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Functional interplay between heat shock protein 90 (HSP90) and heat shock factors (HSFs)

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Abstract

Maintenance of protein homeostasis, also known as proteostasis, is essential for cellular survival under both basal and stress conditions. Proteostasis relies on a coordinated action between molecular chaperones, such as heat shock proteins (HSPs), and stress-responsive transcription factors. HSP90 is an abundant and functionally central ATP-dependent chaperone that supports the stability and function of a great variety of client proteins, while specific members of the heat shock factor (HSF) family orchestrate transcriptional programs in cells exposed to proteotoxic stress. According to the established chaperone titration model, HSP90, together with other chaperones, represses the master regulator HSF1 by maintaining it in an inactive monomeric state. Emerging evidence, however, indicates that also other HSFs, especially HSF2, can form a complex with HSP90 and contribute to constitutive and stress-inducible *HSP* gene regulation, thereby expanding the HSF1-centric view of the chaperone titration model. This review discusses the current understanding of the HSP90-HSF interplay and highlights the recent advances in targeting HSP90 for therapeutic purposes. Together, these insights underscore the HSP90-HSF axis as a regulatory hub of proteostasis in health and disease.

Keywords Cancer · Chaperone · Heat shock transcription factor · HSP90 inhibitor · Proteotoxic stress

Background

The cellular proteome is maintained by a finely orchestrated machinery that regulates biosynthesis of macromolecules, protein folding, quality control, and degradation, commonly known as the proteostasis network.[1] The proteostasis network is an integrated system that protects the proteome while allowing rapid response and adaptation to physiological and environmental stresses.[2] Exposures to various protein-damaging stresses, such as elevated temperatures, toxins, and changes in pH, perturb the native conformation of proteins, which leads to the accumulation of misfolded and aggregation-prone proteins, imposing a heavy burden on cellular homeostasis.[1,3] To mitigate such damage, cells deploy cytoprotective stress-responsive signaling pathways that recalibrate proteostasis capacity. The evolutionary well-conserved heat shock response protects cells from multiple stressors beyond elevated temperatures by inducing heat shock proteins (HSPs).[4] HSPs are primarily sub-grouped by molecular weight into HSP110, HSP90, HSP70, HSP60, HSP40, and small HSPs.[5] Genes encoding HSPs are transcriptionally regulated by heat shock factors (HSFs) that consist of a family of seven members in vertebrates (HSF1–5, HSFX, and HSFY), among which only HSF1, HSF2, and HSF4 are known to be stress-responsive, while the others are mainly involved in physiological and pathological processes.[6-8] The stress-induced

Abbreviations: 17-AAG, 17-N-allylamino-17-demethoxygeldanamycin; DMAG, 7-dimethylaminoethylamino-DBD, DNA-binding domain; GR, glucocorticoid receptor; HR-A/B, heptad repeat A/B; HR-C, heptad repeat C; HSE, heat shock element; HSF, heat shock factor; HSP, heat shock protein; PTM, post-translational modification; RD, regulatory domain; TAD, transactivation domain; TRAP1, TNF-receptor associated protein 1

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activity of HSFs is strictly regulated by a negative feedback loop, where elevated levels of HSPs, especially HSP70 and HSP90, facilitate the attenuation of the heat shock response. Inspired by the pioneering work of Len Neckers in the HSP90 field, this review focuses on the current knowledge of the functional interaction between HSP90 and HSFs.

HSP90 as a key regulator of proteostasis

HSP90 is an evolutionarily conserved molecular chaperone that helps maintain protein homeostasis by assisting in protein folding, activation, translocation, and degradation.[9] HSP90 is highly abundant in most cell types, representing 1–2% of total cellular proteins under normal physiological conditions and up to 10% in cells exposed to various stresses or in many diseases, such as cancer. There are two isoforms, *i.e.*, the cytosolic/nuclear stress-inducible HSP90α and the cytosolic/nuclear constitutively expressed HSP90β. Other organelle-specific forms of HSP90 include Grp94/Gp96 in the endoplasmic reticulum and TNF receptor-associated protein 1 (TRAP1) in the mitochondria.[10] These chaperones interact with a plethora of cognate proteins and regulate the structural stability and functional competence of their substrates, known as client proteins.[11] HSP90 is found as a homodimer inside cells, with each 90-kDa monomer consisting of an N-terminal ATP-binding domain, a substrate-binding middle (M) domain, and a C-terminal dimerization domain (Figure 1). A flexible, charged linker connecting the N-terminal to the M-domain mediates client activation and the binding of co-chaperones, which are accessory regulatory proteins of HSP90, *e.g.*, HOP, HIP, CyP40, and p23.[10] The optimal function of HSP90 depends on this cohort of interacting co-chaperones that are selectively recruited and exchanged in the chaperone machinery to facilitate client maturation while keeping the protein misfolding at bay.[12] In addition, the chaperone functions of HSP90 are modulated by multiple post-translational modifications, especially acetylation, methylation, phosphorylation, and SUMOylation.[13] HSP90 operates through an orchestrated chaperone cycle that undergoes subtle conformational changes, regulated by ATP, to modulate the binding and stability of client proteins (Figure 1).[10] Constitutively, HSP90 is dimerized at the C-terminal end and adopts an open state resembling a V shape. Following substrate binding and ATP incorporation, HSP90 undergoes conformational changes and forms a closed compact structure. Next, ATP is hydrolyzed, releasing the processed clients from the closed complex, and HSP90 regains its open conformation.

The repertoire of HSP90's functions in cellular physiology is broad. HSP90 regulates key signaling cascades

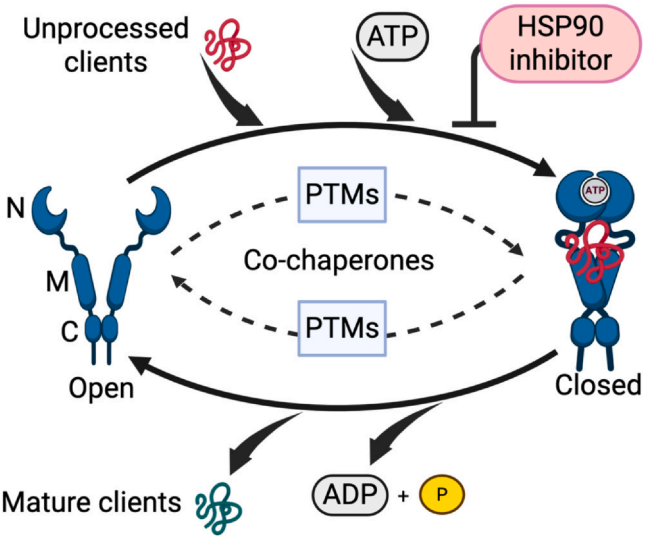

Fig. 1 *The HSP90 chaperone cycle for maturation of clients.* HSP90 functions as an obligate dimer and undergoes an ATP-dependent conformational cycle to assist the folding, activation, or stabilization of a diverse set of client proteins. In the open, nucleotide-free state, the dimer loads clients with assistance from co-chaperones. ATP binding at the N-terminal domains drives formation of the closed, active conformation, where client maturation and ATP hydrolysis occur. Following ATP hydrolysis, HSP90 reopens and releases the client. Multiple rounds of HSP90 interactions can be needed for a client to fold and mature. The activity of HSP90 is extensively regulated by various post-translational modifications (PTMs) as well as by dynamic co-chaperone interactions, all of which fine-tune client specificity and chaperone activity. Many HSP90 inhibitors act by preventing ATP binding at the N-terminal domain, thereby blocking completion of the chaperone cycle and promoting degradation of HSP90-dependent client proteins. N, M, and C depict the N-terminal, middle, and C-terminal domains of HSP90, respectively. Created in BioRender. Roos-mattjus, P. (2026) https://BioRender.com/cmq395a.

by stabilizing and activating a great variety of client proteins, including steroid hormone receptors (*e.g.*, glucocorticoid and progesterone receptors) and numerous kinases (*e.g.*, v-Src, Akt, and Cdk4). Approximately 60% of human kinases, 30% of E3 ubiquitin ligases, and 7% of transcription factors have been identified as HSP90-interacting proteins.[14,15] Beyond signal transduction, HSP90 is involved in cell-cycle progression, cellular differentiation, RNA processing and synthesis, maintenance of cytoskeletal architecture, extracellular matrix remodeling, and DNA damage repair.[11,16] Thus, HSP90 can be placed at the nexus of cellular order and pathological chaos. With regard to pathologies, dysregulated HSP90 activity has been found in many neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis, where β-Amyloid, Tau, and α-Synuclein are all HSP90 clients.[11,17] HSP90 is also associated with autoimmune

Table 1
The different biological processes that HSFs are currently known to be associated with.

	Cellular, developmental and pathological processes
HSF1	Heat shock response, thermotolerance, oxidative stress, cell adhesion, cell cycle, chromatin & ECM remodeling, metabolism, immune system, circadian rhythm, DNA damage repair, proteasome inhibition, aging, corticogenesis, gametogenesis, cancer, neurodegeneration, viral infection, inflammation
HSF2	Heat shock response, oxidative stress, cell adhesion, cell cycle, chromatin & ECM remodeling, metabolism, immune system, proteasome inhibition, corticogenesis, gametogenesis, cancer, neurodegeneration, fetal alcohol spectrum disorder, viral infection, inflammation
HSF4	Heat shock response, oxidative stress, chromatin remodeling, metabolism, immune system, DNA damage repair, lens development, spermatogenesis, olfactory neurogenesis, cancer, cataracts
HSF5	Cell adhesion, cell cycle, immune system, spermatogenesis, cancer
HSFX	Spermatogenesis
HSFY	Spermatogenesis

Table is based on.[7] ECM, extracellular matrix.

diseases, type 2 diabetes mellitus-coupled liver diseases, as well as cardiovascular and fibrotic diseases.[16,18,19] Intriguingly, the vast majority of viruses rely on chaperones, including HSP90, expressed by the host cell, for proper folding and function of viral proteins.[20]

HSP90 has been extensively studied in cancer due to its abundant expression in different types of malignant cells.[11] Due to its extensive client network, many cancer types are highly dependent on HSP90, a phenomenon often referred to as chaperone addiction. Consequently, inhibition of HSP90 creates a pleiotropic therapeutic strategy, enabling simultaneous disruption of multiple oncogenic signaling cascades.[3,21] The natural compound geldanamycin and its derivatives 17-AAG and 17-DMAG were the first class of HSP90 inhibitors investigated to exploit the vulnerability of the N-terminal ATP-binding pocket (Figure 1).[22] Besides N-terminal binding inhibitors, novobiocin and its derivatives represent a different class of molecules that target the C-terminal domain of HSP90. Other ATP-independent inhibitors include thiol-reactive compounds, celastrol, and gambogic acid, which disrupt the chaperone functions and promote the degradation of oncogenic proteins.[22] However, the development of optimal HSP90 inhibitors has been challenging, and the current limitations of HSP90-targeted therapies will be discussed in the last chapter of this review.

Heat shock factors - the guardians of proteostasis

HSP90-dependent regulation of transcription factors is exemplified by steroid hormone receptors, especially the glucocorticoid receptor (GR) as a prototype.[23] GR regulation has been extensively characterized through biochemical and structural studies. In the absence of hormone, GR resides in an inactive cytosolic state, progressing through distinct HSP90-containing chaperone and co-chaperone complexes during its maturation.[12] The co-chaperone FKBP52 can promote nuclear localization of the ligand-bound GR:HSP90 complex, where GR subsequently dimerizes and *trans*-activates its target genes.[24] In the context of stress-inducible transcription, HSP90 is implicated in regulating the activity of HSF1. Within the HSF family, HSF1 is the most widely studied member, as it is considered the master transcriptional regulator of *HSP* genes.[8,25] However, the other members of the HSF family in vertebrates are also important for regulating proteostasis under physiological and pathological conditions. HSF1-5 show amino acid sequence similarity from fish to mammals, whereas HSFX and HSFY orthologs are only found in mammals.[7] A summary of different HSFs, along with their importance in biological processes, is presented in Table 1. Originally identified as heat-inducible transcriptional regulators of *HSP* genes, the HSFs are now known to regulate a multitude of targets beyond those involved in the heat shock response.[6,26-31]

HSFs are multidomain proteins composed of a conserved N-terminal DNA-binding domain (DBD), heptad-repeat domains (HR-A/B and HR-C), a regulatory domain, and a C-terminal transactivation domain (Figure 2a).[7] DNA-binding domain enables HSFs to recognize a *cis*-acting DNA sequence, known as the heat shock element (HSE), that contains an array of the pentamer 5′-nGAAn-3′.[32-34] The heptad repeats HR-A/B and HR-C exhibit conserved leucine-zipper-like characteristics within the HSF family. HR-A/B, the oligomerization domain required for the assembly of trimers, is present only in HSF1, HSF2, and HSF4, which are known to be the stress-responsive members of the HSF family.[6-8] In addition to forming homotrimers, HSF1 and HSF2 interactions can generate a

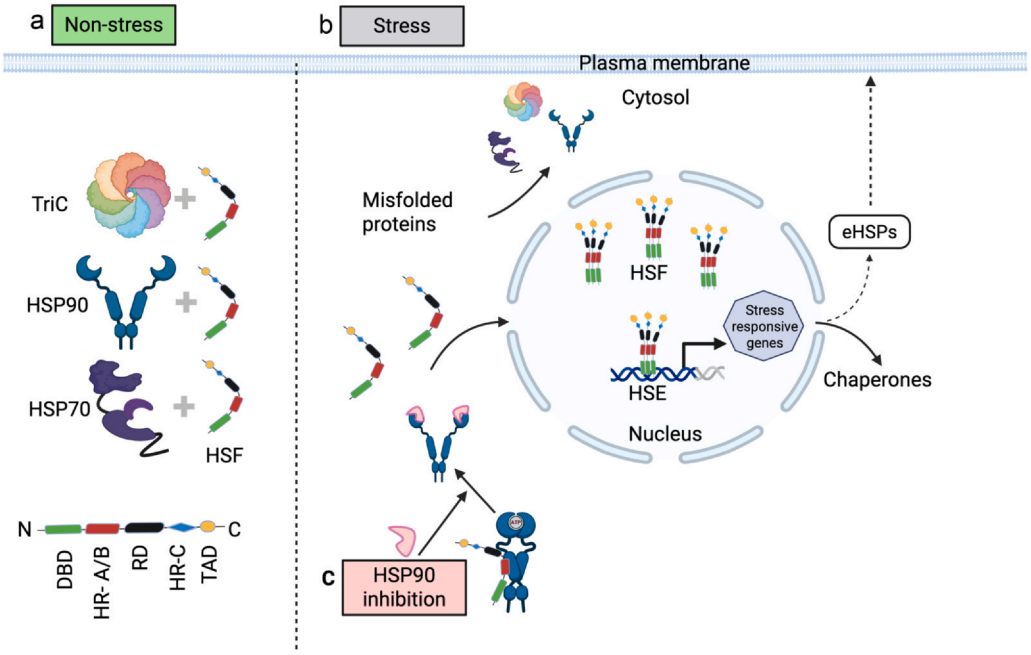

Fig. 2 *The HSF activation cycle according to the chaperone titration model.* (a) According to the chaperone titration model, heat shock factors (HSFs) in non-stressed cells reside as inactive monomers or dimers in the cytosol through association with different molecular chaperones, such as HSP70, HSP90, and TRiC.[36] (b) In response to proteotoxic stress, misfolded or unfolded proteins accumulate and competitively recruit chaperones to protect newly synthesized polypeptides and mature proteins from stress-induced damage or to direct already damaged proteins to degradation. Disruption of HSF-chaperone complexes allows HSFs to form either homo- or heterotrimers and concentrate in the nucleus, where they bind to the *cis*-acting heat shock elements (HSEs) at their target promoters and other regulatory regions in the chromatin to *trans*-activate the genes encoding HSPs among other chaperones and proteostasis factors. Elevated chaperone levels contribute to attenuation of the heat shock response by assisting in releasing HSF trimers from DNA and restoring HSFs to their inactive state (not depicted). In addition to intracellular chaperones, some HSPs, including HSP90, can also be secreted into the extracellular milieu and are called eHSPs.[39] Intriguingly, HSF2 has been found at cell borders, but the functional relevance of this localization is not yet known.[40] (c) Both HSF1 and HSF2 have been shown to associate with HSP90, particularly with conformationally restricted closed HSP90 mutants.[41,42] N-terminal HSP90 inhibitors disrupt this interaction by blocking ATP binding, which promotes HSF release and activation, thereby mimicking the mechanisms of the chaperone titration model. *Note:* Post-translational modifications involved in the regulation of the HSF activation cycle are not included here but are comprehensively reviewed in.[6] DBD, DNA-binding domain; HR-A/B and HR-C, heptad repeat domains A/B and C; RD, regulatory domain; TAD, transactivation domain; eHSP, extracellular HSP. Created in BioRender. Roos-mattjus, P. (2026) https://BioRender.com/5d6ga3d.

heterotrimeric configuration.[33,35] HR-C is required for transcriptional activation and seems to be specific to HSF1 and HSF2. Under physiological conditions, HR-C interacts intramolecularly with HR-A/B, thereby inhibiting trimerization. Transactivation domain serves as a platform for recruiting co-factors and chromatin remodeling proteins, which are critical for the *trans*-activation of *HSPs* and other target genes.[7] Although the molecular mechanisms regulating the intracellular trafficking of HSFs are not fully uncovered, they shuttle between the cytosol and nucleus depending on the cellular milieu.[25,29] Under non-stressed conditions, inactive HSFs are bound to chaperone complexes in the cytosol (Figure 2a). Following exposure to proteotoxic stresses, most chaperones are titrated away, and HSFs are free to translocate to the nucleus, where they form trimers and bind to the HSE to *trans*-activate their target genes (Figure 2b). According to the chaperone titration model, chaperones, when present in sufficient amounts, regulate HSFs through a negative feedback loop, leading to HSF attenuation and termination of the heat shock response.[25,36-38]

Regulatory crosstalk between HSP90 and HSFs

Multiple chaperones have been suggested to regulate HSFs, either positively or negatively. To this end, the interaction between HSP90 and HSF1 lies at the heart of the cellular proteostasis network, playing a vital role under both non-stress and stress conditions. The

presence of nascent polypeptides or metastable proteins increases the demand for molecular chaperones, leading to HSF1 activation. Originally, the Voellmy laboratory identified HSP90 as a repressor of HSF1 using an *in vitro Xenopus* model.[43] HSF1 activation was observed in response to heat shock, non-native proteins, and the HSP90 inhibitor geldanamycin. They proposed that HSP90 plays a non-redundant role in maintaining HSF1 in the cytosol as an inactive monomer and that disruption of the HSP90-HSF1 interaction results in stress-induced HSF1 activation. Depletion of HSP90 co-chaperones, such as HOP, HIP, p23, and CyP40, did not activate HSF1, which suggested that the effect was specific for HSP90.[43] In agreement, overexpression of HSP90 perturbed HSF1 activation and translocation into the nucleus in mouse NIH-3T3 fibroblasts.[44] Already earlier, the HSP90-HSF1 interaction had been shown in an *in vitro* study using cell lysates on immobilized HSP90,[45] and the addition of recombinant human HSF1 protein into reticulocyte lysates decreased binding of HSP90 to HSF1 upon heat shock.[46] These findings demonstrated HSP90-HSF1 interplay, but the functional state of HSF1 (monomeric *versus* trimeric) was not clear. In a separate report, HSP90-HSF1 binding was shown in *Xenopus* oocytes under both non-stressed and stressed conditions.[47] Microinjection of HSP90 antibody into heat-shocked oocytes resulted in a supershift of the HSF-HSE complex in an electrophoretic mobility shift assay accompanied by a delayed attenuation of HSF1 DNA-binding activity. Based on these results, HSP90 was implied to interact with both HSF1 monomers and trimers.[47]

The functional consequence of the interaction between HSP90 and HSF1, as detected in *Xenopus* oocytes and murine cell models, is not fully understood. Using hydrogen-exchange mass spectrometry, the Mayer laboratory investigated alterations in the conformational dynamics of purified monomeric human HSF1 protein, pretreated at 20°C-42°C, and uncovered an intrinsic thermosensory ability of HSF1.[48] Surprisingly, the addition of recombinant HSP90β protein did not inhibit HSF1 trimerization. On the contrary, HSP90β lowered the temperature threshold of HSF1 DNA-binding activity as measured with an electrophoretic mobility shift assay.[48] To address the controversial results of the functional relationship between HSP90 and HSF1, the Neckers laboratory took advantage of the conformational dynamics of the HSP90 chaperone cycle.[41,49] Using ectopically expressed full-length HSF1 in human HEK293T cells, they found in co-immunoprecipitation experiments that the binding of HSF1 was higher to the conformationally restricted closed mutant HSP90α-E47A, representing the stress-inducible isoform, in comparison to the constitutively expressed HSP90β-E42A mutant. Interestingly, treatment with an N-terminal HSP90 inhibitor (17-AAG, STA9090, or SNX-2112), but not a C-terminal HSP90 inhibitor (KU32), disrupted the binding of closed HSP90α-E47A to HSF1 (Figure 2c). These results indicated a mechanism by which the conformational dynamics of HSP90 modulates the interaction between HSP90 and HSF1. This study also suggested that HSP90 can facilitate attenuation of the cellular heat shock response by removing HSF1 trimers from the HSE.[41] However, the chaperone-mediated negative feedback loop of the HSF1 activation cycle is more complex and involves other HSPs besides HSP90 (Figure 2b). Consistently, *in vitro* work from the Mayer laboratory showed that heat shock cognate protein 70, (HSC70), but not HSP90, dissociates HSF1 from DNA.[50] Their study demonstrated that the chaperone HSC70, together with the co-chaperone DNAJB1/HSP40, progressively unzipped DNA-bound HSF1 trimers in a concentration-dependent manner. The role of HSP70 family members in the negative regulation of HSF1 has been established using various model systems, both *in vivo* and *in vitro*, revealing multiple regulatory layers in the HSF1 activation-attenuation cycle.[36]

To date, there is only limited information available on the chaperone-mediated regulation of HSF family members other than HSF1. Nevertheless, we recently reported a physical interaction between conformationally restricted closed HSP90 mutants and endogenous HSF2 in co-immunoprecipitation experiments in HEK293 cells.[42] Exposure to several HSP90 inhibitors, *i.e.*, gambogic acid, gambogenic acid, and 17-AAG, disrupted HSP90-HSF2 binding. Based on these experiments, it is not possible to distinguish if HSF2 is binding to HSP90 directly or *via* HSF1. HSP90 inhibitors extensively disrupted the interaction between HSP90 mutants and HSF1, whereas the interaction between HSP90 and HSF2 was not fully abolished. Since the interaction between closed HSP90 mutants and HSF1 was mapped to the HR-A/B oligomerization domain,[41] our results raise a possibility of an independent binding of HSP90 to HSF2 rather than a heteromeric association with HSF1. Together, we propose that HSF2, like HSF1, forms a drug-sensitive complex with HSP90, revealing a previously unexplored layer of the heat shock response that goes beyond the conventional HSF1-centric model.

Future perspectives and outstanding questions of HSP90-HSF interplay

Understanding how proteostasis imbalance activates HSF1 and how it is restrained under basal conditions is crucial for elucidating the molecular basis of many

proteostasis-related diseases, such as cancer and neurodegeneration. Multiple mechanisms, including oligomerization, post-translational modifications, and subcellular trafficking are known to modulate HSF1 activity. The chaperone titration model provides a common denominator underlying these mechanisms to maintain the balance between HSF1 latency and stress-induced activation.[36] The specific chaperone(s) responsible for maintaining HSF1 in its inactive state has remained unresolved, but several members of the HSP70 and HSP90 families have been reported to bind to HSF1 and regulate its activity.[36,50] Because previous studies *in vivo* and *in vitro* have been performed across diverse model systems, including yeast and higher eukaryotes, direct comparison of the obtained results and conclusions thereof is challenging. Moreover, most of the studies on HSP90 interaction with HSFs have focused solely on HSP90-HSF1 interdependency, overlooking the contribution of HSF2 or other HSF family members. Future studies are warranted to characterize which specific HSP90 isoforms and co-chaperones preferentially participate in the activation-attenuation cycle of HSFs. The HSP90-mediated regulation of HSFs should also be addressed considering the functional impact of the various post-translational modifications that HSP90, its clients, and co-chaperones are subjected to under physiological and pathological conditions.[13]

In addition to the cytosolic and organelle-specific variants of HSP90, it is also secreted, but the functions of extracellular HSP90 (eHSP90) are poorly understood (Figure 2b).[39] Using a cell-impermeable eHSP90 inhibitor (DMAG-N-oxide), the Neckers laboratory observed impaired tumor cell migration and extracellular matrix-dependent cytoskeletal reorganization without affecting intracellular HSP90.[51] Recently, SNX-class HSP90 inhibitors were shown to selectively target eHSP90 and disrupt Fibronectin matrix assembly, highlighting the importance of eHSP90 for the maintenance of the integrity of the extracellular matrix and other components in the extracellular milieu.[52] Important outstanding questions include whether there is a link between eHSP90 and HSFs and whether such interplay would affect cellular properties, for example, adhesion, mechanosensing, motility, and invasion. To date, no extracellular or secreted forms of HSFs have been identified, but HSF2 is found at cell borders in many healthy human tissues.[40] In interactome studies, HSF2 has been shown to directly bind to the focal adhesion adaptor protein Talin-1 and several extracellular matrix proteins.[53] In addition, HSF2-dependent target genes coding for extracellular matrix proteins have been recently reported, supporting a novel role for HSF2 in regulating cell-cell and cell-matrix adhesion.[54-56]

Major challenges posed by the currently available HSP90 inhibitors include their toxicity or potential to induce the heat shock response through disrupting the HSP90-HSF1 complex, which results in the release of HSF1 from the complex, followed by acquisition of its DNA-binding and *trans*-activating capacity. This in turn leads to a vicious circle due to elevated levels of chaperones, including HSP90, thereby counteracting the effects of the HSP90 inhibitors, which can promote malignancy.[22] Despite the negative outcomes of several HSP90 inhibitors for therapeutic purposes in cancer, there is progress in specific cancer types. Pimitespib (TAS-116) was recently approved in Japan for the treatment of gastrointestinal stromal tumors as a monotherapy. Ongoing clinical and preclinical studies are examining the therapeutic potential of pimitespib in combination with immune checkpoint inhibitors and other chemotherapeutic agents, also in other cancer types than gastrointestinal stromal tumors.[22,57] It is worth noting that many of the tested HSP90 inhibitors target all HSP90 family members, leading to toxicity and other adverse effects. Therefore, more recent studies are directed to develop isoform-specific inhibitors. Pimitespib is an example of an inhibitor specific for HSP90α and HSP90β, and it does not bind to Grp94/Gp96 or TRAP1.[57] In addition to the original N-terminal HSP90 inhibitors, new strategies targeting either the C-terminal domain or middle domain of HSP90 have been developed as potential ways to inhibit HSP90 function without inducing the heat shock response. Inhibitors targeting the interaction between HSP90 and its co-chaperones are also considered as possible therapeutic agents in oncology.[58] Inducing the heat shock response through HSP90 inhibitors could be advantageous in neurodegenerative and other diseases, where HSP levels are usually low. For example, HSP90 inhibitors have been used in different neuropathic mouse models, where induction of the heat shock response has beneficial effects.[59] In conclusion, although the development of clinically approved HSP90 inhibitors has been challenging, these compounds have been indispensable for research purposes to elucidate HSP90's functions at the cellular and molecular level.

Despite extensive studies on the chaperone titration model in HSF regulation, several aspects of the HSP90-HSF crosstalk, including the stochiometric relationship, remain unresolved. The question of whether a single HSP90 dimer interacts with HSFs, or whether higher-order chaperone complexes coordinate the activation-attenuation cycle of HSFs, has not been comprehensively addressed. The formation of HSF1-HSF2 heterotrimers and the capacity of HSP90 binding to HSF2 expand the functional consequences of the HSP90-HSF

interplay under various physiological and pathological conditions.[8] A previous study, together with unpublished data from the Roos-Mattjus laboratory indicate that HSF2-deficient U2OS osteosarcoma cells, although still capable of activating HSF1 and the heat shock response, are more sensitive to geldanamycin and 17-AAG than their wild-type counterparts in cell survival assays.[55] In fact, HSF2-deficient cells are almost equally sensitive to the HSP90 inhibitors that induce the heat shock response as HSF1-deficient cells. This suggests that when the heat shock response is induced by HSP90 inhibitors, several HSF1 and HSF2 target genes beyond *HSPs* are activated, potentially providing survival advantages to cancer cells. Therefore, it is important to understand the HSP90-HSF family interdependency when developing novel types of HSP90 inhibitors. The future approaches for development and clinical trials of HSP90 inhibitors for cancer and other diseases require more sophisticated targeting delivery, and precision medical treatments based on improved biomarkers.

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Data availability No data was used for the research described in the article.

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Declaration of Generative AI and AI-Assisted Technologies in the Writing process During the preparation of this work, the authors used ChatGPT and Microsoft Copilot to improve the readability and language of the manuscript. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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