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The Role and Therapeutic Potential of Hsp90, Hsp70, and Smaller Heat Shock Proteins in Peripheral and Central Neuropathies

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Abstract

Heat shock proteins (Hsps) are molecular chaperones that also play important roles in activation of the heat shock response (HSR). The HSR is an evolutionary conserved and protective mechanism that is used to counter abnormal physiological conditions, stressors, and disease states, such as those exemplified in cancer and/or neurodegeneration. In normal cells, heat shock factor-1 (HSF-1), the transcription factor that regulates the HSR, remains in a dormant multi-protein complex that is formed upon association with chaperones (Hsp90, Hsp70 etc.), co-chaperones, and client proteins. However, under cellular stress, HSF-1 dissociates from Hsp90 and induces the transcriptional upregulation of Hsp70 to afford protection against the encountered cellular stress. As a consequence of both peripheral and central neuropathies, cellular stress occurs and results in the accumulation of unfolded and/or misfolded proteins, which can be counterbalanced by activation of the HSR. Since Hsp90 is the primary regulator of the HSR, modulation of Hsp90 by small molecules represents an attractive therapeutic approach against both peripheral and central neuropathies.

Keywords

Neuropathy; Hsp90; heat shock response (HSR); HSF-1; chaperones; neurodegeneration; diabetic peripheral neuropathy (DPN)

Introduction

The Heat Shock Response (HSR) is a major cellular stress relief pathway that has been evolutionarily conserved across various species to refold denatured proteins[1–11]. Under stressful conditions (such as exposure to heat, toxic chemicals, radiation, etc.) the transcription factor, Heat Shock Factor-1 (HSF-1), activates the transcription of genes that encode for various chaperones (Hsps) that coordinate with one another to reverse cellular stress and refold denatured proteins[12,13]. Under normal conditions, chaperones maintain cellular homeostasis by folding nascent polypeptides into their correct three-dimensional conformations, as well as misfolded proteins into functional proteins[14]. However, Hsps

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also facilitate the clearance of misfolded proteins by chaperoning those substrates to the ubiquitin-proteasome pathway for subsequent degradation[15,16]. Along with these functions, Hsps also play an important role in autophagy and lysosomal degradation, which will be expanded upon later. Many pathological conditions, such as diabetes, cancer, dyslipidemia, neurodegenerative diseases, and aging can lead to a dysfunctional HSR and consequently, a loss of HSF-1 activation[17,18]. Researchers have also shown that diminished levels of Hsps (a direct result of deactivated HSF-1) can give rise to additional consequences of diabetes[18,19], such as neuropathy[19–22], retinopathy[23,24], nephropathy[25,26], cardiovascular diseases[27,28], etc. In contrast, it has been shown that the induction of specific Hsps by small molecules can elicit neuroprotection[21,22]. This review will focus on the modulation of Hsps as a therapeutic option to treat both central and peripheral neuropathies.

Although some molecular chaperones are Hsps, not all chaperones are induced by the heat shock response or other cellular stresses[29]. The Heat shock protein family is categorized by molecular weight (in kDa); large heat shock proteins (L-Hsps) such as Hsp100, Hsp90, Hsp70, Hsp40[30] and small heat shock proteins (S-Hsps) such as those with molecular weights between 12 – 43 kDa[31]. These molecular chaperones are also subcategorized into individual isoforms/paralogs[32–34]. Patients with neuropathy or related neurological disorders are known to express lower levels of both L-Hsps and S-Hsps, whereas the activation and/or overexpression of molecular chaperones has proven beneficial in several of these disease states[31,35]. For example, the upregulation of Hsp70 has been shown to reverse Diabetic Peripheral Neuropathy (DPN) by refolding aggregated and damaged proteins, which ultimately leads to the recovery of mitochondrial bioenergetics, dampening of pro-inflammatory cascades, and the reinnervation of nerve fibers[35,36]. Furthermore, patients with high Hsp27 levels manifest better nerve function as compared to those with lower levels[37,38].

In stress-free normal cells, Hsp90 suppresses the transcriptional activity of HSF-1 by existing as an Hsp90-HSF-1 complex (Figure 1)[39–42]. However, under stressful conditions, such as glycemic insult, HSF-1 dissociates from Hsp90, undergoes trimerization, and enters the nucleus to induce the expression of antioxidant proteins and chaperones, such as Hsp70[39,43]. This response leads to the refolding of misfolded proteins and/or their clearance to alleviate cell stress[44–49]. In recent years, several small molecule Hsp90 modulators have been developed that can disrupt the Hsp90-HSF-1 complex.

Modulation of Hsp90 to Induce the HSR

The Hsp90 dimer is comprised of three domains: 1) An N-terminal ATP-binding domain (25 kDa), 2) a co-chaperone and client protein binding middle domain (33 kDa), and 3) a C-terminal dimerization domain (12 kDa) that is essential for maintaining the active homodimer (Figure 2)[50,51]. Hsp90 forms a series of complexes with co-chaperones, Hsp70, and client proteins in order to fulfill its chaperone activity. An interesting phenomenon that makes Hsp90 an intriguing and druggable target is that Hsp90 inhibitors have been shown to act as either cytotoxic or cytoprotective agents, depending on cell type and the cellular stressor[18,21,22].

Hsp90 N-terminal inhibitors:

As mentioned earlier, the Hsp90 N-terminal domain contains an ATP-binding site that is responsible for the hydrolysis of ATP, which provides the energy necessary for the folding and release of Hsp90-dependent client proteins (Figure 3). In 2003, Kamal and co-workers demonstrated that Hsp90 remains in an uncomplexed and homodimeric state in normal cells; however in tumor cells, Hsp90 resides in a heteroprotein complex that manifests ~200-fold higher affinity for ATP than the homodimer alone[52]. A similar phenomenon was later described for Hsp90 in Alzheimer's disease, wherein high-affinity Hsp90-CHIP (carboxy terminus of Hsp70–interacting protein) complexes were found to exist, which is in contrast to normal tissue[53]. In recent years, extensive work to characterize these high-affinity Hsp90 complexes that are responsible for cancer cell survival and disease progression has been pursued. While the normal function of the cellular proteome is maintained by an array of chaperones and enzymes, the chronic disease state manifests an epigenetically different chaperome in stressed cells[54]. In fact, the term "epichaperome" has been proposed to describe the unique heteroprotein complex present in stressed cells[55]. As a result, Hsp90 N-terminal inhibitors represent an attractive therapeutic opportunity that may impart selectivity for stressed cells as a consequence of these heteroprotein complexes and their differential binding affinities.

N-terminal inhibitors have demonstrated the ability to afford neuroprotection against diseases wherein neurodegeneration results from a protein folding disorder. For example, the Hsp90 N-terminal inhibitors 17-AAG[56] (17-(Allylamino)-17-allylamino geldanamycin) (Figure 4) and several synthetic[57,58], semi-synthetic[59] and bio-engineered[60] analogs of GDA (geldanamycin) (Figure 4) reverse the formation of β-amyloid and tau aggregation, while inhibiting the binding of tau to microtubules[61]. The increased levels of Hsp70 induced by these compounds prevent neuronal apoptosis, a common phenomenon found in patients with Alzheimer's, Parkinson's, and Huntington's diseases[62].

There are two isoforms of Hsp90 that reside in the cytosol and these include Hsp90α, which is the inducible isoform, and Hsp90β, which is constitutively expressed[63]. Recent studies have demonstrated that Hsp90α and Hsp90β exhibit differential binding affinities toward both client proteins and N-terminal inhibitors. For example, one resorcinol-based inhibitor, STA-9090, manifests higher affinity for Hsp90β than for Hsp90α, and it is well known that some client proteins are dependent upon a particular isoform for their conformational maturation as well[64,65]. In fact, it has been shown that Hsp90α binds HSF-1 with higher affinity, suggesting that Hsp90α inhibitors may be more effective at induction of the HSR, which could then manifest cytoprotective and/or neuroprotective activity[65].

Hsp90 C-terminal inhibitors:

The size of the C-terminal domain of Hsp90 is approximately one half of the N-terminal domain and allosterically facilitates nucleotide exchange at the N-terminus, but does not exhibit ATPase activity[66]. This domain is primarily responsible for maintaining Hsp90's dimeric form and coordinating interactions with Hsp90 partner proteins that contain a tetratricopeptide repeat (TPR)[67,68]. Despite the interest in Hsp90 function, no co-crystal structure of an inhibitor bound to the C-terminal domain has been solved.

However, medicinal chemistry studies have shown that this region can be modulated by small molecules to promote cytotoxic or cytoprotective activities. In fact, two classes of novobiocin-based inhibitors have emerged for this domain. One class of compounds binds the Hsp90 C-terminal domain to disrupt interactions with Aha1, which then inhibits Aha1-stimulated ATPase activity[69]. For example, KU-174 (Figure 5) exhibits cytotoxicity against prostate cancer cell lines without induction of the HSR[70]. In contrast, the second class of C-terminal modulators induce the HSR without client protein degradation. This latter class of C-terminal modulators, such as A4, KU-32 and KU-596 (Figure 5), exhibit cytoprotective activities that are useful for the treatment of neurodegenerative disorders[71,72]. These distinct activities result from the existence of a large benzamide side chain that leads to cytotoxic activities, as opposed to the smaller acetamide side chain that manifests neuroprotective activity[22]. The C-terminal inhibitor, AEG3482 (Figure 5), an imidazothiadiazole sulfonamide, induces Hsp70 levels by activation of HSF-1. The increased levels of Hsp70 induced by AEG3482 prevent the induction of the c-*jun* N-terminal kinase (JNK) signaling cascade[73], which is responsible for neuronal apoptosis[62]. KU-32, KU-596, and AEG3482 have undergone *in vivo* evaluation and have exhibited efficacy. The effect of KU-32 and KU-596 on neurons will be discussed.

The middle domain:

While the Hsp90 C-terminal domain is responsible for binding proteins with TPR domains, the amphipathic middle domain is responsible for recognizing non-TPR co-chaperones and client protein substrates. Sato and co-workers were the first to demonstrate that the serine/threonine-specific protein kinase (Akt) binds Hsp90 at a location distinct from the N- or C-terminus[74]. Subsequent confirmation was achieved by solution of the co-crystal structure of the middle domain of Hsp90 in complex with Akt[75]. To our knowledge, no molecule that binds the Hsp90 middle domain and manifests neuroprotective activity has been reported to date.

The Nervous System

The nervous system plays an important role as a regulator of many bodily functions. It is divided into two major parts; the Central Nervous System (CNS) and the Peripheral Nervous System (PNS)[76]. The CNS consists of the brain and spinal cord, which receive information, coordinate function, and then influence other parts of our body. The PNS (consisting of nerves and ganglia) connects the limbs, organs and various parts of our bodies with the CNS. Signals from the brain and spinal cord are carried to the periphery by motor nerves, whereas sensory nerves relay the information from the periphery back to the brain. Together, the CNS acts as a “power house” and the PNS plays the role of “supply line and message carrier” as they work in concert with one another to maintain bodily functions[77,78].

Based on a similar division of our nervous system, neuropathies are separated into two major classes as well; peripheral and central neuropathies (collectively called neurodegenerative diseases). The various pathological states and the roles played by Hsps in these diseases are described below as well as the small molecule modulators of Hsps that have demonstrated therapeutic potential.

Diabetic Peripheral Neuropathy (DPN)

According to the World Health Organization, 422 million people were living with diabetes around the globe in 2014. Secondary complications of diabetes mellitus include retinopathy, nephropathy, atherosclerosis and neuropathy[18]. Among these, neuropathy is a major complication that is present in ~50% of diabetic patients[79]. The manifestation of this neuropathy is diverse in nature. For example, one can have sensory numbness (reduced feeling or hypoalgesia in response to temperature change or pain), or in contrast, spontaneous sharp pain or hyperalgesia in the hands, feet and legs, as well as paresthesia and allodynia[80]. The latter is referred to as painful diabetic neuropathy (PDN), and is experienced by one third of diabetic neuropathy patients[81]. The most common phenotype manifested by ~75% of the diabetic neuropathy patients is a “change in sensation”[81,82]. This “change in sensation” occurs due to the neurodegeneration that begins at the distal ends of sensory neurons (axons) and progresses toward the proximal extremities when diabetes remains poorly managed for long periods of time.

Hyperglycemia, neuronal insulin deficiency or resistance, as well as dyslipidemia are the major contributors to DPN[21]. Other biochemical conditions can also cause nerve dysfunction and the degeneration of sensory fibers (unmyelinated C fibers or thinly myelinated Aδ sensory fibers) and aggravate DPN via oxidative/nitrosative stress, mitochondrial dysfunction, etc. Since the etiology of DPN is multifaceted and its presentation multi-symptomatic, a combinatorial therapeutic approach may be required, and at present, therapeutic options to treat DPN are limited to symptomatic relief[22,83].

Managing blood glucose levels by controlling diet, exercise, medication, and insulin levels represent conventional approaches toward the management of DPN[84]. However, α-Lipoic acid (ALA) is an FDA approved therapeutic that can lessen some of the oxidative stress associated with DPN[85]. Other therapeutics under development include; 1) an aldose reductase inhibitor – ranirestat[86,87], 2) a vascular endothelial growth factor gene transfer[88], and 3) a protein kinase Cβ inhibitor – ruboxistaurin mesylate[89–91]. All of these therapeutic options have limitations, as they slow disease progression, but do not significantly reverse DPN pathology. Several reviews[18,21,22,92–104] have been published that outline recent progress toward the elucidation of biochemical pathways that contribute to DPN pathogenesis, as well as some therapeutic strategies to modulate disease progression.

No direct correlation has been found between DPN and any specific misfolded protein; however, it is evident that hyperglycemia can induce protein misfolding by causing oxidative processes that lead to the modification of amino acid residues[47,105,106]. As such, experiments have confirmed that induction of the HSR can elicit a cytoprotective response in neurons against such glycemic/oxidative insults[18,22]. KU-32 (Figure 5) is a novel, novobiocin-based, C-terminal inhibitor that binds Hsp90 but does not disrupt Aha1-Hsp90 interactions. As a result, KU-32 induces the HSR and increases Hsp70 levels, which elicits a cytoprotective mechanism to overcome oxidative stress, mitochondrial degeneration and, as a result, affords neuroprotection against glycemic insult without altering blood glucose levels[107–109]. Another KU-32 inspired C-terminal inhibitor, KU-596 (Figure 5), has been developed to contain a meta-fluorinated biphenyl ring that replaces the coumarin core

of KU-32. KU-596 works in a manner similar to KU-32 and also induces Hsp70 levels in hyperglycemic cells[110–112]. Both KU-32 and KU-596 were shown to restore sensory and motor neuron function in animal models of DPN. Notably, diabetic Hsp70 knockout (Hsp70 KO) mice were unresponsive to KU-596 treatment, highlighting the neuroprotective role played by Hsp70[112] (Figure 6). KU-596 was licensed to Reata Pharmaceuticals and is currently awaiting Phase II clinical evaluation for the treatment of DPN. Mimics of the noviose sugar moiety present in KU-596 have also been investigated and several surrogates or "noviomimetics" have been synthesized and evaluated[110,111]. Recently, a benzyl containing novologue (Figure 5) was identified as the most potent Hsp70 inducer in a luciferase reporter assay[111]. Studies are now underway to further optimize this new class of compounds.

KU-32 can also protect against 5-flurouracil (5-FU)-induced neuropathy. 5-FU is a commonly prescribed chemotherapeutic agent that is used against various cancers including breast, bowel, skin, stomach, oesophageal (gullet), and pancreatic[113]. Unfortunately, 5-FU causes chemobrain and cognitive impairment as a major adverse event[114]. Studies in rats revealed that 5-FU treatment along with KU-32 produced significant neuroprotection against 5-FU induced cognitive impairment[115].

Central Nervous System Neuropathies / Neurodegeneration

The accumulation of misfolded proteins is a hallmark of several neurotoxic pathologies including Alzheimer's disease (AD), Parkinson's disease (PD), and other neurodegenerative diseases. Since Hsps regulate the folding, maturation, and clearance of more than 300 client proteins within the cell[116,117], Hsps have emerged as promising therapeutic targets for the treatment of CNS disorders in which the aggregation of misfolded proteins leads to cellular stress, disruptions in signaling networks, and/or cell death. Microtubule-associated Protein Tau (MAPT, tau) is perhaps the most characterized and well known of the client proteins regulated by Hsps, as the aggregation of oligomeric tau drives the progression of a family of neurodegenerative syndromes collectively called tauopathies.

In 2002, Kakimura and coworkers discovered that Hsp90 levels are increased in both cytosolic and membranous fractions of AD brains and that Hsp90 colocalizes with amyloid plaques[118]; however, the significance of these findings and the contribution of Hsp90 to the pathology of AD and other tauopathies remained unresolved for several years. It has since been established that Hsp90 plays a role in the regulation of tau hyperphosphorylation as well as the seeding of tau fibrils through interactions with various co-chaperones, including FK506 Binding Protein 51 kDa (FKBP51, a peptidyl-prolyl cis-trans isomerase), and the Activator of Hsp90 ATPase Homolog 1 (Aha1, the only co-chaperone known to stimulate Hsp90's ATPase activity). Levels of both Aha1 and FKBP51 correlate directly with Braak stage in human AD brains; however, the mechanisms by which these two co-chaperones cooperate with Hsp90 to facilitate pathological tau progression are quite different (Figure 7).

Knockout of the *FKBP5* gene (which encodes for FKBP51) reduced levels of tau in *Fkbp5*$^{-/-}$ mice, whereas the overexpression of FKBP51 by a viral vector in the rTg4510 tau mouse model disrupted the proteasomal clearance of tau, which led to the accumulation

of oligomeric tau species, and eventually, neuronal cell death. The neurotoxic effects manifested by FKBP51 overexpression were attributed to increased interactions between FKBP51 and Hsp90, but precisely how the two proteins promote tau oligomerization was only recently elucidated. In a series of NMR-based structural investigations of the highly dynamic FKBP51/Hsp90/tau ternary complex, Hsp90 was shown to serve as a scaffold that orients the proline-rich region of tau into the FKBP51 PPIase catalytic site[119]. As tau hyperphosphorylation and aggregation have been shown to be dependent upon isomerization of its proline-rich region, it is believed that Hsp90 facilitates FKBP51-mediated proline isomerization of tau, which propagates tau fibril formation and leads to insoluble tau accumulation.

The mechanism by which Hsp90 interacts with Aha1 to modulate tau accumulation is less studied; however, combinations of both Aha1 and Hsp90 have been shown to be the most potent inducers of tau fibril formation identified to date. Shelton and coworkers demonstrated that the Aha1-E67K mutant, which is unable to bind Hsp90, is incapable of enhancing tau fibril formation; furthermore, these researchers determined that ATP is required for Aha1-stimulated tau aggregation[120]. These findings suggest that Aha1's ability to control the Hsp90 ATPase cycle is critical for tau fibril formation – a proposition that was further supported by the fact that Aha1 overexpression in rTg4510 mice resulted in a significant increase in oligomeric and insoluble tau species, and subsequently led to neuronal loss and cognitive impairment. While the three-dimensional structure of the Aha1/Hsp90/tau complex has not yet been solved, there is precedence that disruption of the Aha1/Hsp90 complex can elicit a reduction in insoluble tau aggregation.

Hsp90, along with its co-chaperones and other smaller molecular chaperones, is also an important regulator of two major pathways that are associated with the clearance of misfolded and aggregated protein substrates – both of which are impaired in several central neuropathies. First, Hsp90 interacts with Heat Shock Cognate 71 kDa (Hsc70 / HSPA8) via the Hsc70-Hsp90 Organizer Protein (HOP) to regulate the Chaperone-Mediated Autophagy (CMA) pathway. Hsc70 is a chaperone that recognizes cytosolic proteins that contain a conserved KFERQ motif and transports them to the lysosomal membrane-bound, LAMP-2A receptor. There, LAMP-2A acts as a transporter to import protein substrates into the lysosome for their degradation and the recycling of amino acids[121] (Figure 8). CMA is an important pathway for the clearance of oxidized cytosolic proteins, and several proteins associated with various neuropathic pathogeneses, such as tau and α-synuclein, are bonafide CMA substrates[122,123]. Interestingly, inhibition of Hsp90 with geldanamycin, a pan-Hsp90 inhibitor, was found to significantly activate the CMA response in IMR-90 cells[124], suggesting that Hsp90 may attempt to refold these protein substrates prior to trafficking them to the lysosome for degradation.

Second, Hsp90 works in concert with Hsp70 and at least three ubiquitin ligases to mediate the proteolytic ubiquitin-proteasome system (UPS), which is the primary catabolism pathway responsible for the degradation of cellular proteins in mammals. Under normal conditions, Hsp90 binds client proteins that are delivered by Hsp70 and stabilizes them by preventing the exposure of hydrophobic residues that are present on client substrates, so that they can be properly folded into their active three-dimensional conformations. However,

mutations or post-translational modifications to the protein substrate can destabilize its interaction with Hsp90. The destabilized complex recruits C-terminal Hsp70-interacting Protein (CHIP), an E3 ubiquitin ligase, to ubiquitinylate the mutated or modified client protein substrate. Consequently, the ubiquitinylated substrate is chaperoned to the proteasome for degradation and the recycling of amino acids (Figure 8). Ubiquitin, an 8 kDa cellular protein that serves as a marker for the proteasomal degradation of proteins, is elevated in the brains of patients with Alzheimer's disease[125] and other neurodegenerative disorders. The increased ubiquitinylation of cellular proteins is a consequence of the cell's attempt to remove aberrant and aggregated proteins in these disease states. An example of an Hsp90 client protein whose clearance is mediated by the UPS is the Huntingtin (Htt) protein, the mutant form of which is known to aggregate and give rise to Huntington's disease. Inhibition of Hsp90 disrupts the interaction between Hsp90 and Htt and ultimately promotes its clearance through the UPS[126]. This pathway has also been shown to be important for the degradation of post-translationally modified tau, α-synuclein, and other neurotoxic proteins whose clearance is disrupted in central neuropathies.

Smaller Hsps have also been studied in the context of central neuropathies. In particular, Hsp27 has been extensively investigated for its role in AD pathology. Hsp27 is significantly upregulated in astrocytes and degenerating neurons within AD brains[127,128], interacts with amyloid-β in amyloid plaques[129], and has been shown to interact physically with hyperphosphorylated tau and GSK3β, a known tau kinase[130]. Importantly, Hsp27 can be co-immunoprecipitated with tau antibodies from AD brains, but not from healthy brains[131]. The overexpression of Hsp27 in AD appears to play a role in the persistence of several cell cycle markers in AD[130] and contributes to microtubule instability by mediating tau phosphorylation. However, it is unclear whether Hsp27 is a contributing factor to AD pathology or whether it plays a role in the cell's effort to combat progression of the disease. In PD, Hsp27 appears to play a neuroprotective role, as the overexpression of Hsp27 manifests a potent anti-apoptotic effect against the damaging effects of wild-type and mutant forms of α-synuclein[132].

Hsp27 and αB-crystallin, Two S-Hsps, in Neurodegeneration

Similarly, αB-crystallin is a polydisperse protein and a member of the S-Hsp family (HSPB5) that exhibits chaperone-like properties (including the ability to prevent denatured proteins from forming insoluble protein aggregates) and is also increased in AD brains and amyloid plaques[129,133]. Although αB-crystallin prevents the formation of $A\beta_{1–40}$ fibrils, it has been shown that αB-crystallin can promote β-sheet formation of amyloid-β[133] and increase $A\beta_{1–40}$-associated toxicity[134], presumably by promoting the nonfibrillar and highly toxic form of $A\beta_{1–40}$. αB-crystallin has also been found to be the most abundant transcript in Multiple sclerosis lesions as compared to healthy brains[168]. Yet, others have found evidence that αB-crystallin confers a protective role against autoimmune encephalomyelitis[135,136], stroke[137], ischemic optic nerve neuropathy[138], and myocardial infarction[139]. For these reasons, it has largely been accepted that αB-crystallin plays a role to combat neuropathic disease progression, but the specific role played by αB-crystallin plays appears to be disease state-specific.

Along with αB-crystallin, Hsp27 has been shown to be critically involved in the pathogenesis of diseases associated with amyloid deposition. Specifically, the N-terminal portion of Hsp27 and αB-crystallin have been shown to prevent amyloid fibril formation and confer cytoprotective activities[140]. Tau protein has also been shown to bind Hsp27 as well as to αB-crystallin, and these interactions are believed to be involved in the mechanism by which cells defend themselves from the type of neuropathic injury associated with pathological tau aggregation[141]. It appears that interactions between beta-strands on S-Hsps such as Hsp27 and αB-crystallin and beta-strands of aggregation-prone proteins can result in either stabilization of their structures, prevention of their aggregation, and/or facilitation of their proteolytic degradation[142].

Hsp90 as a Therapeutic Target for Central Neuropathies

Small molecules that modulate Hsp90's inherent ATPase activity have shown great promise in preclinical models of neurodegeneration, but this success has not yet translated into the clinic. Dickey and coworkers[143] were the first to demonstrate that Hsp90 inhibitors able to cross the blood-brain barrier could decrease tau protein levels *in vitro*. Later, it was discovered that Hsp90 inhibitors enhance the degradation of phosphorylated tau through a mechanism involving the Carboxy Terminus of Hsp70-interacting Protein (CHIP), a tau ubiquitin ligase. In fact, disruption of the Hsp90/CHIP-mediated refolding complex led to decreased levels of phosphorylated tau in a murine model of tauopathy. Furthermore, the Hsp90 inhibitor, 17-AAG, promoted the degradation of Akt/PKB, an upstream regulator of tau kinase Microtubule Affinity-regulating Kinase 2 (PAR1/MARK2). Hence, Hsp90 inhibitors demonstrated the ability to modulate specific interactions between Hsp90 and CHIP, which serve to regulate pathways implicated in neurodegenerative tauopathies.

Geldanamycin, an N-terminal pan-Hsp90 inhibitor, manifested neuroprotective activity in cells that express mutant forms of tau via the increased expression of Hsp90 and Hsp70, which occurs upon N-terminal inhibition[61]. Similarly, A4, a novobiocin-based C-terminal Hsp90 inhibitor, protected primary neurons against amyloid-beta-induced neurotoxicity by inducing the expression of Hsp70 without concomitant inhibition of the chaperone machinery[72]. Clearly, the modulation of Hsp90 and Hsp70 expression represents a viable and promising approach for the treatment of central neuropathies in which the pathologies result from the accumulation of misfolded/aggregated proteins.

By 2008, Hsp90 had emerged as one of the most promising targets for the treatment of Alzheimer's and Parksinson's diseases. Consequently, a class of novobiocin analogs was developed and screened for their ability to protect differentiated SH-SY5Y cells from amyloid-beta-induced cell death via Hsp90 C-terminal inhibition. Data from these experiments showed several of these compounds to manifest neuroprotective activity at low nanomolar concentrations[144]. Not surprisingly, novobiocin-based small molecules continue to be actively pursued for neuroprotection against pathological species of amyloid and tau in neurodegenerative diseases.

Studies performed on mouse models of tauopathy have suggested that hyperphosphorylated tau species are the primary drivers of cognitive deficits in central neuropathies and that

Hsp90 plays a key role in regulating the phosphorylation of tau via several mechanisms[145]. First, it has been shown that Hsp90 inhibition can directly reduce the tau kinase activities of Cdk5[146] and Akt[147] and subsequently lower levels of tau aggregates in both cellular and mouse models of tauopathy. Consequently, direct inhibition of Hsp90 represents a therapeutic opportunity to decrease hyperphosphorylated tau species through disruption of tau kinase activities[148]. Second, Hsp90 influences the stability of hyperphosphorylated tau through interactions with Cdc37, a co-chaperone that co-localizes and interacts directly with tau and tau kinases in neuronal cells. It has been shown that Cdc37 knockdown in HeLa cells significantly alters the phosphorylation state of tau due to the reduced stability of tau kinases[149]. Lastly, Hsp90 appears to regulate the phosphorylation status of tau through interactions with a number of cellular phosphatases. In particular, two Hsp90 co-chaperones have been shown to dephosphorylate tau, PP5 and CacyBP/SIP[150–152]. A recent study found the levels of CacyBP/SIP to be significantly increased in regions of the brain that are implicated in several neurodegenerative diseases[153]. Another study suggested that impaired PP5 activity also contributes to tau hyperphosphorylation in AD brains[150]. Therefore, small molecules that modulate interactions between Hsp90 and these co-chaperones to regulate tau phosphorylation may also represent a therapeutic option to treat patients with AD or other tauopathies.

Small molecules that target Hsp90 and exploit its modulation of the UPS may also be therapeutically useful. The administration of geldanamycin has been shown to inhibit huntingtin protein aggregation in cellular models of Huntington's disease[154] and rescue dopaminergic neurons from degeneration in *Drosophila* models of Parkinson's disease[155], presumably through mechanisms involving the UPS. Hsp90 inhibition has also been shown to promote the proteasomal clearance of Htt[126], suggesting that Hsp90 inhibition may be a therapeutic strategy to reduce the mutant Htt accumulation in Huntington's disease.

Small molecule modulators of Hsp90 have demonstrated promising activities in *in vivo* models of central neuropathies as well. For instance, one CNS-permeable Hsp90 inhibitor, OS47720, was found to promote dendritic spine formation and rescue spatial learning and memory in a Tg2576 mouse model of Alzheimer's disease via an HSF1-dependent mechanism[156]. More recently, a vaccine consisting of Grp94 and α-synuclein was shown to suppress PD-associated microgliosis in the substantia nigra and striatum in a chronic MPTP murine model of PD[157], suggesting that formulations consisting of disease-related misfolded proteins and Hsps – specifically, isoforms of Hsp90 – may be beneficial for the treatment of central neuropathies that involve misfolded proteins. Lastly, the compound PU-AD, an orally administered brain-penetrable inhibitor of Hsp90 epichaperomes discovered by the Chiosis laboratory, is being advanced by Samus Therapeutics to Phase 1 clinical evaluation in Alzheimer's disease. In preclinical studies, PU-AD promoted neuronal survival by preventing the aggregation and hyperphosphorylation of tau, while stimulating its degradation[158].

Aha1 as a Therapeutic Target for CNS Neuropathies

Disruption of the Aha1/Hsp90 complex has emerged as an alternative therapeutic strategy and may provide an additional opportunity to overcome the poor blood-brain barrier

permeability and toxicities associated with direct inhibitors of Hsp90 and Hsp70. Shelton et al. were the first to demonstrate that disruption of the Aha1/Hsp90 complex with small molecules can dramatically reduce tau fibril seeding and formation of insoluble tau species both *in vitro* and in cultured cells[120]. Importantly, the molecules were shown to manifest neuroprotective activity without inhibition of the Hsp90-mediated refolding process. Such data provides evidence that strategic disruption of the interaction between Hsp90 and Aha1 can reduce tau accumulation without affecting Hsp90's ability to fold other client proteins. Therefore, inhibition of the Aha1/Hsp90 complex represents a promising therapeutic strategy for the development of small molecules to treat AD and other tauopathies.

A select number of small molecule Aha1/Hsp90 disruptors have been discovered to date (Figure 9). In the aforementioned study, KU-177 demonstrated the ability to disrupt interactions between Hsp90 and Aha1 in co-immunoprecipitation experiments and ablated Aha1-driven enhancement of Hsp90-dependent tau aggregation[120]. Using a FRET-based screen, Stiegler and coworkers identified another small molecule, HAM-1, that disrupts the Aha1/Hsp90 complex and selectively inhibits Aha1-stimulated ATPase activity of Hsp90, but not Hsp90's basal ATPase activity in the absence of Aha1[159]. In contrast to the well-characterized interaction site between the N-terminal domain of Aha1 and middle domain of Hsp90[75], NMR studies revealed that HAM-1 binds the Hsp90 N-terminus at a site that serves as a transient Aha1 C-terminal domain interaction site. This second interaction site is in close proximity to Hsp90's ATP-binding site and the interaction between the two proteins at this site is transient only enough to allow for stabilization of a rate-limiting, closed state of the Hsp90 ATPase cycle[160,161].

Two other Aha1/Hsp90 complex disruptors, A12 and A16, were identified by amplified luminescence proximity homogeneous assays (Alpha)[162]. Both of these compounds restored chloride channel activity in cells expressing mutant cystic fibrosis transmembrane conductance regulator (CFTR) protein and may be further developed to treat cystic fibrosis, as Aha1 appears to play a disruptive role in CFTRΔ508 degradation during cystic fibrosis pathology[163,164]. A quinaldine red ATPase assay was used to identify one final compound, SEW04784 that binds to the C-terminal domain of Aha1 and disrupts its interaction with Hsp90[165]. This compound inhibits the Aha1-stimulated ATPase activity of Hsp90, but not Hsp90's basal ATPase activity.

HSR Induction and Hsp70 as Therapeutic Targets for CNS Neuropathies

Markers of HSR induction, including increased expression of Hsp70, have been found to accumulate in plaques and neurofibrillary tangles, and have been detected in the brains of patients with AD[166,167]. Interestingly, Hsp70 appears to combat the early stages of AD pathogenesis, as preparations of recombinant Hsp70, its co-chaperone Hsp40, and Hsp90 can block the assembly of amyloid-β oligomers, although these preparations exhibited little effect during amyloid-β fibrillar assembly[168]. In the same study, researchers discovered that the anti-aggregation activity of Hsp70 could be enhanced by pharmacological stimulation of Hsp70 or conversely, inhibited by $ATP_{\gamma}S$, a non-hydrolyzable ATP analog.

In PD, Hsp70, Hsp90, Hsp60, Hsp40, and Hsp27 have been detected in Lewy bodies extracted from patients with cortical Lewy body disease[169]. It is believed that the sequestration of these molecular chaperones into Lewy bodies results in their cellular depletion, and the subsequent loss of chaperone activity may lead to degeneration[155]. In agreement with this hypothesis, HSR induction and subsequent elevations in Hsp70 levels protected against α-synuclein-induced cell death in a yeast model of PD[170] and prevented cell death in the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) model of PD[171,172]. The exact role played by Hsp70 in PD – in particular, its contributions to α-synuclein-induced toxicity – remains unclear. However, it has been shown that Hsp70 binds α-synuclein filaments to mediate their inhibitory effects on the proteasome[173]. Hsp70 has also been shown to bind prefibrillar α-synuclein species and prevent key steps of α-synuclein aggregation[174]. It is clear that stimulation of Hsp70 manifests neuroprotective activity against α-synuclein-associated toxicity, which is supported by the fact that the expression of Hsp70 reduces aggregate formation and toxicity that is induced by C-terminally truncated forms of α-synuclein in cells. Furthermore, Hsp70 overexpression that results upon crossing human α-synuclein transgenic mice with transgenic mice overexpressing rat Hsp70 resulted in a significant reduction of insoluble α-synuclein aggregates[175]. In summary, agents whose activities result in HSR induction, enhancement (or restore) Hsp70 expression, and/or stimulation of chaperone activity are being actively pursued for their ability to protect neurons against toxicities associated with misfolded proteins in both AD and PD.

Outlook

Heat shock proteins (Hsps) are evolutionarily conserved proteins that play a critical role in cells by “chaperoning” newly formed polypeptides as well as minimizing protein aggregation through the refolding of denatured proteins or regulating their degradation through the UPS or CMA. While Hsps maintain cellular homeostasis in normal cells, they form distinct “epichaperome” complexes in diseased cells. In fact, their abnormal function or expression level (elevation or downregulation) can be observed in many pathological conditions, including both peripheral and central neuropathies. In this review, the biological roles played by the heat shock proteins during the pathology of such diseases as well as the therapeutic potential that small molecule inhibitors and/or modulators of heat shock proteins exhibit for the treatment of these diseases is summarized. Hsp regulation continues to be an active and compelling area of research, and may offer therapeutic opportunities to treat additional neuropathies in the future.

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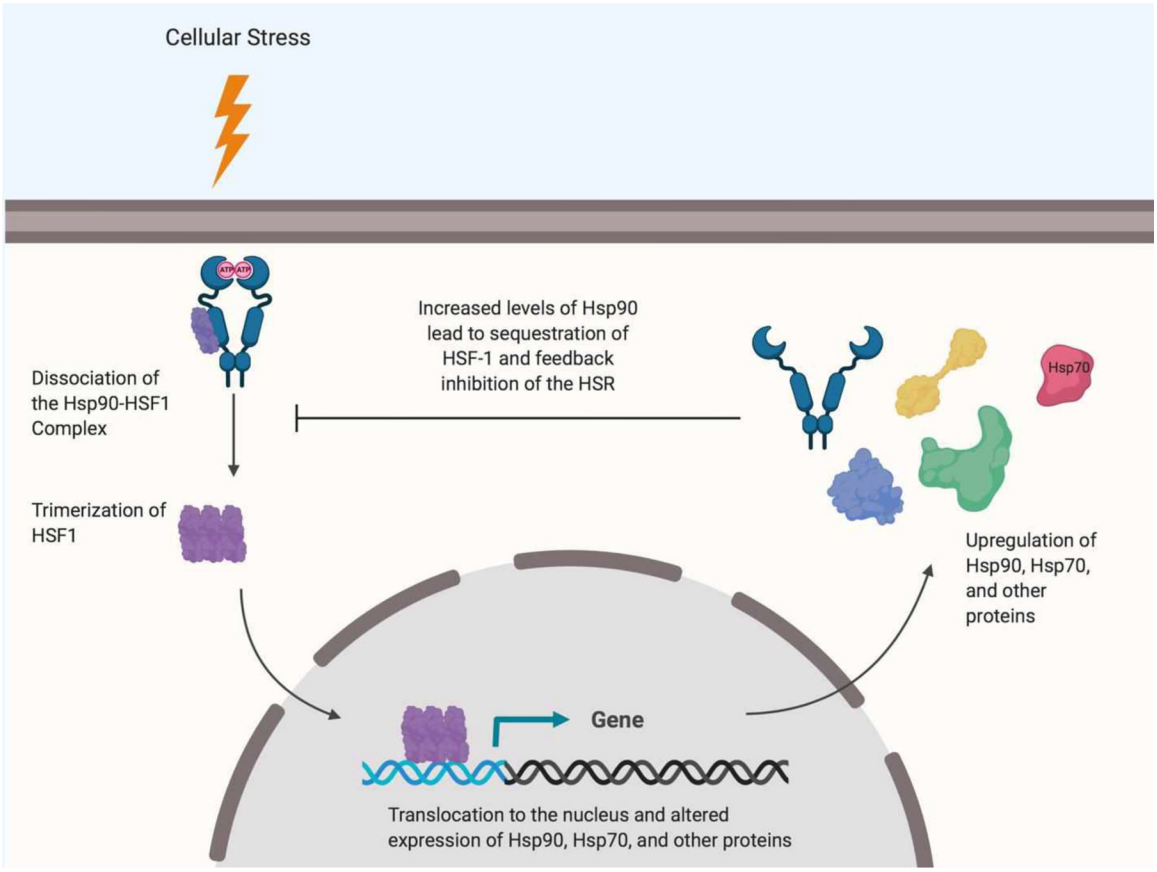

Figure 1.
Mechanism of HSF-1-mediated transcriptional activation

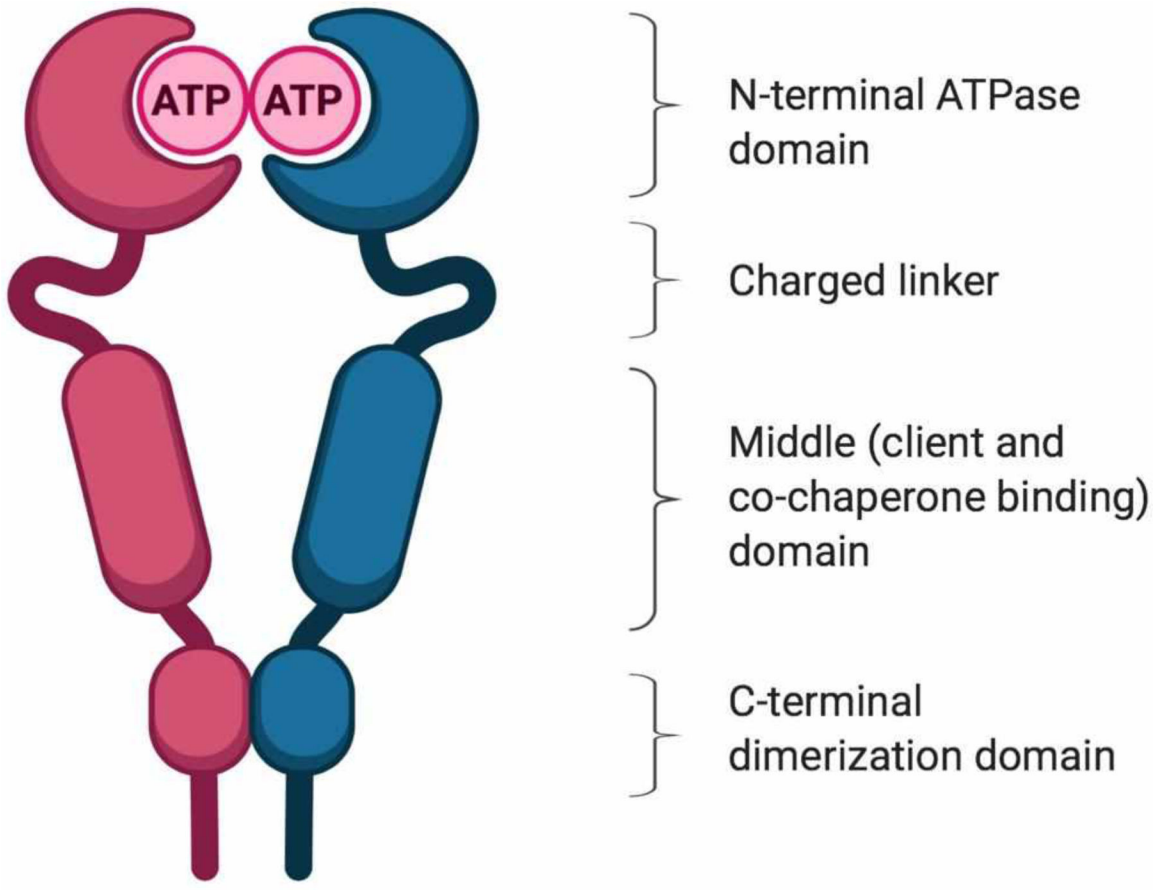

Figure 2.
Structure of the Hsp90 homodimer

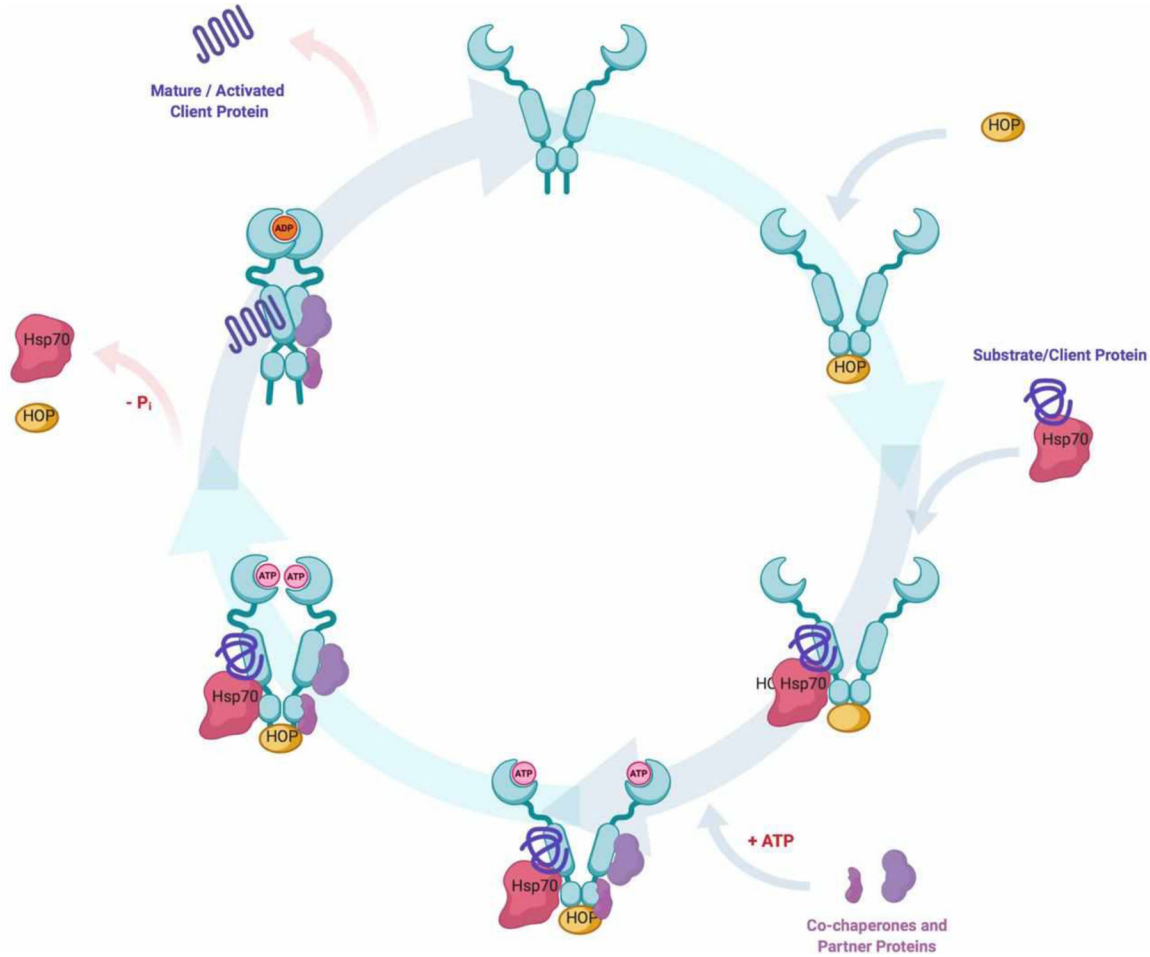

Figure 3.
The Hsp90 ATPase/protein folding cycle

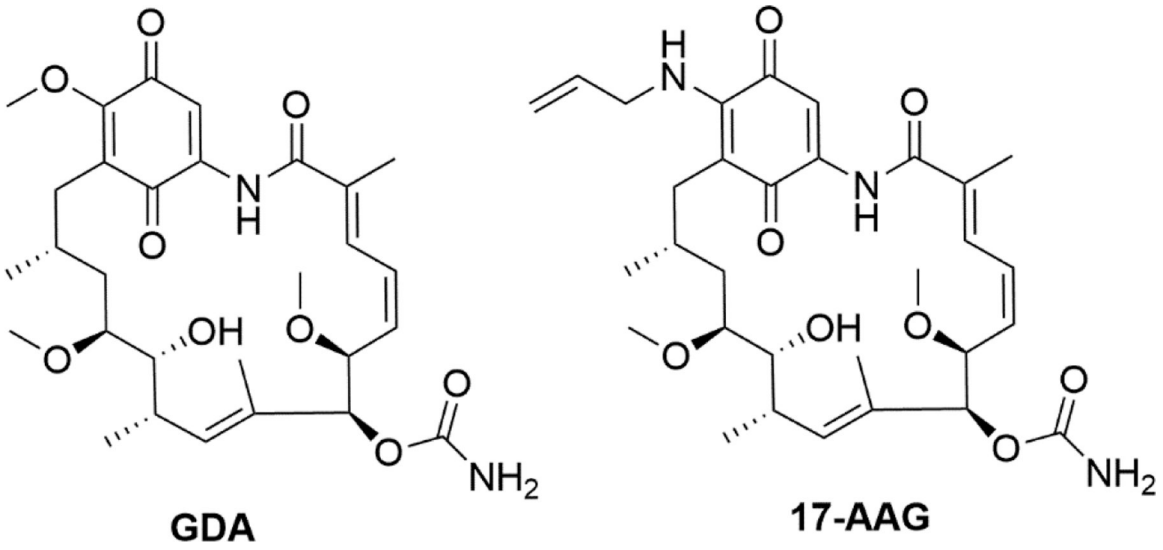

Figure 4.
Structures of select N-terminal Hsp90 inhibitors

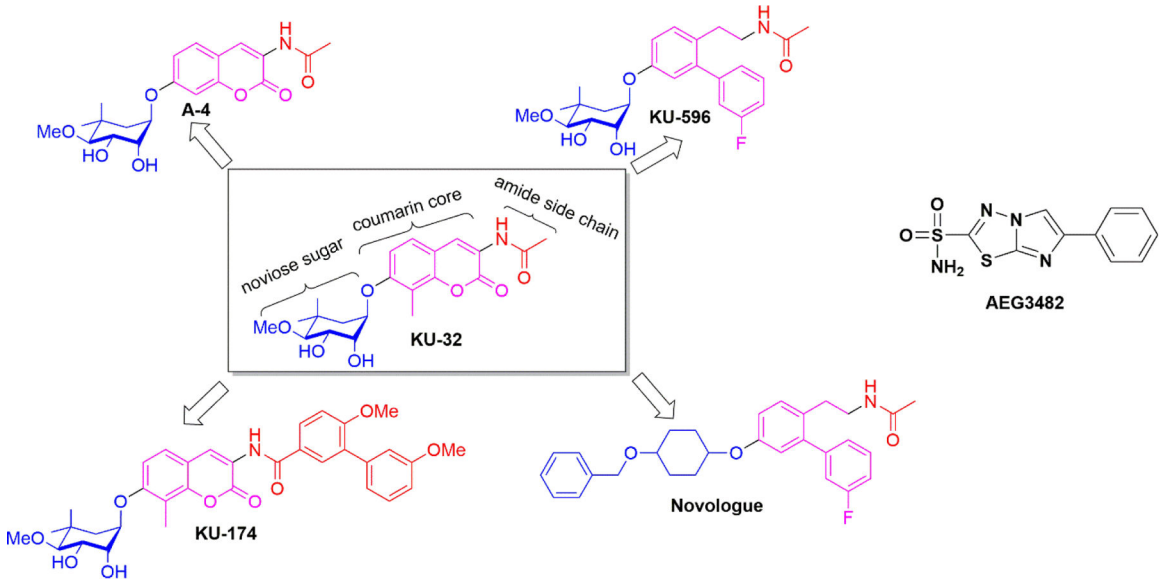

Figure 5.
Structures of select C-terminal Hsp90 inhibitors

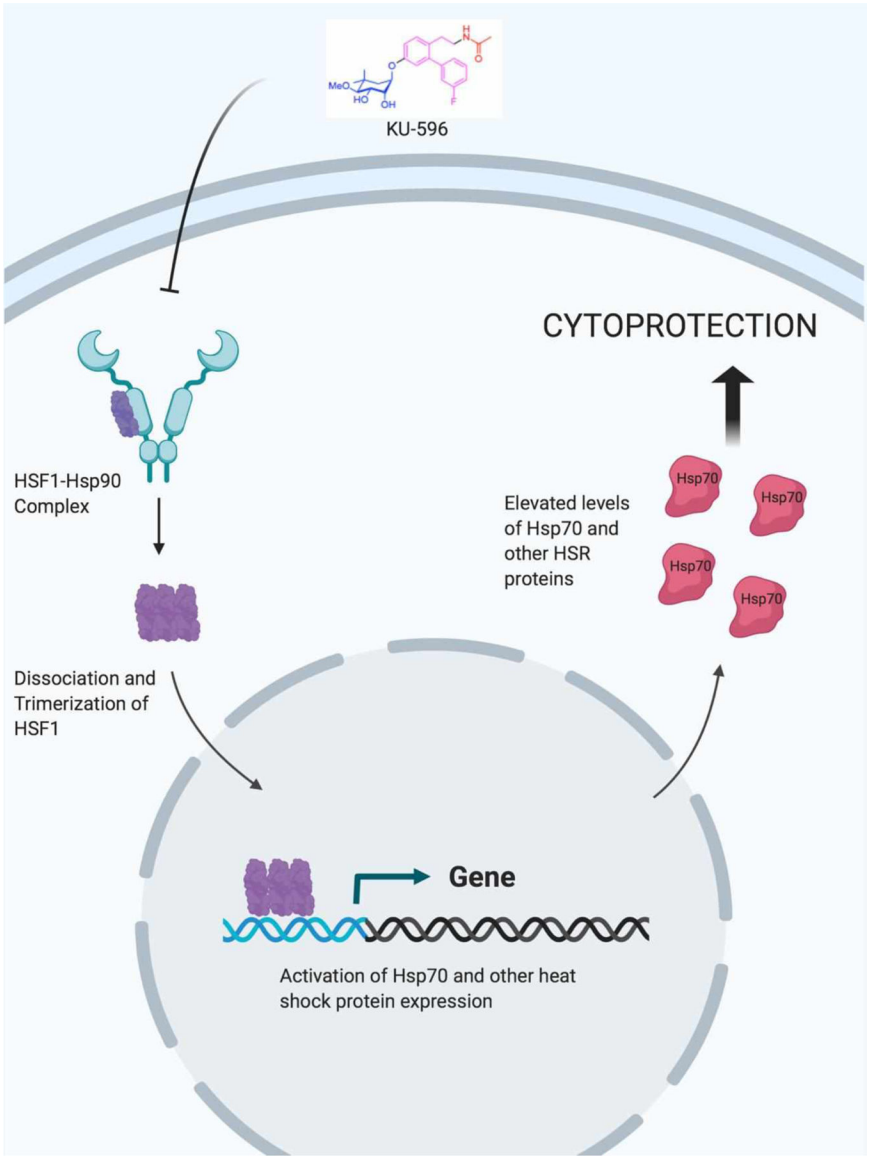

Figure 6.
Mechanism of cytoprotection afforded by KU-596 elicitation of the HSR

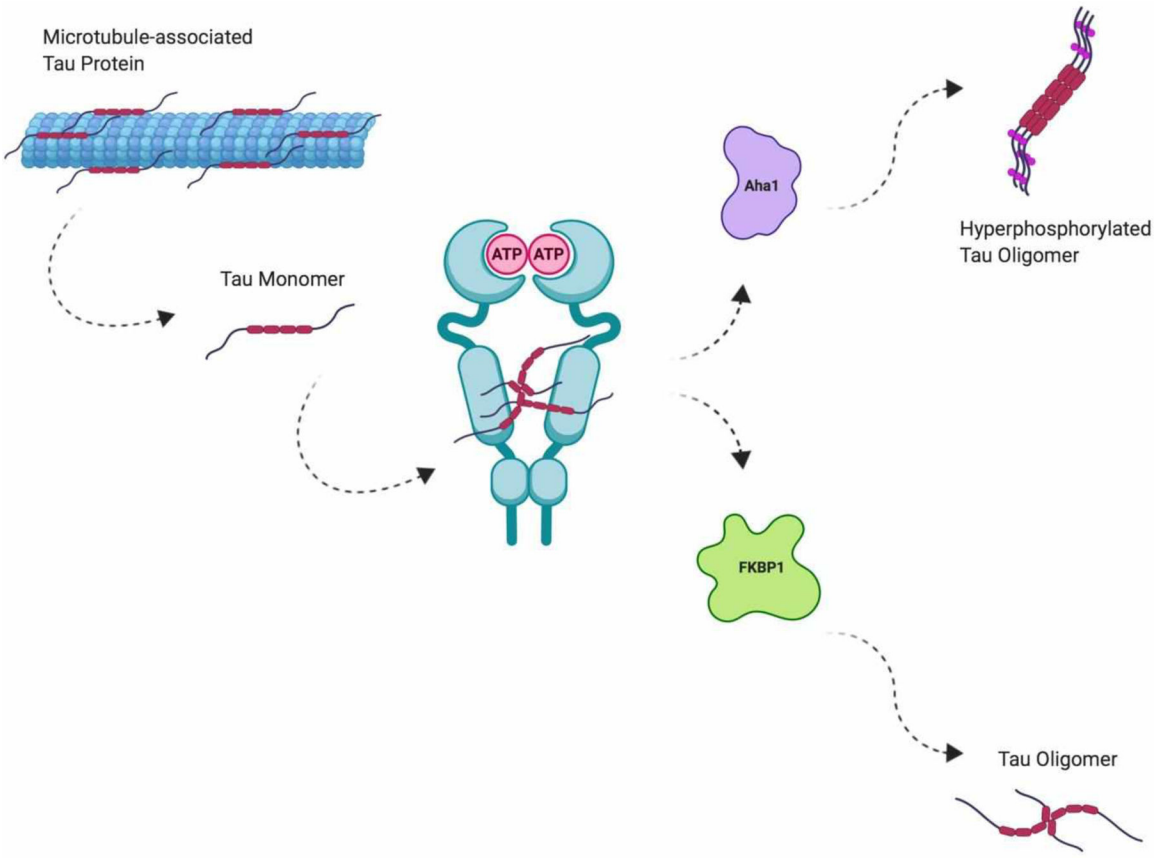

Figure 7.
Hsp90-mediated tau oligomerization

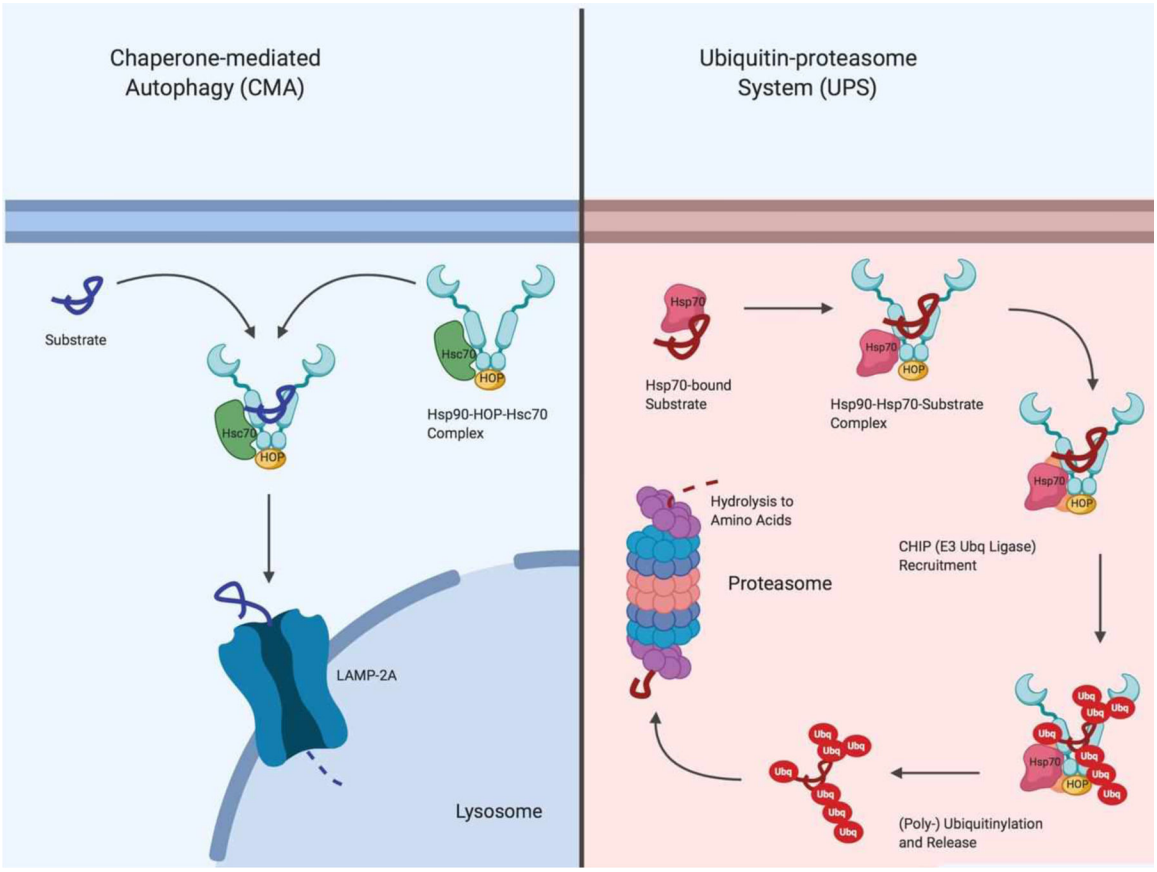

Figure 8.

Chaperone-mediated autophagy versus the ubiquitin-proteasome system for degradation of protein substrates

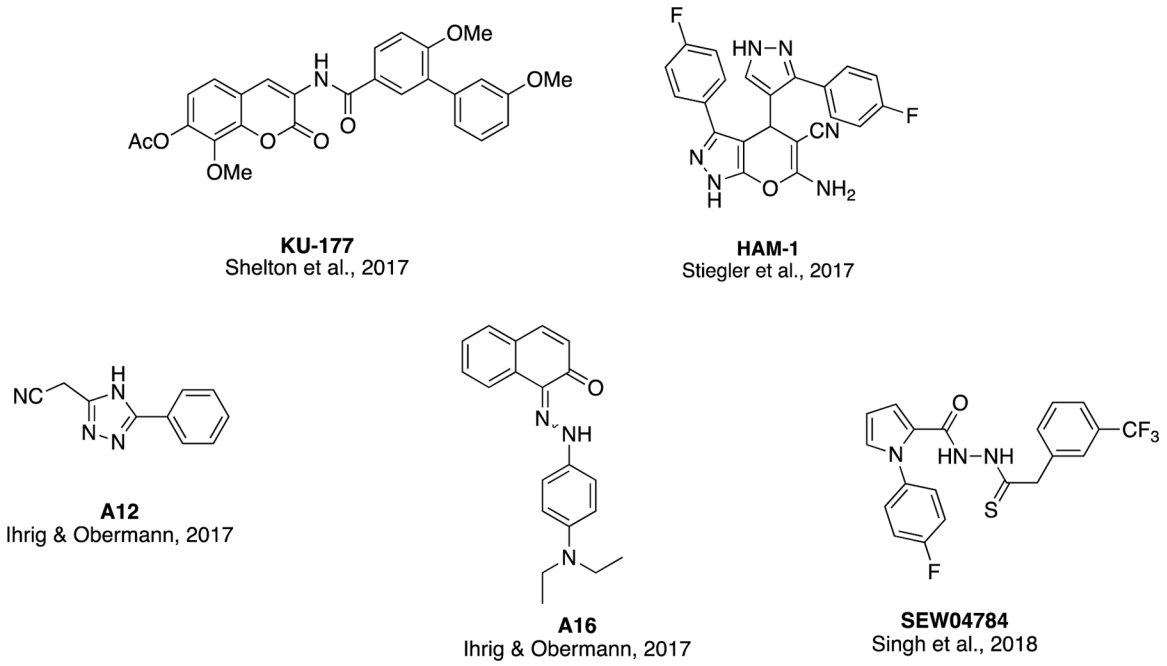

Figure 9.
Structures of select Aha1/Hsp90 disruptors