Chaperone signalling complexes in Alzheimer’s disease

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Abstract

Molecular chaperones and heat shock proteins (Hsp) have emerged as critical regulators of proteins associated with neurodegenerative disease pathologies. The very nature of the chaperone system, which is to maintain protein quality control, means that most nascent proteins come in contact with chaperone proteins. Thus, amyloid precursor protein (APP), members of the gamma-secretase complex (presenilin 1 [PS1] collectively), the microtubule-associated protein tau (MAPT) as well as a number of neuroinflammatory components are all in contact with chaperones from the moment of their production. Chaperones are often grouped together as one machine presenting abnormal or mutant proteins to the proteasome for degradation, but this is not at all the case. In fact, the chaperone family consists of more than 100 proteins in mammalian cells, and the primary role for most of these proteins is to protect clients following synthesis and during stress; only as a last resort do they facilitate protein degradation. To the best of our current knowledge, the chaperone system in eukaryotic cells revolves around the ATPase activities of Hsp70 and Hsp90, the two primary chaperone scaffolds. Other chaperones and co-chaperones manipulate the ATPase activities of Hsp70 and Hsp90, facilitating either folding of the client or its degradation. In the case of Alzheimer’s disease (AD), a number of studies have recently emerged describing the impact that these chaperones have on the proteotoxic effects of tau and amyloid-β accumulation. Here, we present the current understandings of chaperone biology and examine the literature investigating these proteins in the context of AD.

Keywords: Alzheimer's disease • chaperones • heat shock proteins • tau • degradation • protein misfolding

Introduction

Genetic analyses of families presenting with Alzheimer’s dementia revealed that mutations in the amyloid precursor protein (APP) and presenilin 1 (PS1) protein were the cause of the disease for the affected kindred [1–7]. Overexpression of these mutant genes in transgenic mice showed that they enhance production of a 42-amino acid N-terminal peptide from APP, which enters the extracellular milieu [8–13]. This Aβ peptide has amyloidogenic properties, forming multimers in a β-sheet structure [14–17]. As enough of this material is produced, amyloid plaques form spontaneously and remain quite stable over time [18, 19]. Amyloidosis around the vasculature is also found in Alzheimer’s disease (AD), and these plaques have been shown to grow more gradually with time [20]. This plaque production facilitates gliosis, and the role of microglia and astrocytes in AD is an area of intense investigation [21–25]. Microglia or macrophages become activated and can phagocytose Aβ [26, 27]; however, more current work suggests that multiple activation states are found in the brain, and it may be possible to manipulate these states to promote Aβ clearance [28–33]. Although amyloid plaques are the pathological end-point of aberrant Aβ production, a large number of studies have emerged suggesting that oligomeric forms of Aβ are the most pathogenic species [34–38]. A recent study demonstrated that dimeric Aβ...
species isolated from AD brain tissue impair synaptic plasticity and memory function when injected into normal rats [39]. Although sporadic AD follows the same pathological roadmap as the familial cases, a definitive genetic cause has not been established [40, 41]. However, polymorphisms in the APOE (apolipoprotein E) gene have been identified as significant risk factors for late-onset AD (LOAD) [42]. The function of ApoE in AD has been extensively reviewed [43]. Briefly, this protein is produced by microglia and astrocytes in the brain and has a major impact on scavenging of the Aβ peptide from the extracellular space, fostering the clearance of amyloid [44, 45]. The mutations in APOE linked to LOAD reduce the efficiency with which ApoE clears the Aβ peptide, facilitating amyloid accumulation and disease progression [46, 47].

Unfortunately, despite all of these data describing how Aβ is produced and which forms of Aβ are most toxic, recent work using therapies to reduce Aβ burden have met with limited success in the clinic. The immunotherapeutic strategy spearheaded by Elan/Wyeth Pharmaceuticals (Athlone, Ireland) has revealed that reducing amyloid burden does not halt the disease process, but rather slows the decline, and it carries with it a significant risk of cerebral haemorrhagic events [48–52]. In addition, clinical trials carried out by Myriad Pharmaceuticals (Salt Lake City, UT, USA) using the gamma-secretase modulator, flurizan, a drug which potently inhibited the PS1 complex to prevent Aβ 1–42 production in pre-clinical testing, was entirely ineffective at preventing cognitive decline in AD patients enrolled in a phase III clinical trial [53]. The optimistic and hopefully accurate interpretation of these results is that the pharmacological properties of these drugs were insufficient to achieve relevant concentrations at the target site. These trials may also suggest that perhaps the mild-to-moderate patient subsets selected for these studies were already at a stage in the disease process where anti-amyloid therapies may be less effective. Regardless, alternative therapeutic strategies to stop disease progression and even reverse the clinical phenotype should be explored.

Another major pathological component of AD is intracellular aggregation of the tau protein into tangles. Several recent studies have suggested that although Aβ may trigger this dysfunction of the tau protein, ultimately it becomes self-perpetuating [54, 55]. Tau pathology is found in a number of neurodegenerative diseases [56–59], and this generality decreased the enthusiasm for researching modifiers of tau, since it was recently shown that mice transgenic for mutant APP lacked cognitive deficits when the tau protein was deleted [72], pinning down the interface where Aβ triggers tau dysfunction has become a major focus of current research efforts. The most commonly studied tau modification is phosphorylation, and a number of drug-screening efforts have focused on inhibiting the kinases most often associated with this process, namely GSK3β and CdK5 [73, 74]. But in addition to phosphorylation, other aspects of tau biology include folding [75], nitration [76], O-linked glycosylation, ubiquitination [77] and protease cleavage [78]. These modifications can alter tau’s normal function of microtubule (MT) stabilisation; however, they likely contribute to its pathobiology as well. Recent efforts by our group and others have focused on trying to remove those particular tau species that are thought to be disease-related, preserving the normal tau to allow proper MT stabilisation. We have found that facilitating the clearance of these species may be achieved by manipulating the chaperone complex, the cell’s protein quality control system [77, 79–81]. Since then, chaperone biology has emerged as an area of intense investigation with regard to AD research. Therefore, the remainder of this review will focus on the role that chaperones have in the biology and pathobiology of AD-related proteins.

Chaperones: the basics

The term ‘chaperone’ is defined as a guide whose purpose is to ensure propriety or restrict activity. In all cells, there are a group of proteins that have been dubbed chaperones because they carry a very similar function; they make sure that other proteins arrive safely and are functional at their destination within the cell; however, these cellular chaperones also ensure that proteins deemed to be ‘ill-behaved’ or abnormal are destroyed. These unique properties of cellular chaperones bring them into intimate contact with many ‘client’ proteins within cells, including those associated with AD, such as APP, PS1 and tau (for a description of all abbreviations related to chaperones, see Table 1).

Hsp90, Hsp70 and CHIP

Different chaperones work together to form cellular machines to differentially regulate the function of these client proteins by manipulating the ATPase activity of the two main chaperone scaffolds, Hsp70 and Hsp90. These interactions are mainly mediated by a tetratricopeptide domain that tightly binds with the C-terminal EEVD domains present on Hsp70 and Hsp90. A critical TPR-containing chaperone is carboxy-terminus of Hsc70-interacting protein (CHIP), a highly conserved ubiquitin ligase that is critical for quality control and stress recovery systems in most cell types. CHIP mitigates stress-related proteins after a cellular stress response [77, 82] and has anti-apoptotic properties.
Substrate processing

The basic pathway established for most client proteins upon synthesis is recognition by an Hsp40 variant, which then associates with Hsp70. The client is then passed to Hsp70 and either enters an Hsp70-exclusive cycle or, in coordination with Hsp70/Hsp90-organizing protein (Hop), passes the client to Hsp90. Hsp90 has the unique ability to maintain mutated proteins in a folded and partially active state at the expense of ATP, permitting proteins that would otherwise be immediately targeted for degradation to persist within the cell.

Client degradation versus folding

Small molecules aptly named Hsp90 inhibitors have been generated and functionally force these clients to be degraded through the proteasome [83–85]. CHIP is a critical component for this degradation, and since it binds with both Hsp70 and Hsp90, it has an opportunity to interact with and ubiquitinate a number of proteins via their scaffold. Conversely, other chaperones and/or co-chaperones that are part of the complex at the time of the client–Hsp90 interaction can facilitate the ATPase activity of Hsp90, protecting these clients from degradation [79, 80]. For example, tau degradation was prevented by suppressing CHIP or Hsp90, but was enhanced by suppressing co-chaperones that promote re-folding or maintenance of Hsp90 clients, such as prostaglandin E synthase 3 (P23) or Cdc37 [80]. Hsp90 inhibitors also lead to increased activation of heat shock factor (HSF).

Chaperone expression

Hsp90 normally inhibits HSF1 by tethering it to the cytosol, preventing it from translocating to the nucleus. When Hsp90 levels are depleted by Hsp90 inhibition, HSF1 is released. Once it becomes phosphorylated, it trimerises and is able to enter the nucleus and begin transcribing genes containing heat shock elements (HSE), such as Hsp70 and Hsp27. In humans, there are 4 HSF genes, 6 Hsp90 genes, 13 Hsp70 genes and 41 Hs40/DNAJ genes, along with 11 small Hsps (for an extensive review on this topic, see Reference 86). In addition to this, there are a number of other known interacting proteins, such as P23, CHIP and Cdc37.

Small Hsps

Small Hsps such as Hsp22 and Hsp27 participate in the chaperone network in a unique way. These proteins are composed of two domains: a phosphorylation domain and a crystallin domain. Under normal conditions, cellular depots of these proteins are preserved as aggregates; however, upon stress, these aggregates break down into dimers and tetramers following phosphorylation by stress-activated protein kinases (SAPK/P38 MAPK) [87]. These smaller oligomers show enhanced chaperoning activity and can process

| Table 1 Abbreviations | Acronym | Protein name |
|-----------------------|---------|--------------|
| AD                    | Alzheimer’s disease |
| ApoE                  | Apolipoprotein E |
| APP                   | Amyloid-beta precursor protein |
| Aβ                    | Amyloid-beta |
| Bag1                  | BCL2-associated athanogene |
| BIP/Grp78             | ER isofrom of heat shock protein 70 |
| CDC37                 | Cell division cycle 37 kD protein |
| CDK5                  | Cyclin-dependent kinase 5 |
| CHIP                  | Carboxy-terminus of Hsc70-interacting protein |
| DNAJ                  | see Hsp40 |
| FTD                   | Frontal temporal dementia |
| GAPDH                 | Glyceraldehyde phosphate dehydrogenase |
| Grp94                 | ER isofrom of heat shock protein 90 |
| GSK3β                 | Glycogen synthase kinase 3 beta |
| Hsc70                 | Heat shock cognate 70 kD protein 8 |
| HSE                   | Heat shock element |
| HSF1                  | Heat shock factor 1 |
| Hsp                   | Heat shock protein |
| Hsp22                 | Heat shock protein 22 |
| Hsp27                 | Heat shock protein 27 |
| Hsp40                 | Heat shock protein 40 |
| Hsp70                 | Heat shock protein 70 |
| Hsp90                 | Heat shock protein 90 |
| HtrA2                 | Putative serine peptidase |
| MAPK                  | Mitogen-activated protein kinase |
| MAPT                  | Microtubule-associated protein tau |
| MARK2 (PAR1)          | Microtubule affinity-regulating kinase 2 |
| MT                    | Microtubule |
| NFTs                  | Neurofibrillary tangles |
| P38                   | See SAPK |
| PS1                   | Presenilin 1 |
| SAPK                  | Stress-activated protein kinase |
| TPR                   | Tetratricopeptide repeat |
| UPR                   | Unfolded protein response |
proteins to the proteasome in an ATP-independent manner. Small Hsps are also newly transcribed upon stress, perhaps in anticipation of restoring the dormant stockpile following the stress event. Their chaperoning function relies on assistance from other chaperones, the complement of which is unknown. There is also evidence for extracellular localisation of Hsps, which may play an important part in immune signalling and epineuronal protein aggregation, that is, amyloid plaques [88]. Thus, this growing complexity of the chaperone network introduces an entirely new class of potential therapeutic targets, making the necessity for drawing their connection to AD pathogenesis of utmost importance.

**Chaperone regulation in AD**

Involvement of chaperones in the pathogenesis of AD was first proposed following promoter analysis of the APP gene, where an HSE was found within its promoter [89]. Immunohistochemical studies and expression analyses in AD brain tissue showed that expression levels of a number of Hsps, particularly Hsp27 and Hsp70, were elevated in affected regions from AD brain tissue, and this elevation appears to be a hybridisation of activated glia and dysregulated/stressed neurons (Fig. 1A and B) [90–96]. Since then, pathological structures typical of AD have been shown to harbour other chaperone proteins, such as CHIP [97] and Parkin [98]. These findings have served as the foundation for a number of mechanistic studies regarding the impact of chaperones and stress on the contributors to AD pathogenesis.

**Chaperone involvement in APP, presenilins and amyloid processing**

APP is a membrane-associated protein and, as such, is processed through the endoplasmic reticulum (ER) and Golgi complex [99]. The ER chaperone BiP/Grp78 (the ER isoform of Hsp70) associates with APP, likely indicating that Grp94 (the ER isoform of Hsp90) can regulate APP as well [100]. Grp78 is now known to reduce amyloid production, further belying the importance of the ER chaperone system in AD [101]. CHIP also interacts with APP, and this is restricted to the ER and Golgi complex [102]. Another report suggests that the stress-activated protease, HtrA2, can regulate APP degradation at the ER, and when this protease is deleted, APP and consequently Aβ levels are elevated [103].

Although the ER chaperone family regulates APP processing, the cytosolic complement of chaperones, which includes the stress-inducible family, has also been linked to APP and amyloid biology [104]. Several reports demonstrate that small Hsps such as Hsp22 and Hsp27 bind to fibrillar amyloid plaques and actually inhibit their fibrillarisation [105]. Overexpression of the *Caenorhabditis elegans* small Hsp16.2
protected these organisms from Aβ-induced toxicity [106]. Interestingly, the critical pro-inflammatory cytokines, interleukin-1 and tumour necrosis factor-α, facilitate the phosphorylation of small Hsps, perhaps suggesting that inflammation increases the Hsp27 chaperoning function [107].

In addition to small Hsps, cytosolic Hsp70 and Hsp90 were shown to inhibit early stages of amyloid aggregation [108]. Hsp70 was able to protect against intracellular Aβ as well [109]. More recently, administration of Hsp90 inhibitors to primary neurons prevented Aβ-induced neurotoxicity, perhaps by increasing levels of Hsp70 and Hsp90 [110]; however, it is also possible that this improved toxicity profile is due to reductions in aberrant tau by Hsp90 inhibition [80], particularly in light of evidence demonstrating that tau knockout primary neurons are less susceptible to Aβ-induced toxicity [111]. Another critical regulator for all of these proteins is HSF1. While HSF1 transcribes de novo Hsp22, Hsp27 and Hsp27, inducible toxicity [111]. Another critical regulator for all of these proteins is HSF1. While HSF1 transcribes de novo Hsp22, Hsp27 and Hsp27, inducible toxicity [111]. A critical regulator for all of these proteins is HSF1. While HSF1 transcribes de novo Hsp22, Hsp27 and variants of Hsp40, Hsp70 and Hsp90, it also induces the APP gene during stress [112–114]. In a C. elegans model of accumulation, HSF1 was shown to mediate the disaggregation of Aβ fibrils [115]. Thus, there appears to be multiple outcomes from HSF activation with regard to Aβ accumulation that may ultimately lead to a higher availability of toxic oligomeric intermediates; APP expression is elevated, leading to increases in both intra- and extracellular Aβ, amyloid plaques disassociate in response to inductions in Hsps, and APP trafficking is enhanced due to Hsp expression (Fig. 2).

PS1 resides within the cellular membrane and is a central component of the gamma-secretase complex that cleaves the Aβ peptide from APP. Although there is no pathologic accumulation of the PS1 protein in AD, the mutations found in this gene clearly implicate it in the disease process. PS1 has been predominantly found in the ER and can be phosphorylated. PS1 was shown to associate with an unknown protein containing TPR domains, suggesting for the first time that the PS1 may be regulated by the chaperone network. There have been several conflicting reports suggesting that presenilins actually trigger the unfolded protein response (UPR) in the ER, a process that leads to chaperone induction. The UPR is a process that is activated when unfolded or misfolded proteins begin accumulating in the ER lumen. Initially, chaperone protein transcription is increased in an effort to restore homeostasis. When this fails, translation is suppressed and general transcription is decreased. When all of these processes fail to rescue the cell, apoptosis is initiated. Initially, mutant PS1 was shown to down-regulate the UPR in the ER [116]; however, later reports suggested that presenilins were not tied to the UPR process [117]. Although this conflict is yet to be resolved, it is now known that PS1 forms aggregates within the ER upon heat shock stress [118]. The functional consequence of these aggresomes remains unclear.

**Chaperone regulation of the MAPT**

The majority of strides that have been taken with regard to the role of chaperones in AD have revolved around the tau protein and its aberrant intracellular accumulation. Tau is thought to be an inherently unfolded protein that promotes MT polymerisation and stability. Once tau aggregation is induced by hyperphosphorylation, folding and cleavage are thought to follow [75, 119, 120]. These post-translational modifications can impact the interaction of tau with MTs, and thus there may be specific forms of tau that are preferred chaperone substrates relative to others. It was recently reported that chaperone proteins, including Hsp27, HSP70 and CHIP, can recognise abnormal tau and reduce its concentration by facilitating its degradation and dephosphorylation [97, 121, 122]. Hsp27 preferentially binds to hyperphosphorylated tau as well as paired helical filamentous tau but not to non-phosphorylated tau [122]. The expression of another small Hsp, alphaB-crystallin has been found in glial inclusions of tauopathies [123]. Hsp27 also increases tau phosphorylation at Ser262, whereas alphaB-crystallin decreases phosphorylated tau and GSK-3β levels [124]. Interestingly, Hsp27 is cross-linked with tau in NFTs from AD brain [98]. Moreover, positive correlations have been found in the soluble protein levels from AD brain tissue between tau and molecular chaperones including Hsp27, Hsp40, Hsp90, alphaB-crystallin and CHIP [125]. Conversely, the levels of HSPs were inversely correlated with the levels of granulated tau oligomers, an intermediate of tau filaments. In a separate study, increased levels of Hsp70 and Hsp90 were found to promote tau solubility and MT binding in various cellular models [121]. Subsequent studies show that tau binds directly to Hsp70, and Bag1 has a role in this interaction [126, 127]. Taken together, these findings suggest that chaperones are necessary to maintain tau in a non-aggregated state, a consequence that may ultimately be deleterious for the brain.

Other studies have provided new insights into the mechanisms employed by the chaperone network to handle abnormally accumulating tau. Initial studies from our group showed that pharmacologic inhibition of Hsp90 significantly reduced intracellular levels of the disease-associated phosphorylated tau species pS202/T205 and pS396/S404 [128]. These Hsp90 inhibitors primarily facilitated the clearance of phospho-tau via proteasomal degradation, although lysosomal clearance also seemed to play a more minor role [79]. We also found that these inhibitors could reduce tau in transgenic tau mice. However, perhaps, more importantly, we identified a novel mechanism demonstrating that there are two pathways that can lead to opposing outcomes for tau biology with regard to Hsp90; some chaperones preserve tau, whereas others promote its degradation [80]. Furthermore, mutant, but not wild-type (WT) tau, is maintained in tauopathies by Hsp90; and the inhibition of Hsp90 leads to reductions in the pathogenicity of these mutant species [129].

CHIP has also been found to be critical for tau degradation. CHIP is found in tau lesions from AD and Pick’s disease by immunohistochemistry [130]. CHIP also binds to and ubiquitinates tau directly, and this association is facilitated by Hsp70 [97]. This ubiquitination process preferentially occurs on exon 10 (+) tau, the material that abnormally accumulates in a
Fig. 2 Role of chaperones and HSF1 in the processing of Aβ: a cycle of toxic soluble intermediates? Following a stress stimulus, HSF1 is phosphorylated by the stress-activated protein kinase cascade in the cytosol. HSF1 free of Hsp90 binding then trimerises and enters the nucleus, producing de novo copies of heat shock protein and APP mRNA. The HSPS shepherd APP to its destination and more Aβ is released. Extracellular chaperones prevent amyloid plaque formation and preserve soluble toxic amyloid species 90 (oligomers), leading to a stress loop. Intracellular Aβ may facilitate this stress and even further it. Hsp90 inhibition may compound the problem by indirectly allowing more HSF1 to become active.
number of tauopathies [131]. Conversely, mice deficient in CHIP had significant accumulation of hyperphosphorylated tau species that did not aggregate and were ubiquitin-negative [77]. Biochemical analyses showed increased levels of CHIP and Hsp70 in AD, and CHIP levels were inversely proportional to sarkosyl-insoluble tau [132]. We also demonstrated that CHIP is the critical mediator of Hsp90 inhibitor-mediated tau reductions [80]. In aggregate, these studies suggest that ubiquitination may be critical for insoluble tau filament formation, and any clearance mechanisms of tau may be dependent on CHIP.

As these chaperone machines survey the cell, they come in contact with many different proteins, and we speculated as to whether these scaffolds might serve as a nexus for modifying proteins to act on tau. Akt, an oncogenic master kinase that can phosphorylate tau, is also elevated in AD [133]. We found that Akt is also a client of CHIP, and that this interaction is highly dependent on Hsp90 [81]. Akt prevented tau ubiquitination and subsequent degradation by regulating the Hsp90/CHIP complex directly, by competing with tau as a client, or by modifying tau in such a way as to make it a less favourable substrate for the Hsp90–CHIP complex. We also found that Akt can regulate CHIP expression levels and that it has a functional interaction with the MT affinity-regulating kinase 2 (PAR1/MARK2). Akt enhances the activity of PAR1, to promote phosphorylation of tau at S262/S356, a phospho-tau species that is not recognised by the Hsp90/CHIP complex [79]. These data suggest that kinases must be considered as part of the chaperone machinery, perhaps using the Hsp90 scaffold as a tether to interact with potential substrates. This could help to explain the promiscuity of kinases that may lack specific binding domains for each substrate but use Hsp90 or Hsp70 to facilitate the interaction. A model demonstrating our current understanding of tau processing through the Hsp70/Hsp90 network is shown in Fig. 3.

**Fig. 3** Current model of tau processing through the chaperone network. Kinases such as MARK2 and Akt appear to operate in concert with Hsp90 to affect phosphorylation. MARK2 and Akt synergise to phosphorylate tau at KXGS motifs, which prevents tau degradation by the chaperone system. Other aberrant or misfolded tau is recognised by the Hsp40/Hsp70 complex. From here, tau can be either directly degraded by this complex or passed to Hsp90 to form an intermediate Hsp90 complex. Akt is associated with this complex. Here several courses can be taken based on the context: The Hsp90 complex can mature into a refolding machine and repair tau, or tau degradation can be facilitated, either out of necessity or Hsp90 inhibition. When Akt is present, tau degradation is impeded and thus it accumulates; however, when Akt is reduced by siRNA, tau degradation is enhanced. Akt is also a client of Hsp90 and thus is degraded in a fashion similar to tau.

Conclusions

The field of chaperone biology continues to gain momentum because of the critical role that these proteins appear to be playing in a number of diseases. The intricacies of these proteinaceous machines are just beginning to be imagined. For AD, chaperones represent an entirely new aspect of disease biology, an aspect that may provide a common link to a great number of neurodegenerative disorders. However, within this complex system likely lies at least one specific therapeutic target that is yet to be identified for each of these diseases. By gaining insights into the mechanisms of chaperone biology, there is no doubt that these targets will come to light and a new generation of AD therapeutics will emerge.
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