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HSP70 and HSP90 in neurodegenerative diseases

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Abstract

Molecular chaperones have a role to stabilize proteins or assist them in reaching their native fold. Heat shock proteins (HSPs) are a family of molecular chaperons that protect proteins from cellular stress during the assembly of protein complexes and also prevent the proteins from aggregation and disassembly. The immediate increase of HSPs is crucial for cellular adaptation to environmental changes and protection of other proteins from denaturation, thereby maintaining the cellular homeostasis and increasing the longevity of an organism. HSP70 and HSP90 are the most studied HSPs in this very large HSP family. Notably, HSP90 also stabilizes the disease-related proteins in neurodegenerative disorders. Therefore, small molecules that inhibit the HSP90 but also increase the HSP70 has been tested as potential drugs for neurodegenerative disorders.

Introduction

Heat shock proteins (HSPs) are the chaperones responsible for correct folding of proteins during normal conditions and for restoration and refolding of destructed polypeptides in the cells under stress exposure. HSP70 and HSP90 are the most studied HSPs in a very large HSP family [1]. Unlike enzymes with their finely tuned active sites that transduce the specific molecular signaling, chaperones are heavy-duty molecular machines that interact with a wide range of protein substrates.

Heat shock response of cells was first reported as a temperature-dependent change in the transcriptional activity in the fruit fly *Drosophila melanogaster* [2]. In 1974, the HSPs were brought to light when numerous new bands of proteins were noticed in different tissue samples of *Drosophila* followed by heat shock [3]. Almost a decade later, it was proved that HSPs prevent damage to the cells by binding to abnormal proteins resulting from heat shock and thus avoiding their accumulation [4]. The transcription of HSPs is mainly regulated by Heat Shock Factor 1 (HSF1). During unstressed conditions, HSF1 exists as an inactive monomer. Upon exposure to heat or other types of cellular stress, HSF1 is processed to be converted into a trimeric and transcriptionally active state. This allows HSF1 bind to

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promoters of downstream target genes, whereby initiating the transcription [5]. Apart from having role in stressed conditions, HSF1 also plays roles in gametogenesis [6], embryonic development [7], immune response [8], and neurogenesis of olfactory system [9].

Main cause of neurodegenerative diseases is protein misfolding. Various *in-silico*, *in-vitro*, and *in-vivo* studies have been undertaken to understand the misfolding mechanism and to develop therapeutics, and pharmacological induction of molecular chaperones has been found as a solution for prevention of the disease progression. In this review, we will summarize the roles of HSP70 and HSP90 in the onset and progression of neurodegenerative diseases and discuss the potentials for the interventions.

Chaperone machinery of HSP70

In both prokaryotic and eukaryotic organisms, HSP70 and HSP90 as well as their homologous proteins are highly expressed in many cell types. HSP70 comprises of two different domains; a 40 kDa N-terminal nucleotide-binding domain (NBD) that controls the interaction with the client protein, and a 25 kDa C-terminal substrate-binding domain (SBD) that identifies the hydrophobic regions in the client during initial stages of its folding [10,11]. These two domains are connected by a flexible linker. HSP70 possesses a below average ATPase activity when not bound to a client [12]. Thus a co-chaperon, J domain protein family channels client protein to HSP70 vitalizing its ATPase activity [13]. After the J protein leaves this complex, HSP70 is brought to its apo-form by a nucleotide-exchange factor liberating ADP from it. This conformation change makes the NBD free to engage ATP, leading the α-helical lid to “open” and releasing client [13,14]. This cycle continues until the client attains the native conformation or is shifted to other parts of chaperone machinery as shown in Figure 1.

HSP40 (also known as DNAJB1) is a main co-chaperon of J domain protein family that works with HSP70 by monitoring the activities such as; binding of the polypeptide to HSP70, eliminating polypeptide folding before maturation and the ATPase enzymatic function of HSP70 [15–17]. HSP40 is widely expressed in the brain and co-localized with HSP70 [18]. Especially dense co-immunolabeling of HSP40 and HSP70 was found in postsynaptic but not presynaptic compartment, suggesting the functional implication of postsynaptic chaperons in neuronal transmission. The recruitment of client proteins to HSP70 complex is commenced by interaction with another co-chaperon HSP40, followed by transfer of those client proteins to HSP90 complex via another co-chaperone STI1 (also called HOP or HSP-organizing protein in humans) [19–22].

Chaperone machinery of HSP90

In eukaryotes, HSP90 accounts for 1% of all proteins in a cell [4]. Higher eukaryotes contain four HSP90 paralogs: GRP94 in the endoplasmic reticulum, TRAP1 in mitochondria, and HSP90α and HSP90β in the cytosol. The active unit of all HSP90 paralogs is created by a homodimerization of three different regions that are linked via flexible linkers. The N-terminal domain is accountable for binding of a nucleotide, while the middle domain recognizes the client proteins and triggers hydrolysis of ATP. The C-terminal domain serves

as the important site for the dimerization [19,23]. In the apo state, HSP90 adopts a V-shaped open conformation for ATP as shown in Figure 1. ATP binding activates a series of conformational changes including repositioning of the N-terminal lid region and a change in the N terminal-middle domain orientation. This allows the N-terminal region to support the dimerization and engages the middle domain in hydrolysis of ATP via a conserved arginine (R380 in yeast) [24]. HSP90 requires the ATP hydrolysis and structural rearrangement to reconfigure abnormally folded proteins to their normal states [25]. This process is governed by a group of co-chaperons such as stress inducible protein (STI1), cell division cycle 37 (Cdc37), protein phosphatase 5 (PP5), FK506-binding protein 51 (FKBP51), FK506-binding protein 52 (FKBP52) and cyclophilin 40 (Cyp40) [26].

Roles of HSP70 and HSP90 in neurogenerative diseases

Protein accumulation is the characteristic feature of various neurodegenerative disorders including Parkinson's disease (PD), Huntington's disease (HD), Amyotrophic lateral sclerosis (ALS), and Alzheimer's disease (AD) [27] In this section, we will summarize the roles of HSPs in neurodegenerative diseases that were discovered by using animal models and *in vitro* cells.

PD is the second most prevalent neurodegenerative disorder, the major hallmark of which is the loss of dopaminergic neurons in the substantia nigra [28,29]. α-synuclein, a protein consisting of 140 amino-acids that localizes predominantly in presynaptic compartment [30], is linked genetically [31] and neuropathologically to PD [32–34]. It belongs to the synuclein family which also includes β and γ-synuclein. This family share a conserved KTKEGV repeat motifs at the N-terminus [35]. α-synuclein accumulates into intracellular filamentous inclusions with both phosphorylated and ubiquitinated forms [36–38]. *HSP70* overexpression results in 50% reduction of α-synuclein species in the human neuroglioma cells [39]. Furthermore, 17-allylamino-17-demethoxygeldanamycin (17-AAG) that inhibits HSP90 and also increases HSP70 reduces oligomerization of α-synuclein and the neurotoxicity (Table 1)[40].

HD is a neurodegenerative disease caused by a mutation in huntingtin (*HTT)* gene [41]. Long CAG repeats in the *HTT* gene that code for an extended polyglutamine (polyQ) stretch of the HTT protein [42] lead to the aggregation of the HTT protein [43]. Protein aggregates of the mutated HTT form inclusion bodies in the neurons of the spinal cord and several brain regions [44]. Although a study showed *Hsp70.1/Hsp70.3* double knockout mice have increased size of the polyQ inclusion bodies in the cerebral cortex. The overexpression of the *Hsp70* shows moderate effect on delaying the neurodegeneration in mouse models of HD [45–49]. Another study that used cell culture model of HD also demonstrated that overexpression of HSP70 and HSP40 inhibits polyQ accumulation [50].

ALS is a degenerative disorder of nervous system affecting the motor neurons of brainstem, cortex and spinal cord [51,52]. In most cases of the disease, an RNA binding protein called trans-active DNA binding protein-43 (TDP-43) which is normally found in the nuclear region, erroneously localize in the cytoplasm of neurons and glial cells forming aggregates [53]. The HSP70 is drastically reduced in the spinal cord tissues of patients with sporadic

cases of the disease [54]. Knocking down *HSP70* in human neuroblastoma cells considerably increases the toxic TDP-43 accumulated in the cytoplasm [55], suggesting roles of HSP70 in suppressing formation of the toxic forms.

AD is the most common type of dementia, mainly afflicting aging population [56–58]. A major hypothesis for the disease pathology posits the accumulation of misfolded proteins, Amyloid β and Tau in the forebrain [59,60]. In addition to clearly visible extracellular accumulation of Amyloid β [61,62], observation made in rodent models and human postmortem tissues demonstrated the intraneuronal accumulation [63,64]. Similarly, Tau accumulation is also found in both intracellular [65,66] and extracellular compartments [67]. Recent results reveal that Aβ and tau synergize to impair the functional integrity of neural circuits *in vivo* and suggest a possible cellular explanation contributing to disappointing results from anti-Aβ therapeutic trials [68]. Similar to other neurodegenerative diseases, AD-affected brains and animal models show an increase of HSPs and their co-chaperones, including HSP70 [69]. Inhibition of HSP90 by a classical inhibitor, Geldanamycin that had been placed to clinical trials of cancer, has been also tested in preclinical models of neurodegenerative disorders. Administration of Geldanamycin (GA) reduces phosphorylated Tau *in vivo* and *in vitro*, suggesting the protective role of HSP90 for hyperphosphorylated Tau against degradation in mouse brain (Table 1) [70].

As described above, misfolded proteins accumulate to form hard insoluble plaques and fibers that are a leading cause of neurodegeneration [71]. Clearance and refolding of these misfolded proteins are mediated by HSPs, especially by HSP70. On the other hand, the HSP90 rather plays a role in augmentation of neurodegeneration. For instance, pharmacological inhibition of HSP90 suppresses the progression of the neurodegeneration.

Pharmacological inhibition of HSP90 for treatment of neurodegenerative disorders

Based on the observations made in animal models that are described above, it is evident that HSP90 plays a major role in stabilizing the proteins and maintaining the pathology-associated changes, thereby leading to degeneration and dysfunction of neurons in neurodegenerative diseases. Given the proved effectiveness in animal models, HSP90 inhibitory drugs that have been utilized in cancer treatment were also considered for the application to neurodegenerative diseases. The GA and its derivative 17-AAG act as highly selective inhibitors of HSP90 via its specific binding to the ADP/ATP binding pocket so as to block later process that includes interaction with the co-chaperons [72,73]. Inhibition of HSP90 also promotes transcriptions of HSP encoding genes including *Hsp70* and *HSP40* through HSF-1 activation [74]. Unfortunately, 17-AAG failed the phase 1 clinical trials due to hepatotoxicity [75]. This means that many alternative strategies that target HSPs are still required; examples include 1) maintaining a balance between HSP70 and HSP90 activities; 2) targeting co-chaperons that are associated with HSP70 and HSP90 for modifying the activities; 3) testing drugs that target non-canonical pathways of HSF1.

Accumulations of Amyloid and Tau in AD have been suggested as the trigger and bullet in disease pathogenesis [76]. Based on this hypothesis, many attempts including tests of

HSP70 inducer and HSP90 inhibitors, that target clearance of Tau and Amyloid β accumulations were made in animal studies [77–79]. Failure of the HSP90 inhibitors in clinical trials also suggests us to expand alternative approaches other than targeting the aggregation of misfolded proteins, such as the gene therapy of Amyloid Precursor Protein (APP) and Presenilin (PS) mutations [80].

Perspectives

Although the positive results of preclinical tests of HSP-targeted drugs encouraged the clinical application to the neurodegenerative diseases but there is no significant advancement happened in HSP90 inhibitor development process due to increased cytotoxity and lower effectiveness that were confirmed in phase 1 trials for cancer treatment. Therefore, current unmet need is to develop chaperon complex-targeted drugs with reduced toxicity, and this may be achieved by data science-assisted optimization for better pharmacological and pharmacokinetic characterization. This process would be accelerated by aggressive application of mathematical modeling and machine learning using accumulated big data [96–98]

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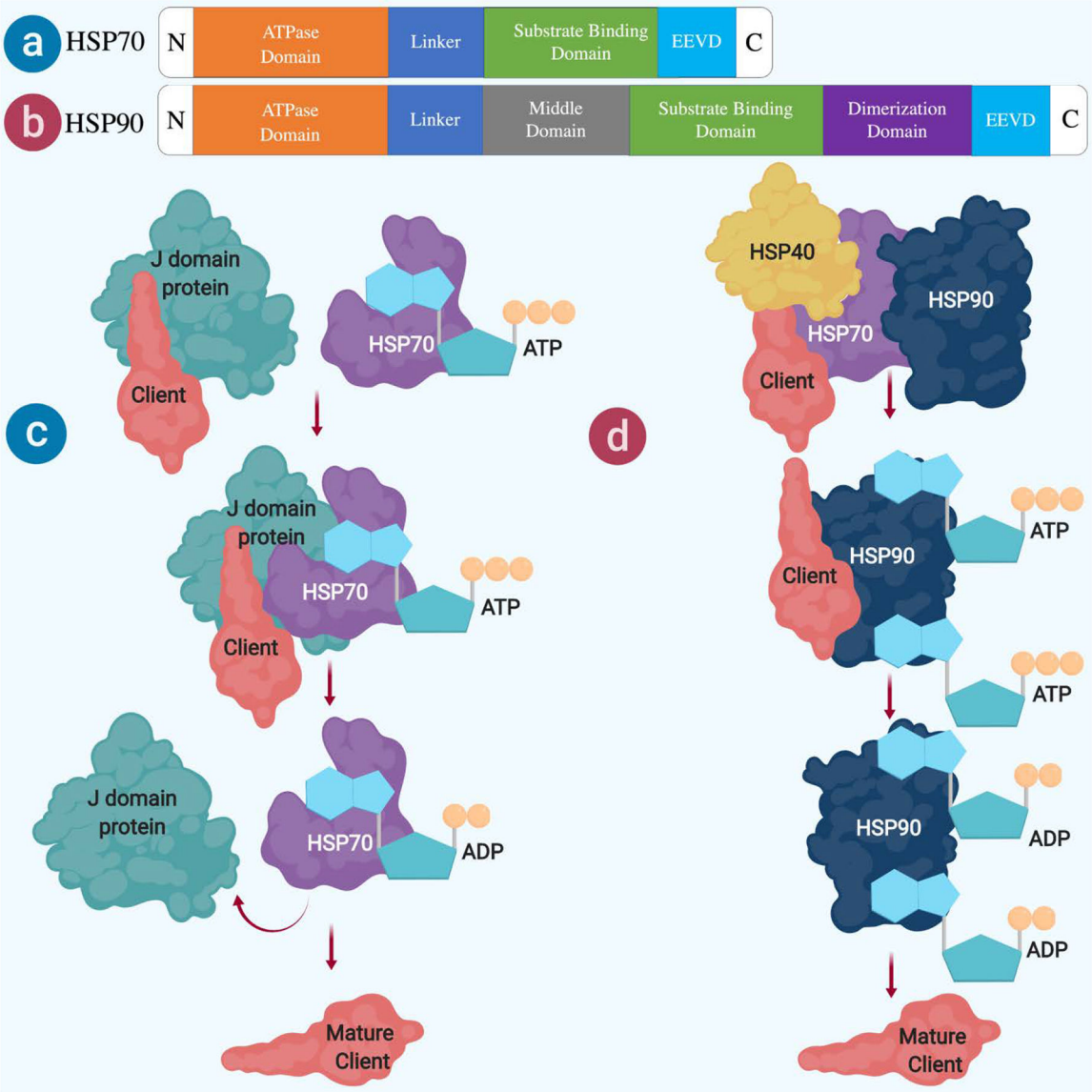

Fig. 1.

Schematic representation of HSP70 and HSP90. (a) HSP70 domains (b) HSP90 domains (c) HSP70 and (d) HSP90 co-chaperons mediated protein folding

Table 1.

Drugs that target HSPs in the clinical trials.

Drug	Primary function	References
YM-01	HSP70 inducer	[77,78]
YM-08	HSP70 inducer	[79]
MKT-077	HSP70 inducer	[78]
JG-273	HSP70 inducer	[77]
JG-48	HSP70 inducer	[77]
GGA	HSP70 inducer	[81–83]
GA	HSP90 antagonist	[70,84–89]
17-AAG	HSP90 antagonist	[89–94]
AUY922	HSP90 antagonist	[95]