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Overview of Alzheimer's Disease Associated with Hsp90 and Its Co-Chaperone Network

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Abstract. Alzheimer's disease has been a serious threat to global health, especially with the aging population. In 2021, around 57 million people worldwide were living with dementia, and 60-70% of these cases were attributed to AD. Dementia is the seventh leading cause of death and a major contributor to disability and care dependency among aging adults. Dementia accounted for US$1.3 trillion in global economic costs in 2019. AD has two histopathological hallmarks: extracellular β-amyloid plaques and intracellular neurofibrillary tangles made up of hyperphosphorylated tau. Despite decades of intensive research, approved drugs have collectively failed to show sufficient clinical efficacy. Hsp90 is an ATP-dependent molecular chaperone and plays a dual role in AD, depending on the co-chaperone with which it associates. Since Hsp90 serves a dual function in AD and most Hsp90 inhibitors lack specificity for a given Hsp90 paralogue, these complexities pose major challenges for therapeutic development. This review outlines the dual role of Hsp90 and its co-chaperone network in AD, with a focus on four key co-chaperones. We also discuss two chaperone-targeting drugs and their mechanisms of action.

Keywords: Alzheimer's disease, Hsp90, tau, co-chaperone, FKBP51

1. Introduction

Dementia is most frequently caused by AD, which also ranks as the most common neurodegenerative disorder [1]. AD usually presents clinically as an insidious and progressive deterioration of cognition, initially marked by memory deficits and evolving into generalized dementia [2]. The etiology of AD is complex and multifactorial, involving aging and genetic susceptibility. In pathological terms, AD is marked by β-amyloid (Aβ) plaques outside cells and neurofibrillary tangles inside cells, with the tangles consisting of hyperphosphorylated Tau [1]. Data from the World Health Organization (WHO) show that dementia ranks seventh among causes of death at present and is a leading source of disability and care dependence in older adults. The global economic cost of dementia was US$1.3 trillion in 2019. In 2021, dementia affected 57 million people around the world; more than 60% of them lived in low- and middle-income countries, and close to 10 million new cases occurred each year [3].

The amyloid cascade hypothesis proposes that the pathological cascade in AD starts with Aβ peptides accumulating and aggregating outside cells in the brain. Aβ contains 38-43 amino acids and is generated through stepwise cleavage of amyloid precursor protein (APP) by β-secretase and γ-

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secretase, with its aggregation producing extracellular senile plaques [1]. Aβ deposition triggers downstream microtubule-associated protein tau (tau) pathology, leading tau to undergo hyperphosphorylation and detach from microtubules. This leads to tau accumulation into intracellular neurofibrillary tangles (NFTs) in neurones. Tau Thr231 phosphorylation promotes further phosphorylation of tau by kinases such as GSK3βto promotes NFT accumulation. This leads to neuronal dysfunction and death [4].

Despite decades of intensive research, AD still lacks adequate treatment, and approved medications have not demonstrated adequate clinical efficacy. A new generation of therapeutic strategies focuses on monoclonal antibodies targeting Aβ deposits. Aducanumab (Aduhelm) was the first such drug approved by the FDA in 2021. However, its controversial efficacy evidence and safety issues have raised widespread concerns. Subsequently, lecanemab and donanemab were introduced, but a Cochrane systematic review concluded that their clinical benefits are minimal to negligible [5]. As of now, no disease-modifying medication that targets tau pathology has received approval.

Given that the treatment protocols of AD still lag behind, and short of effective disease-modifying drugs, there is still a crying need for exploring new medicines. Heat shock protein 90 (Hsp90) is a highly conserved molecular chaperone whose activity depends on ATP. In healthy neurons, it can act together with the E3 ubiquitin ligase carboxyl terminus of Hsc70-interacting protein (CHIP) to direct tau toward proteasomal degradation [2]. In AD pathological conditions, with FK506 Binding Protein 51 kDa (FKBP51) being overexpressed, Hsp90 and FKBP51 form a complex. It interferes with normal tau processing, which is manifested as tau hyperphosphorylation and oligomerization [6, 7]. In studies using the inhibitor LA1011, it was found to reduce Aβ deposition and neurodegeneration in AD mouse models [8].

This review seeks to summarize findings concerning how Hsp90 and its co-chaperone network act in AD, focusing exclusively on four key co-chaperones: PTGES3 (p23), CHIP, FKBP51, and activator of Hsp90 ATPase homolog 1 (Aha1).

2. Alzheimer's disease

2.1. Epidemiology and disease burden

Dementia is a growing global public health challenge. According to the WHO and AD International (ADI), in 2021, dementia affected an estimated 57 million people around the world, and close to 10 million new cases occur each year. More than 60% of them live in low-income and middle-income countries. It is projected that this number will increase to 139 million by 2050. AD is the most common form, accounting for 60-70% of cases. However, public awareness of dementia remains inadequate. Up to three quarters of people with dementia worldwide remain undiagnosed. 62% of healthcare practitioners incorrectly regard dementia as part of normal ageing. 35% of carers have hidden a family member's diagnosis [3].

2.2. Etiology and clinical subtypes

AD has a complex and multifactorial etiology that involves genetic susceptibility, protein misfolding, and neuroinflammation. AD can be divided into a rare early onset disease, accounting for less than 5% of cases, and a predominant late onset sporadic form. Genetic mutations linked to AD usually cause early onset disease. These mutations lead to abnormal production of Aβ [2, 9].

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Late onset disease usually results from age related changes together with various related risk factors [2].

2.3. Core pathological features

The amyloid cascade hypothesis proposes that AD results from Aβ buildup and clustering within the brain. The two major histopathological hallmarks of AD are extracellular neuritic plaques and intracellular NFTs [2, 10]. The extracellular neuritic plaques are mainly composed of aggregated Aβ peptides [1]. The Aβ peptide comprises 38 to 43 amino acid residues. It is generated when β-secretase and γ-secretase cleave the amyloid precursor protein (APP) [2]. APP is thought to act at the cell surface and has been suggested to regulate synaptogenesis and neuroplasticity [2, 11]. A common view holds that reduced clearance of Aβ from the brain results from either an imbalance in pathways utilizing the Aβ peptide or disturbance of homeostatic processes that regulate proteolytic cleavage of APP [12]. As a result, Aβ peptides accumulate outside cells, where they later form oligomers and senile plaques [2]. Hyperphosphorylated tau assembles into paired helical filaments (PHFs) that make up intracellular NFTs. Tau tangles show the strongest association with neurodegeneration and cognitive decline [13]. Tau belongs to the microtubule-associated protein (MAP) family, and physiologically it promotes microtubule (MT) assembly and dynamics [14]. In AD, increased phosphorylation of tau at selected sites leads to the generation of abnormal soluble oligomers and filamentous aggregates. It ultimately forms NFTs and trigger neuronal and glial degeneration [14].

3. The dual function of Hsp90 in AD

Hsp90 is a molecular chaperone that shows strong conservation and accounts for roughly 1–2% of the overall cellular proteome [15]. It is an ATP-dependent chaperone and facilitates the folding of hundreds of client proteins and their degradation through a cyclic process [7]. Under physiological conditions, cytosolic Hsp90 functions as a homodimer [6]. Each monomer is made up of a middle domain, an N-terminal ATP-binding domain, and a C-terminal domain that mediates constitutive dimerization. The dimer converts from an open V-shaped conformation into a closed NTD-dimerized conformation after ATP binding. The Hsp70 molecular chaperone system ensures the protein homeostasis of cells [6].

The function of Hsp90 in AD is both dual and disputed. In 2002, Kakimura discovered that AD brains had elevated average Hsp90 levels in the cytoplasm and membrane components, and that Hsp90 displayed co-localization with amyloid plaques [6]. By contrast, all four paralogous homologues in the Hsp90 family exhibited a down-regulation trend in brains from AD patients [2]. It reflects the compensatory-dysfunctional dynamic changes of Hsp90 in AD.

The exact function of Hsp90 in AD depends on its co-chaperone. When Hsp90 assembles with co-chaperones such as p23 and CHIP into the Hsp70/Hsp90 multichaperone machinery, it tends to be protective [13]. In contrast, Hsp90 interaction with co-chaperone partners including FKBP51 and Aha1 promotes the pathology of tau [16].

Hsp70, Hop, and Hsp90 assemble into the Hsp70/Hsp90 multichaperone machinery at a 1:1:1 molar ratio. In 2022, Moll demonstratedthat tau acts as a substrate for this machinery with high affinity. The apparent dissociation constant (Kd) for the binding of Tau to the Hsp70:Hop:Hsp90 complex is 1.3 μM. In ThT fluorescence experiments, Moll found that at substoichiometric ratios (1:0.2), When Hsp70 or Hsp90 was present alone, tau aggregation was only delayed, and the final ThT signal intensity was not reduced.With the Hsp70/Hop/Hsp90 machinery, the ThT fluorescence

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profile was nearly flat, which indicated inhibition as well as delay of tau fibrillization. The inhibitory effect depended on concentration and reached up to 98% at substoichiometric amounts [13].

3.1. Protective role

p23 is a co-chaperone of Hsp90 that binds the N-terminal ATPase domain of Hsp90 [17]. It maintains Hsp90 in its closed conformation while suppressing its ATPase activity [2]. Through direct binding to tau, p23 stabilizes the whole complex. Upon addition of p23, both Native PAGE and SEC showed reduced amounts of free Hsp70:Hop:Hsp90 machinery, indicating that more machinery is occupied by tau. In ThT fluorescence assays, the Hsp70:Hop:Hsp90 machinery supplemented with p23 inhibited the fibrillization of PTau [13]. p23 inhibits Tau aggregation but may exert a "harmful holding" function [2]. It may stabilize pathologically modified Tau in vivo and increase its levels. The previous findings that both Hsp90 inhibition and p23 silencing reduce phosphorylated Tau levels in vivo can be attributed to the incorporation of phosphorylated Tau into the p23-stabilized Hsp70/Hsp90 multichaperone complex [13].

As a co-chaperone, CHIP contains both a Tetratricopeptide Repeat (TPR) domain and a U-box E3 ligase domain [13]. By competing with Hop for the same TPR binding sites on Hsp70 and Hsp90, it acts as Hop's functional antagonist. When Hsp90 is pharmacologically inhibited, CHIP can recruit to the vicinity of tau, and its U-box domain catalyzes the transfer of ubiquitin chains to tau [6, 13]. CHIP ubiquitinates tau through its U-box domain, causing it to be recognized and degraded by the proteasome [2, 6, 7].

3.2. Pathogenic role

FKBP51 is an immunophilin co-chaperone of Hsp90. It increases with age and further increases in AD cells. In human AD brains, FKBP51 induction levels show a direct correlation with Braak stage [2, 6]. Noddings used cryo-EM to resolve the FKBP51-Hsp90 complex structure and showed that the complex forms when the seventh α-helix at the C-terminus of the FKBP51 TPR domain engages a hydrophobic cleft within the dimer interface of the Hsp90 C-terminal domain [18]. In the Hsp90/FKBP51/Tau complex, Hsp90 serves as a scaffold, positioning the P1 proline-rich region of tau within the PPIase catalytic site of FKBP51 [6]. This ternary complex architecture was revealed by NMR-based structural investigations [19]. Hsp90 presentsthe proline-rich region of tau to the active site of the PPIase in FKBP51, and FKBP51 catalyzes the cis-trans isomerization of tau's proline residues. This conformational change alters the phosphorylation pattern of tau, promoting tau oligomerization and NFT formation. In the brains of FKBP51 knockout mice, tau levels are reduced. FKBP51 overexpression stabilizes toxic tau oligomers and leads to neuronal cell death. As a competitive inhibitor, LA1011 blocks FKBP51 binding to Hsp90 and thereby prevents FKBP51 from catalyzing tau proline isomerization.It reduces phosphorylation that gives rise to tau NFTs and neurotoxicity. In the APPxPS1 transgenic AD mouse model, the competitive inhibitor was found to effectively decrease Aβ plaques and tau aggregates while also preventing neurodegeneration [2, 6, 16].

Among known co-chaperones, only Aha1 enhances Hsp90's ATPase activity. Its activation of Hsp90's ATPase activity can alter the residence time of the Hsp90 chaperone cycle and client protein chaperoning. Aha1 colocalizes with NFT in human AD tissue, and levels of Aha1 correlate with Braak stage in human AD brains. Aha1 overexpression in wild-type mice aged 16 months increased pathological tau levels and impaired associative learning [2, 6, 20]. KU-177, an Aha1-binding

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inhibitor, lowers the formation of tau fibrils and the buildup of insoluble tau species in cultured cells as well as in vitro, exhibiting neuroprotective properties while leaving Hsp90-mediated refolding processes unaffected [2, 6]. To date, the mechanism by which Aha1 increases pathological tau levels remains unclear.

4. Conclusion and future prospects

AD is a multifactorial neurodegenerative disorder that arises from disrupted balance in the processes maintaining APP, Aβ peptides, and tau homeostasis. Hsp90 acts as a chaperone in regulating protein folding, and its function in AD is dual, determined by the co-chaperone it binds. p23 can bind tau and stabilize the complex, blocking tau aggregation. The HSP70-CHIP complex can ubiquitinate tau and direct it to proteasomal degradation. The FKBP51-Hsp90 complex catalyzes cis-trans isomerization at proline residues of tau, and promotes tau phosphorylation, oligomerization and NFT formation. Since most Hsp90 inhibitors lack specificity for a given Hsp90 paralogue, future drug development for AD requires drug that has both effective and non-toxic, capable of crossing the blood-brain barrier, and suitable for long-term administration. Finally, several key questions remain open. The mechanism by which Aha1 increases pathological tau levels is still unclear, and the safety and selectivity of co-chaperone-targeted interventions for drug development need further investigation.

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