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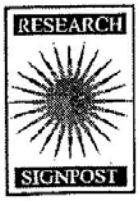

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12 Novel roles of Hsp90 inhibitors and Hsp90 in: Redox regulation and cytoarchitecture

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Abstract

The 90 kDa heat shock protein (Hsp90), the most abundant, highly evolutionarily conserved molecular chaperone in eukaryotic cytosol plays a central role in cell physiology. The Hsp90 chaperone system functions to promote and maintain the conformational maturation of a large variety of client proteins like the hormone receptors. Also the direct and transient association of Hsp90 with cancer-associated signaling molecules like, p53, Bcr-Abl, Raf-1, Akt, HIF-α, Met and Her2/neu is involved in tumor progression. Numerous natural and synthetic Hsp90 inhibitors have been developed in recent years. These drugs change the direction of the Hsp90 complex-mediated assistance from protein folding to protein degradation. Some of these inhibitors are also involved in sensitizing tumor cells to pro-apoptotic insults hence serve as anti-cancer drugs. Here we review these novel Hsp90

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inhibitors and their emerging role in various cellular processes apart from their inhibition of Hsp90 protein function. We focus not only on Hsp90-tumor progression, but also on cytoarchitecture, as the higher levels of cellular organization need constant remodeling, where the role of Hsp90 is worth to be investigated. Our last major aspect deals with protein oxidation, since several Hsp90 inhibitors have pro-oxidant effects.

Introduction

Heat shock proteins (Hsp-s) are highly conserved ubiquitous proteins among species. They are inducible by a variety of stressors, however their constitutive expression under non-stressful conditions shows their important role in the maintenance of cellular homeostasis. Hsp-s are involved in maintaining appropriate folding and conformation of other proteins, hence most of them can also be called as "molecular chaperones". They also help to transport proteins from one compartment to another inside the cell, and present old and damaged proteins to proteasomal degradation [1,2,3,4]. Hsp-s are also believed to play a role in antigen-presentation and to serve as "danger signals" to help the immune system recognize dead or damaged cells [5,6,7].

The accumulation of Hsp-s is seen not only in stressful conditions but also in many pathophysiological conditions and tumors. This accumulation helps in cell recovery refolding partially damaged functional proteins and also by increasing the association of cell survival factors and stabilizing them. Many types of tumors are associated with high expression of multiple Hsp-s compared to their normal parental cells [8,9]. In some instances, the differential expression of Hsp-s specifies the grade and type of tumor [10,11,12,13,14,15]. Conditions, like Alzheimer's disease, prion disease, and Huntington disease, where the accumulation of misfolded proteins is the major cause of neurodegenerative disorders [16,17,18,19,20], invoke therapies, which help Hsp overexpression.

There are multiple Hsp-s and are classified to following major Hsp families, Hsp100, Hsp90, Hsp70, Hsp60 and the large family of small Hsp-s [21,22]. However, the structure and function of these proteins vary between and within families, they all work in co-ordination at different stages of protein folding [3,23]. Both Hsp90 and Hsp70 are shown to be associated with a number of signaling molecules, including v-Src, Raf1, Akt and steroid receptors suggesting an important role for these proteins in malignant transformation and metastasis development [23,24]. The discovery of some of the natural products like geldanamycin and radicicol with antitumor activity through the inhibition of Hsp90 function opened a new era of therapeutic interventions targeting Hsp90 [25,26,27].

Hsp90: Overview

Hsp90 is one of the most abundant proteins in the eukaryotic cells, comprising 1-2% under non-stress conditions. Hsp90 is evolutionarily conserved among species and is proven essential for cell survival. Its contribution to various cellular processes including signal transduction, protein folding and degradation, and morphological evolution was extensively studied. Hsp90 is primarily a cytosolic protein, however, it rapidly accumulates in cell nuclei upon stress [28,29,30]. There are two isoforms for this protein identified,

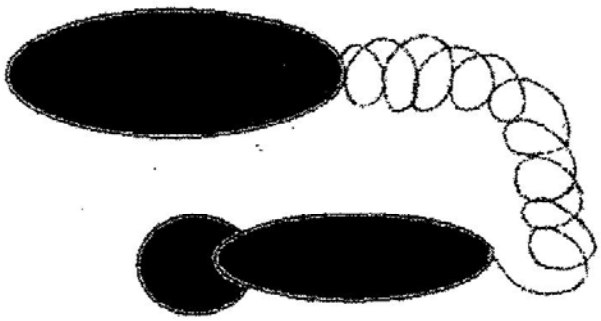

Figure 1. Domain structure of Hsp90 showing three major functional domains and localization of partner binding sites.

namely, Hsp90-α (inducible form/major form) and Hsp90-β (constitutive form/minor form). Its analogues include Grp94 in the endoplasmic reticulum and Hsp75/TRAP1 in the mitochondrial matrix [28]. The full functional activity of Hsp90 is gained in concert with other co-chaperones, playing an important role in the folding of newly synthesized proteins and stabilization and refolding of denatured proteins after stress.

Hsp90 is mainly a constitutive homodimer (αα or ββ), however, its monomers, heterodimers (αβ) and higher oligomers are also present. Its dimerization potential resides mainly at the carboxy-terminal 190 amino acids [31,32,33,34,35]. Hsp90 is a phospho-protein containing 2-3 covalently bound phosphate molecules per monomer [36], and the phosphorylation is thought to enhance its function. The monomer of Hsp90 consists of a conserved 25 kDa N-terminal and a 55 kDa C-terminal domains joined together by a 10 kDa charged linker region. Together with the C-terminal domain, this linker region helps in the dimerization of the protein [37]. Both termini are reported to bind to substrate polypeptides including client proteins and co-chaperones. The N-terminal domain contain an ATP binding site hence, Hsp90 is an ATP-dependent molecular chaperone. ATP binding helps dimerization because of a change in Hsp90 conformation. Hsp90 also exhibits ATPase activity that is necessary for its chaperone function [38]. Recently it was shown that Hsp90 contains a second nucleotide binding site at the C-terminal domain [39,40], however, the biological significance of this second nucleotide binding site needs to be further elucidated. Both the N- and C-terminal domains have been implicated in binding of substrate polypeptides [41,42,43]. The tetratricopeptide repeat present in Hsp90 co-chaperones binds to the C-terminal MEEVD motif and these interactions help in forming the chaperone complex. Apart from its co-chaperones, Hsp90 binds to an array of client proteins, where the co-chaperone specificity varies and depends on the actual client. There is a growing list of Hsp90 client proteins interestingly most of the clients include molecules involved in signal transduction [23].

Hsp90 forms several discrete sub-complexes, each containing different set of co-chaperones that function at different steps during the folding process of client protein [51]. Unlike other chaperones, Hsp90 contains two independent chaperone sites that

Table 1. Members of the Hsp90 molecular chaperone family and their major localization

Name	Localization
Hsp90α	Cytoplasm
Hsp90β	Cytoplasm
Hsp75/TRAP-1	Cytoplasm
Grp94/Gp96	ER

Table 2. Major Hsp90 co-chaperones.

Name	Reference
Hsp70	44,45
Cdc37	46
p23	47
CHIP	48
Immunophilins	49,47,50

differ in their substrate specificity [42,52] probably working in the form of a switch between Hsp90 and Hsp70 client protein interactions. The best understood molecular association of Hsp90-multichaperone complexes was the steroid receptors [53]. The maturation of steroid receptors [54] and their nuclear trafficking requires Hsp90. Steroid receptors also require molecular chaperones for their ligand dependent transcriptional activation [55,56]. Though there are reports that some Hsp90 co-chaperones can work independent of Hsp90 in preventing the aggregation of misfolded protein substrates, the complete competence in folding-assistance requires Hsp90 [57,58,59]. Co-chaperones also help Hsp90-client protein binding [60,61] interactions between Hsp70 client proteins [62] and docking cytoskeletal proteins [63,64].

Hsp90-dependent signal transduction

Over the years, many different tyrosine and serine/threonine protein kinases have been selected as potential pharmacological targets in antitumor therapies, based either on their overexpression and/or dysfunction in a particular organ or tissue, or through their association in deregulated signal transduction/cell cycle pathways. Our current understanding is that a number of distinct tyrosine kinases play role in diverse but fundamentally important aspects of tumor progression such as growth, survival, metastasis and angiogenesis. Hsp90's role is implicated in many kinases from both tyrosine and serine/threonine family members. At cellular level, the ability of a cell to know whether to grow, divide, differentiate or die depends upon extracellular signals and the ability to respond to these signals in an orchestrated manner. Several molecules like hormones, small peptides, surface proteins from other cells etc. are involved in initiating these transduction mechanism through tyrosine and serine/threonine kinase cascades.

Tyrosine kinases

Hsp90 interacts with and stabilizes a growing list of various kinases. One of the major receptor tyrosine kinases (RTKs) is ErbB2 (HER2 or *neu*). This kinase either works alone or in homo/hetero complexes with its homologues. ErbB2 was first identified as an oncogene, hence, the down regulation of ErbB2 signaling emerged as an anti-cancer strategy [65]. ErbB2 was shown as an *in vitro* substrate for Hsp90 chaperone complex, and inhibition of Hsp90 results in the dissociation of ErbB2 from the Hsp90 chaperone-complex [66].

The Src (Rouse sarcoma virus, $p60^{src}$) family of tyrosine kinases was implicated in signal transduction following growth factor stimulation and integrin-mediated cell-substrate adhesion. Both v-Src and c-Src bind to Hsp90, where the chaperone maintains the kinase in an inactive form and helps in its membrane recruitment suggesting that the Src activity is governed by Hsp90 [67].

Abelson leukemia virus tyrosine kinase (v-Abl) and its cellular counterpart, c-Abl, shares sequence homology with Src members. Hsp90 affects the function and stability of this kinase [68,69]. At the nuclear level Wee1 tyrosine kinases catalyzes the inhibitory phosphorylation of the mitotic regulator Cdk1 (Cdc2), preventing mitosis during S phase, and delaying it in response to DNA damage or developmental signals during G2 phase [70,71]. Hsp90 is required for the assembly and/or disassembly of functional Wee1 protein complex [72]. c-Met is an RTK, which stimulates the invasive growth of

Table 3. Major Hsp90 interacting proteins

Name	Reference
Transcriptional factors	
glucocorticoid receptor-GR, estrogen receptor-ER progesterone receptors-PR, androgen receptor-AR , mineralocorticoid receptor-MR	76,77,78,79,80,81,82
Heat shock transcription factor-1	83,84
p53	85,86
Hypoxia-inducible factor-1α	87
SV40 large T-antigen	88
Telomerase	89
cytoplasmic v-erbA	90
Kinases	
erbB2	91
Wee1	92
Raf-1	93
Casein Kinase II	94
eIF2-α	95
Akt/PKB	96
Cdk4	97
Cdk6	98
Cdk9	99
Other proteins	
actin	100
tubulin	101
proteasome	102
lysosome	103
Nitric oxide synthase (NOS)	104,105
Apaf-1	106

carcinoma cells, is tumorigenic, and overexpressed in many solid tumors [73]. c-Met overexpression, as well as activating mutations in the various domains, can lead to carcinogenesis in multiple tumors. c-Met, on activation by autophosphorylation, can associate with and activate multiple signal transducing intermediates, such as Grb2, p85 sub unit of PI3k, Stat-3, and Gab1 [73]. Though there is no direct association of Hsp90 and the c-Met/HGF pathway, the co-ordinate regulation of c-Met and Hsp90 levels were shown [74,75].

Serine/threonine kinases

The most important serine/threonine kinase members involved in malignant transformation and tumor progression include the major signaling cascades consisting of the Ras, Raf, MEK, and mitogen-activated protein kinase (MAPK) [107,108,109]. Raf-1 is the most extensively studied member of the Raf family. Active Ras, in its GTP-bound state binds to the amino-terminal regulatory domain of Raf-1 leading to recruitment of Raf-1 into the cell membrane. Raf-1 is primarily located in the cytosol, and the cytosolic Raf-1 exists in a complex with Hsp90 [110,111], where Hsp90 binding to Raf is shown to be required for its activity [112]. Both casein kinase II [94] and the heme-regulated eukaryotic initiation factor (eIF-2α) kinase were identified in Hsp90 complex [113]. Apart from its tight binding to Hsp90, casein kinase II also phosphorylates both isoforms of Hsp90 as well as the ER-resident Grp94 [114]. Hsp90 also binds both co-translationally as well as post-translationally to eIF-2α kinase, and this binding is essential for maintaining the activity of the kinase [95,115]. Protein Kinase B or Akt (Akt/PKB) is a downstream target for phosphoinositide 3-kinase (PI-3K) involved in the regulation of cell growth [116]. Several studies show that Akt forms complexes with Hsp90, which enhance cell survival. However, this complex formation requires Cdc37, a co-chaperone of Hsp90 [117,118]. At the nuclear level the major and initial cell cycle transition regulators, Cdk4/Cdk6 were also shown to form complexes with Hsp90, however, their binding is involves their association with the co-chaperone, Cdc37 [97,119]. Recently it is shown that Cdk9 acts preferentially by controlling processes such as transcription and the balance between differentiation and apoptosis, suggesting that this kinase can serve as a switch between many important cellular processes [120]. Although Hsp70 is a general chaperone for Cdk9, Hsp90 is also been shown to play a role in the regulation of Cdk9 *via* Cdc37 [99].

Transcription factors

The role of Hsp90 in glucocorticoid receptor (GR), progesterone receptor (PR) regulation was the best studied among chaperone-dependent signaling events related to trascription factors [23]. Hypoxia-inducible factor-1 (HIF-1α) is associated with hypoxia induced transcription of genes together with the nuclear protein, aryl hydrocarbon receptor nuclear translocator (ARNT). The resulting HIF-1α/ARNT heterodimers interact specifically with the hypoxia-responsive element (HRE), thereby increase the transcription, where Hsp90 modulates the conformation of HIF-1αARNT heterodimers [121].

The p53 tumor suppressor is an important regulator of cellular response to stress, abnormal cell proliferation, and DNA damage. In normal cells, p53 is maintained at very

low levels because of rapid degradation through the ubiquitin-dependent proteasome pathway and is under the control of MDM2 (murine double minute-2) protein [122]. Hsp90 binding has been shown to contribute to the accumulation of mutant p53 [123]. Binding of Hsp90 inhibits the ability of MDM2 to promote p53 ubiquitinylation and degradation, resulting in the stabilization of both mutant p53 and MDM2 [124,125]. Hsp90 appears to inactivate MDM2 by blocking the central domain of MDM2 normally involved in p53 regulation (alternative reading frame protein product), thereby mimicking the effect of ARF to prevent mutant p53 degradation [126].

Heat shock transcription factor-1 (HSF-1) tightly regulates the inducible transcription of heat shock genes [127]. Hsp90 negatively regulates the HSF-1 [128] and is involved in the inhibition of induced stress response.

Non-signaling molecules that interact with Hsp90

The other major non-signaling molecules associated with Hsp90 are the cytoskeletal proteins actin [100,129], tubulin [101,130], intermediary filaments [131,132], dynein [133], Tau protein, which stabilizes the microtubules [134], the G-protein family members G protein $\beta\gamma$ [135], $G\alpha_o$ [136], $G\alpha_{12}$ [137], nitric oxide synthases [104,105], the anti-apoptotic protein, Apaf-1 [106]. As the list of Hsp90 associated proteins is growing enormously [23] it is difficult to explain each molecular interaction, hence, only some of the major molecular interactions were mentioned.

Hsp90 inhibitors

Over the years, Hsp90 gained much of attention because of its role in steroid receptor activation and in other pathways of signal transduction. However, its role in malignant transformation stabilizing the signaling intermediates leading to tumor development and helping tumor survival extended the importance of this molecular chaperone as a new target for anticancer drug development. Tumors are known for their induced proliferative ability, where they are in high demand of signaling events to sustain their need and these events are associated with the deregulated cell cycle and escape from programmed cell death due to accumulation of certain mutations [138].

In several tumor models the selective inhibition of Hsp90 function causes a selective degradation of important signaling proteins that are involved in cell proliferation, cell cycle regulation, and apoptosis [139]. This finding can be explained by the proposition that many growth-regulating proteins in tumor cells depend upon either stable or transient interactions with Hsp90 for their function. Hence, inhibition of Hsp90 function through pharmacological interference makes these tumor cells more vulnerable for anti-Hsp90 drugs. The advantage of using Hsp90 inhibitors over other pharmacological targets is its selectivity on multiple signaling pathways, whereas other drugs may target one or limited signaling pathways, which do not count for an extensive signaling network. In addition, tumor cells may find alternative pathways to circumvent specific drug effects. In such cases, alternative pathways help them in the development of drug resistance as well as contribute for the malignant as well as metastatic phenotype. Towards this direction there are several Hsp90-specific drugs developed and some of them are already in clinical trials.

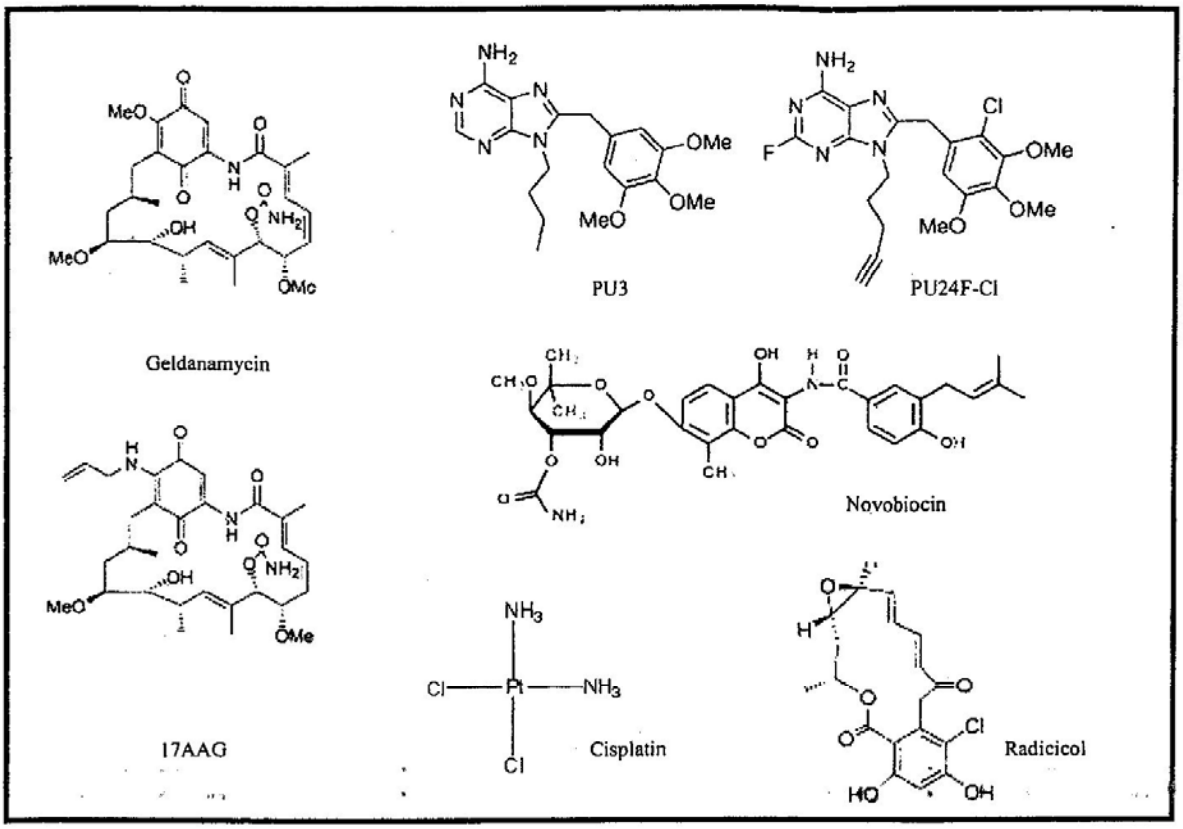

Figure 2. Chemical structure of Hsp90 inhibitors

Geldanamycin

The first Hsp90 inhibitor drug with antitumor potential identified was geldanamycin, a natural product isolated from *Streptomyces hygroscopicus* [140]. Though the antitumor potential of geldanamycin was initially thought to be due to specific tyrosine kinase inhibition [141], later studies revealed that the antitumor potential relies on the depletion of oncogenic protein kinases *via* the ubiquitin proteasome pathway [142]. The major regulatory signaling proteins which are affected by geldanamycin include, proto-oncogenes- erbB2, EGF, v-Src, Raf-1 and Cdk4 and the nuclear hormone receptors which include, both estrogen and androgen hormone receptors [23].

Subsequent immunoprecipitation [143,144] and X-ray crystallographic [145] studies revealed that geldanamycin directly binds to Hsp90, and inhibits the formation of Hsp90-multichaperone complex required for client protein maturation, resulting in the ubiquitin-mediated degradation of Hsp90-client proteins. Geldanamycin binds to the N-terminal domain of Hsp90 and competes for ATP binding. The geldanamycin-Hsp90 crystal structure also shows that this binding inhibits the substrate protein binding [145,146]. Geldanamycin also binds to Grp94, the Hsp90 analogue which is abundant in ER and coordinately regulated by other ER chaperones [147].

Though geldanamycin shows both anti-tumor and selective Hsp90 binding potential, it had difficulties to enter clinical trials due to its high hepatotoxicity in some of the human tumor models [148]. Thus a search for new classes of Hsp90 inhibitors with less toxicity began, and was successful in developing the analogue 17AAG (17-allylamino-17-demethoxy-geldanamycin). 17AAG possesses all the Hsp90-related characteristics of

geldanamycin [149,150] with lesser toxicity [151], hence, 17AAG could enter Phase I clinical trials. Though 17AAG is metabolized to 17AG [17-amino-17-demethoxy-geldanamycin] by cytochrome P450 CYP3A4, this metabolite was found be a stable form, and retains both Hsp90 inhibitory and antitumor activities [150]. Both geldanamycin and 17AAG can be metabolized by NADH quinone oxidoreductase 1 (NQO1), which is known to potentiate antitumor activity by stabilizing the tumor suppressor p53 [150,152]. Similarly to geldanamycin, 17AAG also binds to Grp94 [153]. Several geldanamycin-testosterone compounds [154,155] and ligand-geldanamycin compounds [156] were also developed, and showed selective effects in certain tumors. Interestingly, the comparison of various tumor and experimental models suggests that the mode of action of Hsp90 inhibitors vary. In some cases, they induce apoptosis [157] and in other cases they induce either differentiation or cytostasis [158].

Radicicol

Radicicol is a macrocyclic antibiotic isolated from *Monosporium bonorden* [159]. Because of its potential to reverse the malignant phenotype similar to geldanamycin [160,161], it was also initially thought to be a tyrosine kinase inhibitor. However, later studies showed its role in Hsp90 client protein degradation [162]. Radicicol is involved in the degradation of NQQ1 followed by the degradation of mutant p53, which is involved in the malignant transformation [163]. The antitumor potential for NQQ1 is because of its involvement in stabilizing the tumor suppressor protein p53 [163] and failure of these results in p53 mediated apoptosis. Radicicol inhibits the peptide binding to Grp94 though the peptide binding and radicicol binding sites are different in Grp94 [164]. However, radicicol lacks antitumor activity *in vivo* in experimental models because of its unstability. The oxime derivatives of radicicol [165], exhibit antitumor activity *in vivo* as well as *in vitro* hence serve as good anticancer drug candidates. Radicicol binds to the N-terminal domain of Hsp90 with much higher affinity than the structurally different drugs, geldanamycin and 17AAG [166].

Cisplatin

Cisplatin, cis-diammine-dichloro-platinum (II) was first identified 125 years ago [167]. Its clinical development started in the 1970's for its effective antitumor activity in a wide variety of tumors [168,169]. Its biochemical ability to form DNA-adducts thereby interfering with the DNA transcription was thought to be the major cause of its antitumor activity [170]. Its non-DNA targets include phospholipids, especially phosphatidyl serine and RNA [171,172]. However, it also interacts with thiol-containing proteins and peptides, such as cytoskeletal proteins [173]. The specific binding of cisplatin to Hsp90 was also demonstrated [174]. Later studies showed that cisplatin binds to the C-terminal domain of Hsp90, and specifically interferes with the nucleotide binding at this site [175].

Novobiocin

Novobiocin belongs to the family of coumarin antibiotics, and is known to inhibit bacterial DNA synthesis by direct binding to DNA gyrase. The novobiocin binding site of DNA gyrase is similar to the Hsp90 ATP-binding site [176]. Its structural analogues, such as chlorobiocin and coumermycin A1 also bind to Hsp90 resulting in the destabilization and proteolytic degradation of a number of proteins. Novobiocin binds to

a previously unrecognized ATP-binding domain in the carboxy terminus of Hsp90, and inhibits its function. However, binding of novobiocin to Hsp90 inhibits geldanamycin binding suggesting an extensive interaction between the N- and C-terminal domains in regulating Hsp90 chaperone function [177].

Purine based inhibitors

Hsp90 contains a conserved N-terminal ATP/ADP binding pocket and nucleotide binding regulates the chaperone function of the protein [178]. Earlier studies with various Hsp90 inhibitors showed that most of Hsp90 inhibitors developed so far directly bind to the N-terminal ATP/ADP site resulting in a change of Hsp90 conformation and a consequent interference with its chaperone function [179]. In a recent development, PU3, a purine-based Hsp90 inhibitor was designed using X-ray crystallographic data [180]. PU3 has similar effects like geldanamycin in inhibiting Hsp90 client protein degradation and in possessing a robust antitumor potential. However, the trials to modify and improve PU3 led to the development of PU24F-Cl, which binds to the N-terminus of Hsp90 with 30-folds higher affinity than the parent compound, PU3 approximating the binding affinity of 17AAG. PU24F-Cl was found more selective over Hsp90 inhibitors. Its water-solubility is also an advantage over geldanamycin and 17AAG [181]. However, PU24F-Cl might not show the specific intracellular accumulation typical to the more hydrophobic geldanamycin analogues.

Taxol

Taxol is a plant-derived antitumor agent. Its antitumor action is ascribed to its ability to block mitosis by binding and stabilizing microtubules [182,183]. Members of the Hsp90 and Hsp70 families were recently identified as targets of taxol [184]. However, taxol-induced cell death is found independent of the Raf kinase, which is one of the usual targets of Hsp90 [185].

Overlapping specificity of Hsp90 inhibitors

The benzoquinone ansamycins, geldanamycin and 17AAG both inhibit Hsp90 ATPase activity through their direct binding to the N-terminal ATP-binding site required for Hsp90 chaperone activity [139]. This results in the failure of Hsp90 binding to its client proteins and their recruitment for proteasome-mediated degradation. Similarly, radicicol binds to the N-terminal domain of Hsp90 and inhibits its intrinsic ATPase activity [166]. The small molecular inhibitors PU3 and PU24F-Cl also show specific binding to the N-terminal domain of Hsp90 [181] and are potent inhibitors of Hsp90 function. In contrast, cisplatin binds to the second nucleotide-binding site at the C-terminal domain of Hsp90 [39,175].

Advantages of Hsp90 inhibitors

In most cases Hsp90 inhibition was shown to induce either cytostasis or apoptosis [158]. However, there are some reports showing that at low doses Hsp90 inhibitors induce cell differentiation [186]. Though the differences in the downstream effects of Hsp90 inhibition leading to these various final outcomes in the fate of the cells are not known, several prominent features of Hsp90 inhibition are associated with all of these

effects [187,188,189]. There is a selectivity of drug-induced effects among the type and grade of tumor. Clark *et al* [190] showed from human colon carcinoma cells that 17AAG depletes Raf and Akt through Hsp90 inhibition without affecting other client protein expression. In certain cancers, single administration of an Hsp90 inhibitor, such as 17AAG was shown more effective for a variety of client protein degradation [191]. Despite of this, Hsp90 inhibition results in either differentiation or apoptosis depending on the cell type [187]. Cell cycle arrest is the crossroad for this decision, geldanamycin and 17AAG [186,192] were shown to induce G1 arrest. Small molecular purine inhibitors were also exhibit similar phenomenon [180]. These pre-clinical studies emphasize the important role of Hsp90 inhibitors in the clinical implications, of course with certain exceptions. However, the combinatorial treatment with low doses of these drugs will be much more effective. For example, in case of Bcr-Abl positive leukemias, a low dose of geldanamycin is sufficient to sensitize these cells to apoptosis in presence of ineffective concentrations of doxorubicin through caspase activation [193]. In other example, taxol resistant ErbB2 overexpressing breast cancer cells, 17AAG in combination with taxol shows more cytotoxic effects [194,195].

Table 4. Hsp90 inhibitors already in clinical and pre-clinical trials

Lead molecule	Effect	Firm and web-site	Reference
Geldanamycin analogues	Hsp90 inhibition	Conforma Inc. (www.conforma.com)	27
Geldanamycin testosterone	specific Hsp90 inhibition		209
Radicicol	Hsp90 inhibition	Kyowa Hakko Kogyo Ltd. (www.kyowa.co.jp)	210
Purine-scaffold inhibitors	Hsp90 inhibition		181
?	Hsp90 inhibition	RiboTargets Co. (www.ribotargets.com)	

Redox Homeostasis

Oxidative stress is a an imbalance between oxidant exposure and anti-oxidative protection within the cellular environment resulting in a range of responses that differ greatly from with the type of stress and is associated with the sensitivity of the cell function and viability. There is a cross talk between the amount of Hsp-s and the intracellular redox homeostasis. Hsp-s, like α-crystalline, Hsp27 and Hsp70 were extensively studied for their antioxidant properties. These proteins also contribute for maintaining the intracellular redox homeostasis [196,197]. Though the exact involvement of Hsp90 in redox homeostasis regulation is not known, Hsp90 was shown to possess reactive cysteines and was able to reduce cytochrome c suggesting a role for this chaperone in modulating the redox status in resting and apoptotic cells [198].

Cytoarchitecture

The eukaryotic cytoskeleton contains three major components, microfilaments, intermediate filaments, and microtubules. Extensive research on this field showed the importance of Hsp-s in stabilizing the cytoskeleton by direct interaction with cytoskeletal proteins [199,200]. It was also proposed that apart from these known cytoskeletal interactions of various Hsp-s, Hsp90 is also involved in maintaining a fine cytoplasmic meshwork, called microtrabecular lattice [28,201]. The growing list of Hsp90-interacting cytoskeletal proteins suggests that Hsp90 plays a major role in preserving these structures, hence it is involved in maintaining the cell shape. In accordance with this, Hsp90 inhibition is associated with disturbances in the cytoskeleton and cytoskeletal signaling [202]. Though Hsp90-actin binding was shown indirect, and is through a TPR containing protein, UNC-45 [203], several lines of indirect evidence, such as diffusion anomalies show that the hypothesis on Hsp90 involvement in the maintenance of the cytoarchitecture is still valid [201].

Limitations of anti-Hsp90 drugs

Though Hsp90 inhibitors exhibit selective effects inducing the degradation of Hsp90 client proteins, they are also associated with other effects unrelated to their binding to Hsp90. Geldanamycin, which contains a quinone group is known to induce reactive oxygen species, and in general, the cytotoxicity of the ansamycin antibiotics has been attributed to free radical generation [204,205,206,207]. Radicicol is also involved in the free-radical formation from non-peroxide compounds [208], while cisplatin and novobiocin have multiple targets, which are independent of Hsp90.

Conclusions and future perspectives

The word "cancer" can be regarded as a gross term for a vast number of many different disease conditions with distinct characteristics and therapeutic requirements. Though the general features of cancer include unrestrained cell proliferation, a great variety of mutations as well as deregulation of numerous genes can cause this. Among the hallmarks of cancer [211], upregulation of growth signals and evasion of apoptosis are the most important. As most of the growth regulatory signals depend on Hsp90 for their functional stability, Hsp90 is an ideal molecule to intervene in complex oncogenic pathways. Hence, most of the drugs targeting Hsp90 are much more beneficial than the selective oncogene pathway inhibitors.

Besides these general benefits, Hsp90 inhibition also suffers from the problems of most chemotherapeutic interventions: in principle, the drug inhibits normal cells and tumor cells equally. Moreover, Hsp90 inhibition also induces Hsp-s including Hsp90 itself by releasing HSF-1 from its Hsp90 inhibitory complex and (in some cases like that with geldanamycin) by inducing reactive oxygen species, which serve as an additional stress leading to Hsp induction. The larger Hsp90 requirement of tumor cells may overcome in many of these limitations, but a detailed comparison of the complexity of Hsp90 inhibition in normal cells versus tumor cells is clearly lacking. Another way to circumvent the general effects of Hsp90 inhibitors is to increase their specificity targeting them to a tumor-specific Hsp90 client protein, which is a clear task for future drug development in the field of Hsp90 inhibitors.

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