Chapter 14
Role of Heat Shock Protein 90 in the Cause of Various Diseases: A Potential Therapeutic Target

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Abstract Different classes of Heat shock proteins (HSP) play a diverse role in influencing proper assembly, folding, and translocation of cellular proteins. HSP90 is one such kind of molecular chaperone which has been implicated the formation of number of diseases like cancer and various kinds of neurodegenerations. The chaperone, HSP90 assists in folding, maturation and maintains the functional stability of many proteins that includes many oncoproteins like p53 as well as neuronal proteins like tau. It also regulates transcription factors including Heat shock factor-1 (HSF-1). In addition to its well characterized functions in malignancy, recent evidence from several laboratories suggests a role for HSP90 in maintaining the functional stability of neuronal proteins of aberrant capacity, whether mutated or over-activated, allowing and sustaining the accumulation of toxic aggregates. Preclinical studies have demonstrated that disruption of much client proteins chaperoned by HSP90 is a possible strategy to reduce tumorigenesis but could suppress many neurodegeneration both in vivo and in vitro. Thus, inhibition of HSP90 has been found to be a novel strategy to target such diseases and pave the novel way of battling with these lethal diseases.

Keywords Heat shock proteins • HSP90 • Cancer • Neurodegenerations • HSP90-inhibitors • Geldanamycin

Abbreviations

17-AAG	17-allylamino-17-demethoxygeldanamycin
17-DMAG	17-(Dimethylaminoethylamino)-17-demethoxygeldanamycin
AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
AR	Androgen receptor

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CTD	C-terminal domain
EGFR	Epidermal growth factor receptor
GA	Geldanamycin
HD	Huntington's disease
HIF	Hypoxia-inducible factor
HSF-1	Heat shock factor-1
HSP	Heat shock protein
HSR	Heat stress response
HTS	High throughput screening
NTD	N-terminal domain
PD	Parkinson's disease
polyQ	Polyglutamine diseases
SBMA	Spinal and bulbar muscular atrophy
SCA	Spinocerebeller ataxia
UPS	Ubiquitin–proteasome system

14.1 Introduction

Molecular chaperones, commonly known as heat shock proteins (HSP) serve as multifunctional molecules and their role includes assist in the folding of cellular proteins, intracellular disposition, and proteolytic turnover of many key regulators of cell growth, differentiation, and survival. HSP normally assist proteins in maintaining a conformation that allows appropriate folding, recognition, and modification by the ubiquitination systems or hydrolysis by the proteasome [1, 2]. HSP ensure that these proteins maintain their native conformations during stressed condition [2]. HSP comprise of several highly conserved families of related proteins. They prevent misfolding, aggregation of proteins and facilitate to achieving a correct conformation of a nonnative protein, often through an ATP-dependent manner. HSP typically recognize and bind to the exposed hydrophobic residues of non-native proteins through non-covalent interaction [3].

Mammalian HSP have been classified mainly in four families according to their molecular weight: HSP90, HSP70, HSP60 and small HSP (15–30 kDa) that include HSP27. HSP are expressed either constitutively or regulated inductively, and are present in different subcellular compartments. Large HSP (HSP60, HSP70, etc.) are ATP-dependent chaperones whereas small HSP (like HSP27) function in an ATP-independent fashion. Based on various research reports, it has been observed that HSP specifically recognize and bind to the exposed hydrophobic patches or residues of unfolded/partially folded (non-native) proteins, through hydrophobic interaction [1]. In addition, HSP are required for protein trafficking to target organelles and to facilitate the transfer of misfolded proteins to the proteasome for degradation [4]. HSP can be induced by various stresses such as heat shock, ischemia, hypoxia, heavy metals, and amino acid analogs [4]. Some HSP are expressed constitutively in unstressed cells [5].

Although various HSP have different mechanism of action, in the present chapter we will only focus on HSP90 and its role in various diseases and its use as therapeutic approach in such diseases. HSP90 has been reported in many studies as responsible agent for the cause of tumorigenesis and cancers [6]. Its role in cancer has received much attention in the last decade since HSP90 has been found to assist number of proteins (called 'client proteins') includes many oncogenic proteins in their folding, maturation, transportation, etc. In many cases such as breast cancer, HSP90 was found to be overexpressed along with its clients like p53.

Since number of neuronal proteins is also the clients of HSP90 (like 'tau' protein), it has also been implicated with various neurodegeneration like Alzheimer's disease [7], etc. In cells, the combined functions of molecular chaperones like HSP, the UPS (ubiquitin–proteasome system) and lysosome-mediated degradation pathway are normally sufficient to prevent the accumulation of misfolded proteins in cells. However, under certain pathological circumstances, the protein quality control machinery is overloaded and misfolded proteins can accumulate to a dangerous level. AD, PD, Prion disease and the polyglutamine (polyQ) disease are all characterized by the accumulation of this kind of proteins, mutations of which cause misfolding and subsequent aggregation leading to severe, inherited forms of diseases.

Inhibition of HSP90 has been reported to be the recommended strategy to find therapeutic avenue in these diseases and hence, several selective HSP90 inhibitors have been discovered and are currently undergoing clinical evaluation. Much of the recent progress in understanding the complex role of heat shock proteins in tumorigenesis has been made possible by the discovery of several natural product antitumor antibiotics like geldanamycin and their analogues that selectively inhibit the function of the chaperone HSP90. These agents have been used as probes to define the biological functions of HSP90 at the molecular level and to validate it as a novel target for anticancer drug action.

This chapter focuses on the role of HSP90 in the cause of these diseases like cancer and neurodegenerations. We also discuss here the potential use of HSP90 inhibitors in clinical areas as therapeutic agents.

14.2 Cellular Heat Shock Proteins 90 (HSP90)

HSP90 is a highly abundant and ubiquitous molecular chaperone (approximately 1–2 % of total protein present in the cytosol) which plays an essential role in many cellular processes including cell cycle control, cell survival, hormone and other signaling pathways [6]. HSP90 is an ATP-dependent molecular chaperone which is essential in eukaryotes. It is required for the activation and stabilization of a wide variety of client proteins and many of them are involved in important cellular pathway. In the last one decade, it has become a major therapeutic target for various diseases like cancers and in various neurodegenerative disorders. The structure of HSP90 consists of three domains i.e., the N-terminal domain, the middle-domain and the C terminal domain [8]. These domains are composed of nearly 732 amino acids [8]. HSP90 has two isomers HSP90α and

HSP90β, which are mainly present in the cytosol [9]. The N–terminal domain is an amino terminal domain and contains a fold known as bergerat fold, which possesses the ATP and drug-binding site [10]. The middle domain possesses a co-chaperone interacting motif, which provides binding sites for client proteins and co-chaperones. These binding sites play an important role in forming the active ATPase [8]. The C-terminal domain is the carboxy terminal domain, which possesses a dimerization motif. This is known as the second drug-binding site and the site where HSP90 also interacts with the other co-chaperones [8]. Dimerization of HSP90α monomer mediated through C-terminal, which is essential for its chaperoning function [11]. After dimerization, HSP90 binds to ATP in its open state facilitating the attachment of co-chaperones and client protein binding. The closed conformation is mediated by ATP hydrolysis [8] (Fig. 14.1).

14.3 Functions of HSP90 in Various Biological Processes

HSP90 is one of the most abundant cellular chaperone proteins comprising up to 1–2 % of total cellular protein and increases to 4–6 % of cellular proteins under stress. It increases by twofold to tenfold during environmental stress and this up-regulation could be explained as a part of the protective mechanisms that enhance cell survival [13]. HSP90 exerts essential housekeeping functions as a molecular chaperone, such as facilitating protein refolding, translocation of proteins between cellular compartments, suppression of protein aggregation, supporting functional maturation of signaling proteins and facilitating normal protein turnover [6]. It functions in a multi-component complex of chaperone proteins that may include p60/Hop, p50Cdc37, HSP40/HDJ2, p23, HSP70 and one of a variety immunophilins [14]. Unlike other chaperones, HSP90 distinguishes itself in that most of its known clients are protein kinases or transcription factors involved in signal transduction [14].

14.4 HSP90 Client Proteins and Diseases

More than ‘200’ client proteins covering almost all cellular processes have been identified so far (http://www.picard.ch/downloads/Hsp90interactors.pdf). Many of these client proteins are intimately associated in critical cellular functions that promote cell growth, proliferation and cell survival. A significant number of cancer associated proteins have been identified as HSP90 client proteins which includes apoptotic mediators (Bcl-2, Apaf-1), cell cycle regulatory proteins (CDK4, hTERT), tumor suppressors genes (p53), mediators of tissue invasion and metastatics (MMP2), transportation factors (HSF-1, HIF-1), signaling molecules (AKT, RAF-1), steroid hormones (androgen, progesterone, glucocorticoid receptors).

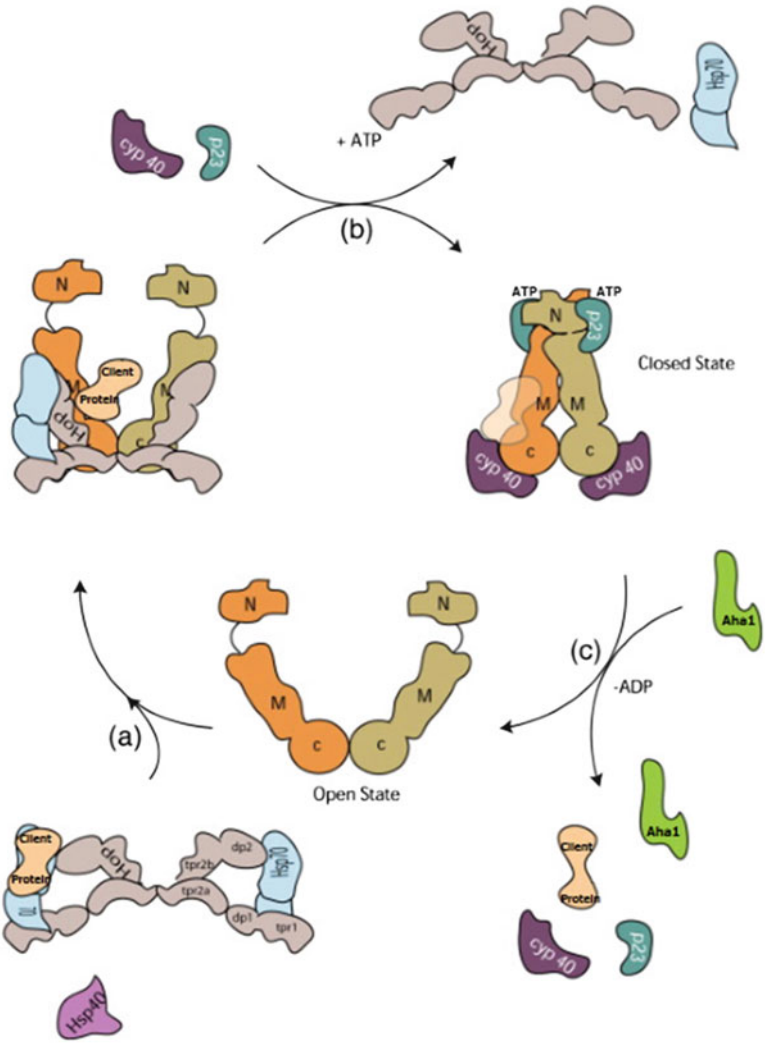

Fig. 14.1 Model of the conformational cycle of HSP90 (Adapted from [12])

Moreover, recent findings have revealed that HSP90 assist in the stability of many neuronal aberrant proteins, and thus it favors the process of accumulation of toxic protein aggregates [7, 15]. For example, in AD, in addition to β-amyloid aggregation, it has been found that there is an accumulation of abnormal species of hyperphosphorylated protein tau, which leads to the formation of toxic neurofibrillary tangles [7, 15]. This hyperphosphorylation is caused by abnormal kinases like CdK4, GSK-3β activities and the stability of function of them is maintained by HSP90 [16, 17]. Experiments suggest a role for HSP90 in maintaining the functional

stability of neuronal proteins, which are aberrant in nature, whether mutated or over-activated [18]. These phenomena results in the accumulation of toxic aggregates.

HSP90 functions by recruiting many co-chaperones viz, Cdc37, Hop, p23, HSP70 and HSP40 [19]. The complex formation is an energy requiring step and involves sequential ATPase cycles [20]. Client proteins of HSP90 are several kinases viz, AKT, B-Raf mutant, MET and CDK4; Transcriptional factors HIF-1A, ERA-receptors mutant p53th regulates cell proliferation and survival and chimeric fusion proteins [21].

14.5 HSP90 and Cancer Development

HSP90 is a molecular chaperone [22] that participates in the quality control of protein folding. More than 200 client proteins covering almost all cellular processes have been identified so far. It is involved in the maturation and stabilization of a wide range of oncogenic client proteins which are crucial for oncogenesis and malignant progression [23]. Indeed the cancer cells are particularly dependent on proper HSP90 function [24, 25]. Many of these client proteins such as p53, BCR-ABL, HER2, epidermal growth factor receptor (EGFR), CRAF, BRAF, AKT, MET, VEGFR, FLT3, androgen and estrogen receptors, hypoxia-inducible factor (HIF-1α), and telomerase are involved in critical cellular functions that promote cell growth, proliferation and cell survival. Many of these client proteins are mutated and/or overexpressed in cancers [26]. Moreover, the harsh environmental conditions found in tumors such as hypoxia, low pH, and bad nutritional status may tend to destabilize proteins, making them even more dependent on HSP90 activity [23, 27, 28].

It has also been observed that HSP90 is constitutively expressed at manifold levels in tumor cells compared to their normal counterparts [29, 30], suggesting that HSP90 is critically important for tumor cell growth and and/or survival and its inhibition would help to check the proliferation of cancer cells. Inhibition of HSP90 causes client protein degradation via the ubiquitin-proteasome pathway, and is a mechanism that might simultaneously down-regulate several redundant pathways crucial for cell viability and tumor development.

Therefore, in many cancers such as non-small cell lung cancer, oesophageal squamous cell carcinoma, pancreatic carcinoma and advanced malignant melanoma the over-expression of HSP90 has been observed [31–34]. In addition, studies showed that HSP90 stabilizes various key oncogenic proteins such as survivin, Akt, Erb-2 and HIF-1α in cancer cells [35–37].

Cancer cells are stressed cells and heavily depend on HSP90 chaperoning and thus show higher levels of expression of HSP90, therefore HSP90 has emerged as a target for cancer therapy [38]. Many drugs targeting ATP binding domain have been developed and are under clinical trials. Geldanamycin a prototype example of ansanamycins antibiotic showed exciting results disrupting multiple pathways but was toxic to normal cells and hence could not enter clinical trials [39].

Analogues of geldanamycin, 17-AAG and 17-DMAG were designed which was non toxic to human cells. HSP90 inhibitors found in literatures have mostly been discovered by structure based virtual screening, generating derivatives from already existing inhibitors or finding new scaffolds by HTS [40]. Recently Shepherdin, a novel anticancer agent was designed based on the interaction between HSP90 and surviving [41]. Survivin is a mitotic regulator and antiapoptotic protein involved in many pathways [42]. The structure of shepherdin was based on modelled interface between HSP90 and survivin.

14.6 HSP90 in Neurodegeneration

In addition to its well-characterized functions in malignancy, recent evidence from several laboratories suggests a role for HSP90 in maintaining the functional stability of neuronal proteins of aberrant capacity, whether mutated or over-activated, allowing and sustaining the accumulation of toxic aggregates. One such example is tau protein responsible in the cause of Alzheimer's disease [43]. In addition, HSP90 regulates the activity of the transcription factor heat shock factor-1 (HSF-1), the master regulator of the heat shock response, mechanism that cells use for protection when exposed to conditions of stress.

Recent evidences revealed a very crucial role for HSP90 in neurodegeneration. Many of the client proteins of HSP90 have been found the central cause of neurodegeneration. HSP90 maintains the functional stability of such neuronal proteins of aberrant capacity, thus, allowing and sustaining the accumulation of toxic aggregates [18, 44, 45]. Recent findings have also revealed that HSP90 assists in the stability of many neuronal aberrant proteins, and thus it favors the process of accumulation of toxic protein aggregates [18, 44, 45]. For example, in AD, in addition to β-amyloid aggregation, it has been found that there is an accumulation of abnormal species of hyperphosphorylated protein tau, which leads to the formation of toxic NFT [7, 17]. This hyperphosphorylation is caused by abnormal kinases like CdK4, GSK-3b activities, and the stability of function of them is maintained by HSP90 [17].

14.7 HSP90 Inhibitors Targeting Co-Chaperone/HSP90 Interactions

For the proper functioning of HSP90, a series of co-chaperones are required. Binding and leaving of the co-chaperones at various stages provide regulatory control to the chaperoning process of HSP90 [46]. Therefore, blocking the chaperone cycle at these stages by targeting different co-chaperone/HSP90 interactions is likely to achieve similar results with the direct inhibition of HSP90 [47]. Various co-chaperones targeted so far are cdc37/HSP90, HSP70/HSP90, HOP/HSP90 and Aha1/HSP90 [12, 48–50].

14.8 HSP90 Inhibitors as Cancer Chemotherapeutics

HSP90 plays an important role in the maintenance of multiple oncogenic pathways, and is essential for maintaining folding, stability, and conformation of several oncoproteins to help retain aberrant activity and sustain the malignant state [51]. Although directed toward a single molecular target, HSP90 inhibitors simultaneously block multiple signaling pathways implicated and are essential to maintain folding, stability and conformation of several oncoproteins to help retain aberrant activity and sustain the malignant state [52]. Because many of its clients include oncoproteins with important functions in the development and promotion of cancer, HSP90 is an important target in cancer therapy. Thus, HSP90 inhibition has been a promising strategy for targeting cancer therapy.

Small molecule HSP90, inhibitors bind to the ATP binding pocket and cause the catalytic cycle arrest of HSP90, in the ADP bound conformation, leading to the inactivation of chaperone activity, premature ubiquitination and proteasomal degradation of the client proteins [53]. This results in depletion of oncoproteins, cell cycle arrest and apoptosis [54]. Inhibition of HSP90 function has already been proved effective in killing cancer cells that developed resistance to kinase inhibitors [55]. One of the key inhibitors used for HSP90, inhibition is Geldanamycin (GA). Despite its potent anti-tumor effects, GA was never evaluated in clinical trials because of its poor "drug-like" properties including poor solubility, limited in vivo stability and significant hepatotoxicity in animals [56] and [57].

After the failure of GA in the clinical trials, research was more focused on its more water-soluble derivatives like 17-AAG. 17-AAG (17-N-Allylamino-17-demethoxygeldanamycin) has shown less toxicity but it shows less affinity for HSP90 than GA [58]. It is poorly water soluble which affects its formulation development during clinical trials [59].

Another analogue of GA is 17-DMAG (17-Dimethylaminoethylamino-17-demethoxygeldanamycin); this was considered to be very effective but like others, this drug could not be used for a prolonged period and it also showed limited metabolism which resulted in problems associated with drug clearance [43]. To resolve the problems that are associated with NTD (N-terminal domain) inhibitors, various CTD (C-terminal domain) inhibitors have been developed. Till date, a variety of drugs which have been identified as the HSP90 CTD-inhibitors such as Novobiocin, Clorobiocin, EGCG, Derrubone, etc. binds at the ATP binding site of HSP90, CTD (Fig. 14.2) (Shumaila and Paul 2014). Hence, in the present investigation, we attempted to find the residues involved in the ATP binding site in CTD and a potential inhibitor which can block this ATP binding site in the C-Terminal domain.

Many evidences suggested that HSP90 in tumor cells has greater affinity for HSP90-inhibitors like 17-AAG than that found in normal cells. This difference may result from the bulk of HSP90 being tied up in multiprotein complexes in tumor cells, whereas a substantial pool of free dimers with low ATPase activity and low drug affinity exists in normal cells [29, 30, 60].

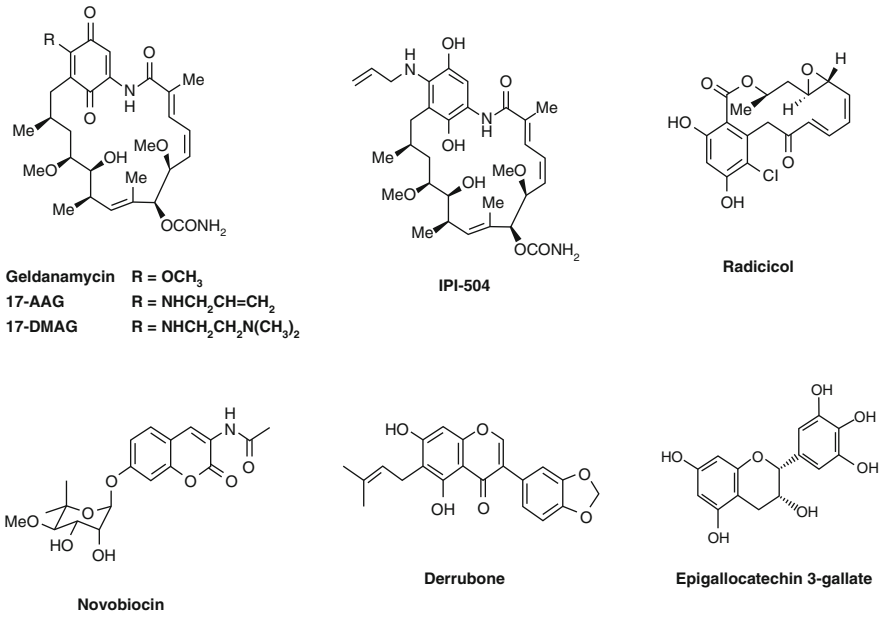

Fig. 14.2 Chemical structure of the naturally occurring HSP90 inhibitors (Adapted from [40])

Collectively, these findings implicate an important role for HSP90 in the development of Alzheimer's disease and other neurodegenerative diseases and suggest that HSP90-interfering drugs may represent a potential novel class of drugs to promote the survival of neurons. They also imply that, because of their specificity for high-affinity HSP90, small molecule HSP90 inhibitors may selectively target neurodegenerative disease processes without toxicity toward normal tissues.

14.9 HSP90-Inhibition: A Therapeutic Target in Neurodegeneration

It has been found that inhibition of HSP90 activates heat shock factor-1 (HSF-1), a transcriptional regulator of heat shock proteins, to induce the cellular expression of HSP70 and HSP40 and other molecular chaperonins, which in turn, trigger disaggregation of protein aggregates and protein degradation [61–63]. Moreover, direct inhibition of HSP90 function also facilitates mutant or aberrant protein degradation. These biological functions, therefore, propose HSP90 inhibition as dual therapeutic modality in neurodegenerative diseases. First, by suppressing aberrant neuronal activity, HSP90 inhibitors may ameliorate protein aggregation and its associated toxicity. Second, by activation of HSF-1 and the subsequent induction

Table 14.1 HSP90-inhibitors induce HSP70 expression and triggers neurodegenerative suppression [3]

HSP90-inhibitors	Disease
GA	AD, HD, PD
17-AAG	Spinal and bulbar muscular atrophy, PolyQ, SCA, HD
17-DMAG	HD, spinal and bulbar muscular atrophy
Celastrol	Polyglutamine disease, amyotrophic lateral sclerosis, AD
Herbimycins D−F	Proposed in neurodegeneration

of heat shock proteins, such as HSP70, HSP90 and thus the inhibitors may redirect neuronal aggregate formation, and protect against protein toxicity.

Moreover, there are various experimental findings which revealed that various HSP90-inhibitors when used in diseased cellular models the cellular expression level of HSP70 and HSP40 was increased by multi-folds. It was already observed that the overexpression of HSP70 and HSP40 suppressed various neurodegeneration conditions. Hence, inhibition of HSP90 using various inhibitors like Geldanamycin (GA), 17-allylamino-17-demethoxygeldanamycin (17-AAG), 17-(Dimethylaminoethylamino)-17-demethoxygeldanamycin (17-DMAG), radicicol, novobiocin, etc. (see the structures in Fig. 14.2) have been used to inhibit of protein aggregation progress. A list of the inhibitors name and working system of HSP90-inhibitors in various neurodegeneration was given in tabular form in Table 14.1. Moreover, it is worthy to mention that Kitson and his group recently reported the synthesis of 19 GA substitute HSP90 inhibitors which exhibited much less toxicity and when tested in human breast cancer and dopaminergic neural cells, they demonstrated them to act as potential therapeutic agent against both cancer and dopaminergic cells [64].

Protective effects of GA in a Drosophila model and in a mouse model of Parkinson's disease (PD) was observed [65, 66]. Few studies also proved that 17-AAG increased the degradation of androgen in SBMA mouse model and in a familial model of ALS [44, 67, 68]. 17-AAG treatment successfully suppressed neurodegeneration in a Drosophila model of SCA3 and Huntington's disease (HD), and it was found to be the most effective agent among the other HSF1-activating compounds in suppressing polyQ-related neurodegeneration in Drosophila model [69]. In the SBMA model system, 17-DMAG, and 17-AAG, preferentially caused HSP90 client protein degradation and upregulation of HSP70 and HSP40 [68]. In another study, 17-DMAG was found modulated the AR-HSP90 chaperone complex from a mature stabilizing form to a proteasome-targeting along with Hop [70]. Celastrol, a drug exhibited inhibition the interaction of HSP90 with its cochaperone cdc37 and also caused induction of HSP, moreover, in another study, it was shown that Celastrol could provide neuroprotection against polyglutamine toxicity, both in vivo and in vitro [71–73]. They were also found to reduce the β-amyloid amount in a transgenic mouse model of AD and HD [73, 74].

Sittler and colleagues reported for the first time that GA reduced the aggregation of mutant huntingtin protein by inducing molecular chaperones in cell culture [75]. The mechanism was that GA caused disruption of the complex between HSP90 and HSF1, the master stress-inducible regulator, which activates the heat stress response (HSR) in mammalian cells. Treatment with GA upregulated HSP70 and HSP40 expression and resulted in inhibition of huntingtin aggregation in a cell-culture model of HD and in a primary culture model of familial amyotrophic lateral sclerosis (ALS) [75, 76]. GA is also responsible for modulating α-synuclein pathology and its solubility and it was also found to decrease α-synuclein aggregation in neuroglioma-transfected cells and protects them against toxicity [77].

It was recently reported by Waza et al. that in SBMA model, one of the polyQ diseases, the administration of 17-AAG significantly ameliorated polyQ-mediated motor neuron degeneration by reducing the total amount of mutant androgen receptor (AR) [44]. 17-AAG accomplished the preferential reduction of mutant AR mainly by inhibiting HSP90 function. It was also proposed from experimental findings that 17-AAG induces the up-regulation of HSP70 and HSP40 in vivo and overexpression of them might support the degradation of mutant protein and thus suppress the disease severity.

14.10 Conclusion

Inhibition of HSP90 offers very selective binding, however, many facts yet to be explored regarding the molecular basis for their interactions. The precise knowledge is the key to understand how the client/HSP90 interaction is targeted for studying the structure and biochemistry of the molecular complexes.

A common cause of cancer pathogenesis and neurodegeneration was clearly observed through a common regulator HSP90 which was found deregulated from various experimental findings. A well established role of HSP90 thus has been observed in the cause and therapeutic target for the cancer and neurodegeneration using various HSP90 inhibitors like geldanamycin, its derivatives like 17-DMAG and others. Interestingly, the chaperoning function of HSP90 depends upon both cellular HSP70 and HSP40. Therefore, targeting HSP90 might be a therapeutic route for multiple diseases including neurodegeneration. Although few HSP90-inhibitors like geldanamycin, 17-AAG, 17-DMAG, Celastrol have been used so far in neurodegeneration, the actual number of existing HSP90-inhibitors is more. Therefore, other inhibitors also should be attempted. Moreover, the analogues of existing inhibitors and peptide-based novel inhibitors have also been proposed to be the HSP90-inhibitors [3]. It may be recommended to use such analogues in neurodegeneration conditions.

However, most of the details of the client/chaperone interactions are still unclear, and therefore, the strategy of targeting these associations is more challenging.

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References

1. Fink AL (1999) Chaperone-mediated protein folding. Physiol Rev 79:425–449
2. Chaudhuri TK, Paul S (2006) Protein-misfolding diseases and chaperone-based therapeutic approaches. FEBS J 273:1331–1349
3. Paul S, Mahanta S (2014) Association of heat-shock proteins in various neurodegenerative disorders: is it a master key to open the therapeutic door? Mol Cell Biochem 386:45–61
4. Chen S, Brown I (2007) Neuronal expression of constitutive heat shock proteins: implications for neurodegenerative diseases. Cell Stress Chaperones 12:51–58
5. Morimoto RI, Kline MP, Bimston DN, Cotto JJ (1997) The heat-shock response: regulation and function of heat-shock proteins and molecular chaperones. Essays Biochem 32:17–29
6. Whitesell L, Lindquist SL (2005) HSP90 and the chaperoning of cancer. Nat Rev Cancer 5:761–772
7. Dickey CA, Kamal A, Lundgren K et al (2007) The high-affinity HSP90-CHIP complex recognizes and selectively degrades phosphorylated tau client proteins. J Clin Invest 117:648–658
8. Trepel J, Mollapour M, Giaccone G, Neckers L (2010) Targeting the dynamic HSP90 complex in cancer. Nat Rev Cancer 10:537–549
9. Sreedhar AS, Kalmar E, Csermely P, Shen YF (2004) Hsp90 isoforms: functions, expression and clinical importance. FEBS Lett 562:11–15
10. Bergerat A, de Massy B, Gadelle D et al (1997) An atypical topoisomerase II from Archaea with implications for meiotic recombination. Nature 386:414–417
11. Wayne N, Bolon DN (2007) Dimerization of Hsp90 is required for in vivo function. Design and analysis of monomers and dimers. J Biol Chem 282:35386–35395
12. Onuoha SC, Coulstock ET, Grossmann JG, Jackson SE (2008) Structural studies on the co-chaperone hop and its complexes with Hsp90. J Mol Biol 379:732–744
13. Buchner J (1999) Hsp90 & Co. – a holding for folding. Trends Biochem Sci 24:136–141
14. Goetz MP, Toft DO, Ames MM, Erlichman C (2003) The Hsp90 chaperone complex as a novel target for cancer therapy. Ann Oncol 14:1169–1176
15. Luo W, Dou F, Rodina A et al (2007) Roles of heat shock protein 90 in maintaining and facilitating the neurodegenerative phenotype in tauopathies. Proc Natl Acad Sci U S A 104:9511–9516
16. Stepanova L, Leng X, Parker SB, Harper JW (1996) Mammalian p50Cdc37 is a protein kinase-targeting subunit of Hsp90 that binds and stabilizes Cdk4. Genes Dev 10:1491–1502
17. Dou F, Chang X, Ma D (2007) Hsp90 maintains the stability and function of the tau phosphorylating kinase GSK3β. Int J Mol Sci 8:51–60
18. Waza M, Adachi H, Katsuno M et al (2006) Modulation of Hsp90 function in neurodegenerative disorders: a molecular-targeted therapy against disease-causing protein. J Mol Med 84:635–646
19. Li J, Soroka J, Buchner J (2012) The Hsp90 chaperone machinery: conformational dynamics and regulation by co-chaperones. Biochim Biophys Acta 1823:624–635
20. Richter K, Walter S, Buchner J (2004) The Co-chaperone Sba1 connects the ATPase reaction of Hsp90 to the progression of the chaperone cycle. J Mol Biol 342:1403–1413
21. Theodoraki MA, Caplan AJ (2012) Quality control and fate determination of Hsp90 client proteins. Biochim Biophys Acta 1823:683–688
22. Csermely P, Schnaider T, Soti C, Prohászka Z, Nardai G (1998) The 90-kDa molecular chaperone family: structure, function, and clinical applications. A comprehensive review. Pharmacol Ther 79:129–168

23. Chiosis G, Neckers L (2006) Tumor selectivity of Hsp90 inhibitors: the explanation remains elusive. ACS Chem Biol 1:279–284
24. Pearl LH, Prodromou C, Workman P (2008) The Hsp90 molecular chaperone: an open and shut case for treatment. Biochem J 410:439–453
25. Didelot C, Lanneau D, Brunet M et al (2007) Anti-cancer therapeutic approaches based on intracellular and extracellular heat shock proteins. Curr Med Chem 14:2839–2847
26. Solit DB, Chiosis G (2008) Development and application of Hsp90 inhibitors. Drug Discov Today 13:38–43
27. Gress TM, Mullerpillasch F, Weber C et al (1994) Differential expression of heat-shock proteins in pancreatic-carcinoma. Cancer Res 54:547–551
28. Ferrarini M, Heltai S, Zocchi MR, Rugarli C (1992) Unusual expression and localization of heat-shock proteins in human tumor-cells. Int J Cancer 51:613–619
29. Workman P (2004) Combinatorial attack on multistep oncogenesis by inhibiting the Hsp90 molecular chaperone. Cancer Lett 206:149–157
30. Workman P (2004) Altered states: selectively drugging the Hsp90 cancer chaperone. Trends Mol Med 10:47–51
31. Becker B, Multhoff G, Farkas B et al (2004) Induction of Hsp90 protein expression in malignant melanomas and melanoma metastases. Exp Dermatol 13:27–32
32. Wu X, Wanders A, Wardega P et al (2009) Hsp90 is expressed and represents a therapeutic target in human oesophageal cancer using the inhibitor 17-allylamino-17-demethoxygeldanamycin. Br J Cancer 100:334–343
33. Gallegos Ruiz MI, Floor K, Roepman P et al (2008) Integration of gene dosage and gene expression in non-small cell lung cancer, identification of HSP90 as potential target. PLoS One 3, e0001722
34. Ogata M, Naito Z, Tanaka S, Moriyama Y, Asano G (2000) Overexpression and localization of heat shock proteins mRNA in pancreatic carcinoma. J Nippon Med Sch 67:177–185
35. Fortugno P, Beltrami E, Plescia J et al (2003) Regulation of survivin function by Hsp90. Proc Natl Acad Sci U S A 100:13791–13796
36. Citri A, Gan J, Mosesson Y et al (2004) Hsp90 restrains ErbB-2/HER2 signalling by limiting heterodimer formation. EMBO Rep 5:1165–1170
37. Meli M, Pennati M, Curto M et al (2006) Small-molecule targeting of heat shock protein 90 chaperone function: rational identification of a new anticancer lead. J Med Chem 49:7721–7730
38. Hong DS, Banerji U, Tavana B et al (2013) Targeting the molecular chaperone heat shock protein 90 (HSP90): lessons learned and future directions. Cancer Treat Rev 39:375–387
39. Fukuyo Y, Hunt CR, Horikoshi N (2010) Geldanamycin and its anti-cancer activities. Cancer Lett 290:24–35
40. Li Y, Zhang T, Schwartz SJ, Sun D (2009) New developments in Hsp90 inhibitors as anti-cancer therapeutics: mechanisms, clinical perspective and more potential. Drug Resist Updat 12:17–27
41. Plescia J, Salz W, Xia F et al (2005) Rational design of shepherdin, a novel anticancer agent. Cancer Cell 7:457–468
42. Duffy MJ, O'Donovan N, Brennan DJ, Gallagher WM, Ryan BM (2007) Survivin: a promising tumor biomarker. Cancer Lett 249:49–60
43. Khalid S, Paul S (2014) Identifying a C-terminal ATP binding sites-based novel Hsp90-Inhibitor in silico: a plausible therapeutic approach in Alzheimer's disease. Med Hypotheses 83:39–46
44. Waza M, Adachi H, Katsuno M et al (2006) Alleviating neurodegeneration by an anticancer agent: an Hsp90 inhibitor (17-AAG). Ann N Y Acad Sci 1086:21–34
45. Luo W, Rodina A, Chiosis G (2008) Heat shock protein 90: translation from cancer to Alzheimer's disease treatment? BMC Neurosci 9(Suppl 2):S7
46. Neckers L (2002) Heat shock protein 90 is a rational molecular target in breast cancer. Breast Dis 15:53–60

47. Gray PJ Jr, Prince T, Cheng J, Stevenson MA, Calderwood SK (2008) Targeting the oncogene and kinome chaperone CDC37. Nat Rev Cancer 8:491–495
48. Cortajarena AL, Yi F, Regan L (2008) Designed TPR modules as novel anticancer agents. ACS Chem Biol 3:161–166
49. Holmes JL, Sharp SY, Hobbs S, Workman P (2008) Silencing of HSP90 cochaperone AHA1 expression decreases client protein activation and increases cellular sensitivity to the HSP90 inhibitor 17-allylamino-17-demethoxygeldanamycin. Cancer Res 68:1188–1197
50. Smith JR, Clarke PA, de Billy E, Workman P (2009) Silencing the cochaperone CDC37 destabilizes kinase clients and sensitizes cancer cells to HSP90 inhibitors. Oncogene 28:157–169
51. Xu W, Neckers L (2007) Targeting the molecular chaperone heat shock protein 90 provides a multifaceted effect on diverse cell signaling pathways of cancer cells. Clin Cancer Res 13:1625–1629
52. Wang Y, Trepel JB, Neckers LM, Giaccone G (2010) STA-9090, a small-molecule Hsp90 inhibitor for the potential treatment of cancer. Curr Opin Investig Drugs 11:1466–1476
53. Mimnaugh EG, Chavany C, Neckers L (1996) Polyubiquitination and proteasomal degradation of the p185c-erbB-2 receptor protein-tyrosine kinase induced by geldanamycin. J Biol Chem 271:22796–22801
54. Okamoto J, Mikami I, Tominaga Y et al (2008) Inhibition of Hsp90 leads to cell cycle arrest and apoptosis in human malignant pleural mesothelioma. J Thorac Oncol 3:1089–1095
55. Pashtan I, Tsutsumi S, Wang S, Xu W, Neckers L (2008) Targeting Hsp90 prevents escape of breast cancer cells from tyrosine kinase inhibition. Cell Cycle 7:2936–2941
56. Neckers L (2006) Chaperoning oncogenes: Hsp90 as a target of geldanamycin. Handb Exp Pharmacol 172:259–277
57. Supko JG, Hickman RL, Grever MR, Malspeis L (1995) Preclinical pharmacologic evaluation of geldanamycin as an antitumor agent. Cancer Chemother Pharmacol 36:305–315
58. Schulte TW, Neckers LM (1998) The benzoquinoneansamycin 17-allylamino-17-demethoxygeldanamycin binds to HSP90 and shares important biologic activities with geldanamycin. Cancer Chemother Pharmacol 42:273–279
59. Ge J, Normant E, Porter JR et al (2006) Design, synthesis, and biological evaluation of hydroquinone derivatives of 17-amino-17-demethoxygeldanamycin as potent, water soluble inhibitors of Hsp90. J Med Chem 49:4606–4615
60. Kamal A, Thao L, Sensintaffar J et al (2003) A high affinity conformation of Hsp90 confers tumor selectivity on Hsp90 inhibitors. Nature 425:407–410
61. Klettner A (2004) The induction of heat shock proteins as a potential strategy to treat neurodegenerative disorders. Drug News Perspect 17:299–306
62. Brown IR (2007) Heat shock proteins and protection of the nervous system. Ann N Y Acad Sci 1113:147–158
63. Muchowski PJ, Wacke JL (2005) Modulation of neurodegeneration by molecular chaperones. Nat Rev Neurosci 6:11–22
64. Kitson RR, Chang CH, Xiong R, Williams HE, Davis AL, Lewis W et al (2013) Synthesis of 19-substituted geldanamycins with altered conformations and their binding to heat shock protein Hsp90. Nat Chem 5:307–314
65. Auluck PK, Meulener MC, Bonini NM (2005) Mechanisms of suppression of {alpha}-synuclein neurotoxicity by geldanamycin in drosophila. J Biol Chem 280:2873–2878
66. Shen HY, He JC, Wang Y, Huang QY, Chen JF (2005) Geldanamycin induces heat shock protein 70 and protects against MPTP-induced dopaminergic neurotoxicity in mice. J Biol Chem 280:39962–39969
67. Waza M, Adachi H, Katsuno M et al (2005) 17-AAG, an Hsp90 inhibitor, ameliorates polyglutamine-mediated motor neuron degeneration. Nat Med 11:1088–1095
68. Tokui K, Adachi H, Waza M et al (2009) 17-DMAG ameliorates polyglutamine-mediated motor neuron degeneration through well-preserved proteasome function in an SBMA model mouse. Hum Mol Genet 18:898–910

69. Fujikake N, Nagai Y, Popiel HA et al (2008) Heat shock transcription factor 1-activating compounds suppress polyglutamine-induced neurodegeneration through induction of multiple molecular chaperones. J Biol Chem 283:26188–26197
70. Whitesell L, Cook P (1996) Stable and specific binding of heat shock protein 90 by geldanamycin disrupts glucocorticoid receptor function in intact cells. Mol Endocrinol 10:705–712
71. Zhang T, Hamza A, Cao X et al (2008) A novel Hsp90 inhibitor to disrupt Hsp90/Cdc37 complex against pancreatic cancer cells. Mol Cancer Ther 7:162–170
72. Salminen A, Lehtonen M, Paimela T, Kaarniranta K (2010) Celastrol: molecular targets of Thunder God Vine. Biochem Biophys Res Commun 394:439–442
73. Zhang YQ, Sarge KD (2007) Celastrol inhibits polyglutamine aggregation and toxicity though induction of the heat shock response. J Mol Med (Berl) 85:1421–1428
74. Paris D, Ganey NJ, Laporte V et al (2010) Reduction of beta-amyloid pathology by celastrol in a transgenic mouse model of Alzheimer's disease. J Neuroinflammation 7:17
75. Sittler A, Lurz R, Lueder G et al (2001) Geldanamycin activates a heat shock response and inhibits huntingtin aggregation in a cell culture model of Huntington's disease. Hum Mol Genet 10:1307–1315
76. Batulan Z, Taylor DM, Aarons RJ et al (2006) Induction of multiple heat shock proteins and neuroprotection in a primary culture model of familial amyotrophic lateral sclerosis. Neurobiol Dis 24:213–225
77. McLean PJ, Klucken J, Shin Y, Hyman BT (2004) Geldanamycin induces Hsp70 and prevents alpha-synuclein aggregation and toxicity in vitro. Biochem Biophys Res Commun 321:665–669