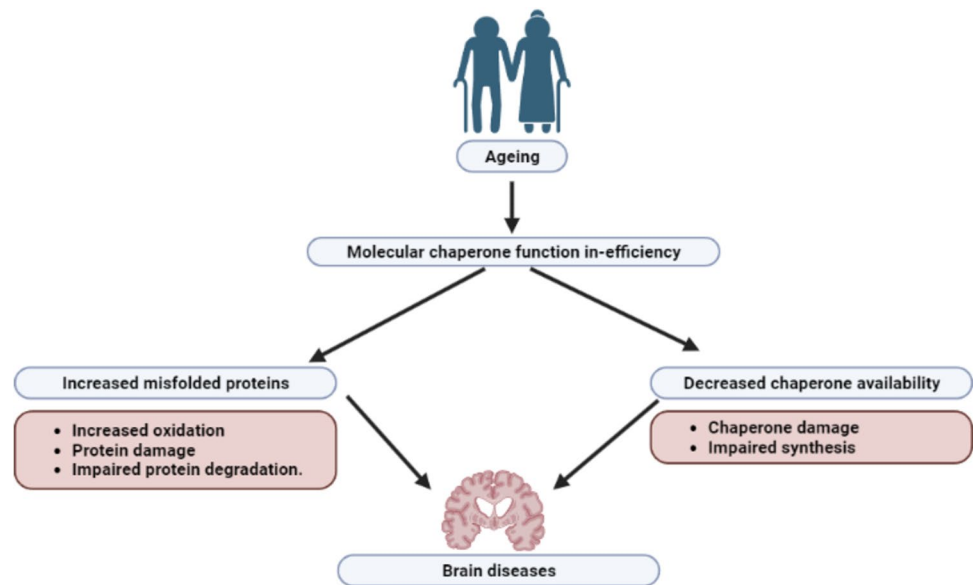
Parkinson Disease

Parkinson's disease (PD) progressively causes the breakdown of dopamine neurons in the substantia nigra part of the brain. It is related to the formation of the so-called Lewy bodies which are abnormal protein aggregates and the main component of them is insoluble alpha synuclein protein [123, 124]. Mutations in the SNCA gene, responsible for producing the α -synuclein protein, have been linked to PD. These mutations speed up protein aggregation and cause the death of dopaminergic neurons [125]. Hsp70, Hsp90, Hsp40, and Hsp27 are among the additional protein quality control system elements found in the Lewy bodies [126]. According to research, Hsp70 is crucial in PD for preventing misfolded α -synuclein from aggregating and becoming toxic [127, 128]. Patients with PD have been found to exhibit a substantial rise in the expression of Hsp70 genes which react to the increase in misfolded α -synuclein and the resulting toxicity [129]. Different Hsp70 domains have been used to illustrate the chaperone's effectiveness in vitro. Hsp70 recognizes the hydrophobic segment of misfolded α -synuclein through its substrate binding domain (SBD). Specifically, by lengthening the lag phase during the nucleation phase, the SBD by itself is effective in enabling Hsp70 to inhibit α -synuclein aggregation [130, 131]. Either the chaperone or its C-terminal

Table 2 Table depicting changes that occur in chaperone with aging

| Chaperone | Changes | Reference |
|----------------------|---|------------|
| Hsp27 | The process of heat induction is compromised. | [112] |
| Hsp32 | Oxygen damage induction is compromised. | [113] |
| Superoxide dismutase | The process of heat induction is compromised. | [114] |
| Hsp60 | The process of heat induction is compromised. | [112] |
| Hsp70 | Heat, ischemia, and mitogen induction are impaired. | [115, 116] |
| Hsp70 | The process of exercise induction is maintained. | [117] |

Fig. 3 Aging and molecular chaperones: Aging causes molecular chaperone functional in-efficiency. This leads to increased amount of misfolded proteins in cell and formation of aggregates that leads to brain diseases



domain stabilizes α -synuclein monomers and/or small aggregates. Studies have demonstrated Hsp70's ability to impede α -synuclein aggregation in vivo by overexpressing this chaperone in flies [132–134]. Additionally, it has been demonstrated that reducing Hsp70 expression causes an increase in α -synuclein cytotoxicity, which is followed by neuronal degeneration [135]. Hsp90, one of the primary chaperones found in Lewy bodies, has also been associated with PD in addition to Hsp70. Hsp90 was actually found to lessen α -syn toxicity in yeast genetic screens [136]. Furthermore, a great deal of research has shown that Hsp90 influences the progression and buildup of α -synuclein-triggered toxicity. Hsp90 has been shown in vitro to interfere with the regions related to vesicle binding and amyloid fibril assembly of α -synuclein by Falsone et al. [137]. They proved that α -syn assembly is regulated by Hsp90, and vesicle binding is prevented in an ATP-dependent manner [138, 139]. According to studies with one of the synuclein A53T mutations, all three Hsp90 domains can bind and inhibit A53T aggregation by associating with soluble oligomers [140]. Only Hsp27 and β -crystalline interact with α -synuclein at this time, despite the fact that sHsps have been demonstrated to exhibit strong inhibitory effects on α -synuclein in vitro in contrast to the aforementioned chaperones. These two chaperones have been shown to defend against the toxicity of α -synuclein by blocking its aggregation [141–143]. It proved that there is a significant reduction in α -synuclein aggregation when Hsp27 and α - β -crystalline are overexpressed. Additionally, it has been shown in vivo that Hsp27 shields dopaminergic neurons from the harmful effects induced by α -synuclein [144]. Not to mention, as already said, Hsp70, Hsp90, and sHsps effectively inhibit the aggregation of α -synuclein in both in vitro and in vivo settings. However, once protein aggregates have

been generated, these chaperones are unable to resolve them. Hsp104 can solubilize disordered protein aggregates in this situation; however, its effectiveness against human neurodegenerative disorders is limited.

Amyotrophic Lateral Sclerosis

In the motor neuron disease most commonly observed in adults, amyotrophic lateral sclerosis (ALS) causes muscle atrophy, paralysis, and eventual death typically occurring within 2 to 5 years after diagnosis [145]. It affects the brainstem, spinal cord, and cortex. Most cases of ALS are sporadic, while 5–10% are familial and are caused by gene mutations. ALS has been linked to a variety of genetic alterations. One of these is a mutation in the free radical-scavenging enzyme SOD1, which accounts for 20% of familial ALS cases. Protein misfolding has become one of the most predominant theories associated with ALS. The mutations enhance the accumulation of misfolded proteins and their aggregates that make up cytoplasmic inclusions in ALS-affected degenerated motor neurons resembling features of other neurodegenerative disorders [146–149]. These protein aggregates are thought to occur in ALS due to a variety of molecular chaperones. Several mutant forms of SOD1 can actually form complexes with Hsp70/Hsp40, Hsp25, B-crystalline, and Hsp27. In ALS mouse models, it was discovered that Hsp70 overexpression alone was insufficient to decrease SOD1 toxicity [150]. In the pathophysiology of ALS, Hsp27 also functions as a preventive factor. Small heat shock proteins like B-crystallin and Hsp27 have also been found in vitro tests to be able to prevent SOD1 from aggregating [151]. Studies conducted in living organisms have demonstrated that overexpressing Hsp27 prevents mutant

SOD1-induced cell death [152]. HSP1A, another protective protein, demonstrates a protective function opposing the development of aggregates of mutant SOD in the advanced stage of the disease involves interacting with the mutated form of SOD1G93A, facilitating its ubiquitination, and promoting proteasomal degradation [153].

Prion's Disease

Prion diseases constitute a cluster of neurodegenerative disorders, such as Jakob-Creutzfeldt disease, fatal familial insomnia, Gerstmann-Sträussler-Scheinker syndrome, and variant Jakob-Creutzfeldt disease. These diseases are characterized by the presence of misfolded proteins called prions. Prions can be acquired, genetic, or sporadic in nature. The normal form of the prion protein (PrP^C) adopts a primarily α -helical structure. However, in prion diseases, the normal PrP^C undergoes a conformational change, converting into an abnormal form known as proteinaceous infectious particle (PrP^{Sc}). PrP^{Sc} possesses a predominantly β -pleated sheet structure [154]. These particles act as a catalyst, inducing the conversion of PrP^C into additional PrP^{Sc} when they come into contact, leading to the generation of more prions. This process can perpetuate and amplify the prion population exponentially. In sporadic Jakob-Creutzfeldt disease, which comprises the majority of prion disease cases (80 to 95%), the transformation from PrP^C to PrP^{Sc} is commonly considered a spontaneous process. Yet, in genetic prion diseases (constituting 10 to 15% of cases), it is theorized that mutations in the prion protein gene, PRNP, heighten the vulnerability of PrP^C to undergo conformational changes (misfolding) into PrP^{Sc} [155]. The role of chaperones has been examined in various prion systems, including [PSI⁺], [PIN⁺], and [URE3] in *Saccharomyces cerevisiae*, as well as human prions such as SOD1 and its mutations. Several distinct molecular chaperones and co-chaperones have been identified to mitigate the aggregation of mutant SOD1 and promote cell survival in humans. These include small heat shock proteins (HSPB8, HSPB5, HSPB1), DNAJB1, Hsp70 (HSPA1), BAG1, and CHIP. Notably, in the animal model SOD1G93A of ALS, molecular chaperones have been shown to confer neuroprotection at advanced stages of the disease. Recent research highlights examining the contribution of HSP1 (DNAJB2), a member of the Hsp40 protein family, to mitigating the aggregation of mutant SOD1 and enhancing the survival of motor neurons in ALS models [156–159].

Huntington's Disease and Polyglutamine

Polyglutamine (Poly Q) disorders encompass a range of neurodegenerative disorders marked by the gradual deterioration of the brain. These disorders arise due to the anomalous repetition of the trinucleotide CAG, leading to the functional impairment and increased toxicity of the associated proteins,

thereby giving rise to poly Q-related pathologies. Notably, it has been observed that the propensity for protein aggregation is directly influenced by the length of the polyQ expansion. Multiple disorders, including Huntington's disease (HD) associated with the spinocerebellar ataxias, and huntingtin protein arising from ataxin, have been identified as being driven by the expansion of poly Q repeats [160, 161]. In 1998, Cummings and colleagues conducted a groundbreaking study utilizing a cellular model of polyQ disease, which highlighted the potential of molecular chaperones as regulators of protein aggregation. Specifically, they demonstrated that DnaJ had the ability to decrease the aggregation of ataxin-1. Subsequent investigations in the field of HD have predominantly focused on investigating the involvement of Hsps in averting protein aggregation linked to polyQ diseases. Subsequent research revealed that elevated levels of Hsp100, Hsp70, Hsp60, and Hsp40 exhibit the capacity to reduce protein aggregation induced by polyglutamine, thereby slowing down the progression of the disease [162]. Actually, it was discovered that increased poly Q aggregates generated in transgenic models and transfected cell cultures were co-localized with Hsp70 and its cochaperone, among molecular chaperones [163]. A considerable reduction in poly Q aggregation, for instance, was observed when cells expressing abnormally extended poly Q were treated with an inducer of chaperone expression, such as Hsp90, Hsp70, or hsp40 [164]. In accordance with additional reports from various groups, overexpressing Hsp40 or Hsp70 in cell cultures can inhibit the clustering of poly Q proteins [165–168]. Additionally, enlarged poly Q proteins are less harmful when Hsp70 and its co-chaperone Hsp40 are overexpressed in models of *Drosophila* [169, 170]. Studies conducted *in vitro* have shown that Hsp70 and its cochaperones exert an ATP-dependent inhibitory effect on the aggregation of poly Q polypeptides. This mechanism promotes the creation of non-fibrillar aggregates soluble in SDS, which are proposed to be non-toxic [171]. In the presence of polyQ expanded aggregates, additional heat shock proteins, including Hsp84 from the Hsp90 family and Hsp105, were found to be upregulated. This upregulation contributes to the reduction of polyQ aggregation and mitigates its toxicity [172]. Last but not least, it was discovered that the expression of HSP104 in mammalian cells reduced aggregation in a mouse model of Huntington's disease [173].

Alzheimer's Disease

Alzheimer's disease (AD), the most common neurodegenerative disorder, primarily affects the elderly population. It is characterized by the deposition and accumulation of misfolded proteins, including A β (Amyloid- β) both outside and inside neurons, as well as the formation of hyperphosphorylated tau protein NFTs (neurofibrillary tangles) within neurons [174–179]. In various animal models

Table 3 Brain disease associated with molecular chaperones

| Brain disease | Involved gene | Aggregating protein | Chaperone involved | Reference |
|-------------------------------|---------------------------|--|-------------------------|------------|
| Parkinson disease | α -synuclein | α -synuclein | HSP70, HSP40 | [190] |
| Amyotrophic lateral sclerosis | SOD1 | Mutant SOD1 | HSP70 | [191] |
| Huntington's disease | Huntingtin | Mutant huntingtin | HSP70 | [171] |
| Alzheimer's disease | Amyloid precursor protein | A β peptides, hyper-phosphorylated tau | HSP72 HSP27 HSP90 | [192, 193] |

with reduced levels of Hsp40, Hsp70, and Hsp90, the toxic effects of amyloid β have been shown to be attenuated [180]. Immunohistochemical techniques have revealed the elevated levels of Hsp70 in neurofibrillary tangles (NFTs) and neuritic plaques observed in AD brains [181]. Furthermore, in cell culture models of AD, Hsp70 has demonstrated its ability to inhibit the aggregation of A β and reduce cytotoxicity [182]. Experimental evidence has shown that there is interaction between A β and recombinant Hsp70, Hsp40, and Hsp90. These chaperones exhibited a concentration-dependent ability to slow down the rate of peptide aggregation, directing the aggregation pathway towards the formation of soluble circular oligomers rather than amyloid fibrils. Interestingly, when Hsp70, Hsp40, and Hsp90 were combined, they were capable of modifying the structure of pre-existing fibrils and oligomers, whereas their individual additions did not produce noticeable effects [183, 184]. A prominent characteristic of AD pathogenesis is the buildup of hyperphosphorylated tau proteins, resulting in the creation of insoluble neurofibrillary tangles (NFTs) within brain cells. The hyperphosphorylation of tau alters its conformation, promoting increased aggregation, destabilization of microtubules, and subsequent neurodegeneration [185, 186]. Multiple studies have provided

evidence that various Hsps and their co-chaperones, such as Hsp90, Hsp27, Hsp90, and α -crystallin, possess the ability to recognize hyperphosphorylated tau species and facilitate their clearance or recycling. In 2014, Karagoz et al. revealed the structure of the Hsp90-tau complex, providing insights into the simultaneous binding of Hsp90 and Hsp70 to the unstructured tau protein [187, 188, 189] (Table 3).

Molecular Chaperones as Drug Target in Brain Diseases

Molecular chaperones have emerged as promising targets for therapeutic interventions aimed at controlling the aggregation and cytotoxicity of protein clumps in neurodegenerative disorders. Increasingly, preclinical investigations, both pharmacological and gene therapy methods, have been explored to boost chaperone function, demonstrating encouraging outcomes. Pharmacological drugs designed to target molecular chaperones primarily focus on the Hsp70 system and can be categorized into three groups: (1) Direct chaperone function compounds, (2) HSF-1 modulators, and (3) Hsp90 inhibitors. Table 4 provides a summary of

Table 4 Different substances used to target molecular chaperones in brain diseases. 17-Allylamino-17-demethoxygeldanamycin (17-AAG), 17-dimethylaminoethylamino-17-demethoxygeldanamycin (17-DMAG)

| Brain disease | Material used | Target chaperone system | Reference |
|-------------------------------|------------------------|---------------------------|-----------|
| Parkinson disease | Geldanamycin | Hsp90 | [194] |
| | 17-AAG | Hsp90 | [195] |
| | SNX-0723 | Hsp90 | [196] |
| | Trehalose | Direct chaperone function | [197] |
| Amyotrophic lateral sclerosis | Geldanamycin | Hsp90 | [198] |
| | 17-AAG | Hsp90 | [199] |
| | Celastrol | Hsp90 | [200] |
| | Trehalose | Direct chaperone function | [201] |
| | Human Hsp70 | Chaperone activity | [202] |
| polyQ diseases | Geldanamycin | Hsp90 | [203] |
| | 17-AAG | Hsp90 | [204] |
| | 17-DMAG | Hsp90 | [205] |
| | Geranylgeranyl acetone | Hsp70 | [206] |
| Alzheimer's disease | Geldanamycin | Hsp90 | [207] |
| | Celastrol | Hsp90 | [208] |
| | Trehalose | Direct chaperone function | [208] |

the various agents used in the treatment of different brain disorders.

Conclusion

Experimental evidence strongly supports the critical role of molecular chaperones in modulating neurodegeneration and protein aggregation. However, the precise mechanism by which chaperones contribute to the understanding of neuroprotection that is still limited. Aberrant protein interactions, resulting from altered conformations in disease-causing proteins, likely initiate the cascade of pathogenic events leading to neuronal dysfunction prior to the formation of inclusion bodies. The identities of the proteins engaged in these interactions, and how they contribute to neuronal dysfunction, and the specific rescue mechanisms employed by molecular chaperones require further investigation, particularly through molecular genetic approaches in animal models. Studies in animals have demonstrated that chaperones can support neuroprotection without influencing the formation of inclusion bodies. This implies that protective interactions might occur with small, diffusible aggregate assemblies or misfolded monomeric conformations. Developing tools to detect these distinct misfolded conformations and assemblies in vivo and understanding how their interaction with cellular proteins, including molecular chaperones, which modify pathogenesis are crucial. Effective therapies will likely involve modulating multiple components of the protein quality control system, with molecular chaperones playing a central role. Given that molecular chaperones act as the initial line of defense against misfolded proteins, operating during the early stages of disease pathogenesis, they represent an exciting prospect for pharmacological intervention.

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