

Mechanisms of Action of HSP110 and Its Cognate Family Members in Carcinogenesis

Rongqi Guo^{1,2,*}, Rui Wang^{1,2,*}, Weisong Zhang^{1,2}, Yangyang Li^{1,2}, Yihao Wang^{1,2}, Hao Wang^{1,2}, Xia Li³, Jianxiang Song^{1,2}

¹Department of Thoracic Surgery, Affiliated Hospital 6 of Nantong University, Yancheng Third People's Hospital, Yancheng, 224000, People's Republic of China; ²Medical School of Nantong University, Nantong, 226007, People's Republic of China; ³Department of General Medicine, Affiliated Hospital 6 of Nantong University, Yancheng Third People's Hospital, Yancheng, 224000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xia Li; Jianxiang Song, Email yycsy161317@163.com; jxsongycsy@163.com

Abstract: Tumors, as chronic malignant diseases that account for about 20% of all deaths worldwide, are the number one threat to human health. Until now there is no reliable treatment for most types of tumors. Tumorigenesis and cellular carcinogenesis remain difficult challenges due to their complex etiology and unknown mechanisms. As stress process regulating molecules and protein folding promoters, heat shock proteins (HSPs) play an important role in cancer development. Most studies have shown that HSPs are one of the major anticancer drug targets. HSPs are not only modulators of the cellular stress response, but are also closely associated with tumor initiation, progression, and drug resistance, so understanding the mechanism of the HSP family involved in cellular carcinogenesis is an important part of understanding tumorigenesis and enabling anticancer drug development. In this review, we discuss the functions and mechanisms of key members of the HSP family (HSP70, HSP90, and HSP110) in participating in the process of tumorigenesis and cell carcinogenesis, and look forward to the prospect of key members of the HSP family in targeted cancer therapy.

Keywords: HSP70, HSP90, HSP110, mechanisms, cancer

Introduction

Cancer accounts for approximately one sixth of all annual deaths worldwide and continues to pose a great challenge to human society as one of the most serious health problems worldwide. With the aging of the global population and changes in lifestyles, the incidence and mortality rates of cancer have increased significantly. It is projected that in 2024 the number of cancer deaths worldwide will reach 10 million. The five-year survival rate for all cancers is approximately 67%. The current common treatments based on chemotherapy and radiotherapy have high side effects and produce drug resistance and other defects; therefore, there is an urgent need to identify new targets for tumor therapy. HSPs, or heat shock proteins, are a class of genetically highly conserved proteins that act as important molecular chaperones in maintaining cellular homeostasis. In addition to their cytoprotective function, they play a key role in the process of cancer onset, progression, metastasis, and drug resistance, and are potential targets for tumor therapy. Heat shock proteins (HSPs) are shown to be overexpressed in many cancers including, but not limited to, breast, endometrial, ovarian, gastric, colon, lung, and prostate cancers, and high levels of HSP expression have been associated with poor prognosis and treatment resistance in cancer patients.¹⁻³ Furthermore, for cancer regulation, in addition to the classical transcriptional regulators that would be involved in the regulation of tumorigenesis and cellular carcinogenesis, heat shock proteins (HSPs) play an important role in a variety of cancer signaling pathways, including tumorigenesis, carcinogenesis, and apoptosis.⁴⁻⁶ Therefore, the role of HSPs as a cancer biomarker is becoming increasingly evident. Cellular carcinogenesis is the terminal manifestation of a destabilized cellular state, and disturbances in cellular proteostasis are among the factors that may drive tumor cell proliferation and metastasis. Thus, tumor cells rely on robust protein folding mechanisms to maintain conformational stability of proteins required for their proliferation. And as key signaling molecules involved in stress processes, Hsp members are closely associated with cancer progression. The Hsp

family broadly consists of Hsp70, Hsp90, Hsp40, and Hsp60.⁷⁻⁹ Among them, the key members of the HSP family are HSP70 and HSP90, of which, the HSP70-associated HSP family responses are classified into classical and nonclassical, where HSP110 belongs to the nonclassical member of HSP70 and plays an important role in cancer. Representative members of the HSP family act as key stress state-sensing molecules involved in tumor cell metastasis, uncontrolled angiogenesis, evasion of anti-growth signals, evasion of apoptosis, cell proliferation, and evasion of senescence. The HSP family of proteins is involved in a wide range of tumor regulation and their interactions occur in tumors. As more and more research related to the HSP family has been conducted, relevant cancer therapeutic drugs as well as regimens targeting HSPs have emerged. Therefore, this paper reviews the functional roles as well as the structural properties of the key members of the HSP family, HSP70, HSP90, and HSP110, in cancer, and outlines their respective therapeutic research. The aim of this paper is to discover the potential of the heat shock protein family as anticancer therapeutic targets.

The Mechanism of HSP70, HSP90, HSP110/Grp170 in Carcinogenesis

The family of HSP thermal proteins includes several subfamilies that are categorized based on their molecular mass and function, with the HSP70 family being the main widely studied and understood branch of the entire family. This family plays a key role in protein folding, assembly, and transport, and protects cells from protein degradation when they are exposed to stressful conditions. The HSP90 family is essential for the regulation of several cell signaling pathways involved in the cell cycle, apoptosis, and stability regulation of multiple signaling proteins. The HSP60 family is mainly active in mitochondria and is involved in protein folding and assembly, which is critical for maintaining mitochondrial function and preventing abnormal protein aggregation. The HSP40/DnaJ family acts as an accessory protein to HSP70 and synergistically participates in protein folding and depolymerization processes, as well as playing an important role in protein mass detection and translocation. Together, these heat shock protein families form a complex and coordinated system that plays an indispensable role in normal cellular function and stress resistance.¹⁻³

HSP70 possesses two major structural domains, the N-terminal nucleotide-binding structural domain (NBD, ~45 kDa) responsible for ATPase activity and the C-terminal substrate-binding structural domain (SBD, ~25 kDa) required for peptide binding. The HSP70 chaperone protein operates in a different state during the functional cycle for the purpose of collaboration with the chaperone protein. HSP70 has its own network with its chaperone proteins, divided into internal and external. In the internal network, HSP70 will play its role by directly interacting with client proteins. The HSP40 chaperone protein plays an important role in the HSP70 mechanism. HSP40 will deliver the client to HSP70, which in turn will stimulate the ATPase structural domain and ultimately put HSP70 into a high affinity (ADP) state.¹⁰ In cells with more HSP40 than HSP70, in particular, under certain conditions, such as high temperature and oxidative stress, HSP40 can rise rapidly before HSP70 when cells are in a high-temperature environment to help HSP70 fold proteins or repair damage more efficiently, which in turn helps protect cells from thermal damage. Studies have shown that heat shock induces the synthesis of HSP40, which enhances the cellular stress response. The presence of oxidizing agents (eg hydrogen peroxide) stimulates the expression of HSP40, which helps cells respond to oxidative damage and repair damaged proteins. This is essential for maintaining cell function and survival.^{11,12} In the tumor microenvironment, HSP40 may have higher expression levels than HSP70 in some cancers due to metabolic abnormalities and protein mutations.^{13,14} The expression of HSP40 is naturally higher than that of HSP70 in some tissues, such as neurons and muscle, where the control of protein folding and misfolding is particularly important.¹⁵ Pathological conditions, where cells need extra help with protein folding, also show significant expression of HSP40 compared to HSP70.¹⁶ The J protein does not require a complete structure to stimulate HSP70 ATPase activity. In addition, the J protein will not interact directly with the client protein itself, but rather will direct HSP70 to the client protein when increased at the level of a specific J structural domain. Thus, HSP40 has an effect on the function of HSP70, which could be useful for subsequent cancer studies.¹⁷ In the external network, HSP70 transfers client proteins to its cooperating chaperone machinery for further folding or explanation. “Explanation” refers to the assessment and processing of the quality and status of client proteins. Specifically, it refers to the process by which HSP70, when delivering proteins to other chaperone proteins (eg HSP90), ensures that these proteins are correctly folded, need to be refolded or should be degraded. This “explanation” process helps to maintain normal function and homeostasis of proteins within the cell. The

two results of the newly synthesized peptide include one spontaneously folded after release by HSP70. The second is degraded after transfer to the HSP90 chaperone protein.

HSP90 exists as a homodimer, and each protomer consists of three structural domains, the N-terminal structural domain (NTD), the middle structural domain (MD), and the C-terminal structural domain (CTD). HSP70 interacts directly with a region of the middle structural domain.^{18,19} HSP90 not only synergizes with HSP70 as an ATP-dependent molecular chaperone, but also maintains enzymatic activity (binding to client proteins and blocking their ability to aggregate). In addition, the enzymatic activity of HSP90 is not dependent on ATP binding and hydrolysis. HSP70–HSP90 organizing protein (HOP), which is composed of tetrapeptide repeat structural domains (TPRs), mediates the interaction of HSP70 with HSP90, with the primary function of delivering client proteins. In addition, the HSP70–HSP90–HOP complex was found to be expressed in many tumors. It has been shown that HSP70–HSP90–HOP action is an indirect mechanism of HSP70 translocation to the surface of tumor cells.²⁰ Objectively, HSP90 undergoes a variety of post-translational modifications such as phosphorylation, acetylation, oxidation, ubiquitination, SUMOylation, S-nitrosylation, and methylation, these modifications maintain tumor cell survival, angiogenesis, anti-apoptosis, and therapeutic resistance by altering the activity, structure or interaction of HSP90 with client proteins. Phosphorylation enhances its binding to key signaling proteins (eg B-Raf, Akt), whereas acetylation inhibits HSP90 interaction with client proteins and promotes their degradation. Oxidation and lipid peroxidation reduce its chaperone function, whereas ubiquitination mediates client protein degradation via CHIP.²¹ SUMOylation and S-nitrosylation alter HSP90 activity and cellular response, and the addition of nitric oxide (NO) groups affects angiogenesis. Methylation increases the binding of HSP90 to client proteins and contributes to cancer cell proliferation and malignant transformation. These are all processes that are mechanisms by which HSP90 chaperones are involved in cancer.²²

HSP110, a member of the HSP70 superfamily, has anti-apoptotic and concomitant properties and is considered one of the key chaperone proteins in cancer cells. This protein is anti-aggregation and exhibits synergistic refolding activity with HSP70, thus promoting efficient protein homeostasis. HSP110 plays an important role in the face of different stress conditions. Especially, it plays a key function in response to cellular adversity and environmental stress.^{23–25} Hsp110 protein and Grp170 are non-canonical branches of the Hsp70 family, which are structurally and functionally similar, with the difference being their respective functions in their different cells, but terminology is generally used without distinction. Hsp110 has an extended acidic insertion located within the substrate-binding domains, SDB- β , and SDB- α subunits, as well as a unique TEDWYLEE motif and a linker fragment that differs from typical HSP70. There are four isoforms of HSP110–HspH1, HspH2, HspH3, and Grp170, of which HspH1, as a key heat shock response protein, plays a crucial role in cellular response to heat shock stress.^{26,27} It effectively prevents cellular damage triggered by heat shock by helping proteins maintain their normal structure and function. In addition, it was found that the content of N^6 -methyladenosine (m^6A) in the 5'-untranslated region (5'-UTR) of HSPH1 mRNA was increased under heat shock conditions, which promoted the synthesis of the HSPH1 protein, revealing a significant role of m^6A modification in regulating HSPH1 expression.²⁸ It has been found that all HSP110 isoforms are associated with the cell cycle protein G-dependent kinase GAK, which is closely related to cell proliferation as well as tumorigenesis. In addition, HspH3 and HspH2 interact with a variety of nuclear pore proteins (eg, POM121, TPR, Nup98, and Nup214) that are implicated in prostate cancer and other cancer types. HspH3 and Grp170 will also interact with EDEM3, which is associated with thyroid cancer. It has been reported that HspH3 interacts with the SUMO protein RANBP2 and influences cell signaling and tumorigenesis by regulating SUMOylation and thereby affecting cell signaling.^{29–32} HSP110 will bind directly to canonical HSP70 through NBD–NBD interactions, thereby facilitating HSP70-mediated protein folding. HSP110, being a chaperone protein for HSP70, will facilitate the exchange of ADP and ATP through canonical HSP70, thereby permitting the release of folded peptides.³³ Overall, HSP110 serves as a chaperone member of proteogenesis and maintains the stability of cellular proteins together with other chaperone proteins such as HSPs. The mutual chaperone cooperation among HSPs members is multifunctional and will satisfy the continuous functional cellularity of oncoprotein complementation in cancer, where altered protein–protein interactions are a major factor in malignant transformation. Therefore, the mutual chaperoning of HSPs family members plays a crucial role in cancer.

The Function of HSP70, HSP90 and HSP110 in Carcinogenesis

HSP70, HSP90, and HSP110, as key members of the HSP family, are considered to be important regulators of cancer cell survival and disease progression, and in cancer, each plays a different mechanism of action. HSP70, HSP90, and HSP110 are all involved in tumor cell metastasis, uncontrolled angiogenesis, evasion of anti-growth signals, evasion of apoptosis, cell proliferation, and evasion of senescence.

The Function of HSP70 in Carcinogenesis

HSP70 inhibits multiple apoptotic pathways, regulates necrosis, bypasses the cellular senescence program, interferes with tumor immunity, promotes angiogenesis, and supports metastasis in order to establish a tumor dominance, and is immunogenic. HSP70 is immunogenic and can trigger an antigen-specific immune response by binding to tumor-derived antigenic peptides. Exosomes release HSP70 to stimulate NK cell activation. The interaction of HSP70 with NK cells is enhanced in the presence of interleukin-2 (IL-2) or IL-15. HSP70 also activates T regulatory cells and promotes inflammatory responses or modulates immune responses through interactions with antigen-presenting cells (APCs). It has been found that two types of HSP70 are present in the serum of cancer patients, one is exosomal HSP70 released by living tumor cells and the other is HSP70 released by dead cancer cells as damage-associated molecular patterns (DAMPs). Initial release of HSP70 suppresses tumors, but HSP70 overload may promote tumor progression.³⁴ In terms of HSP70 affecting the apoptotic pathway enabling cancer progression. During TNF- α -induced apoptosis, the HSP70-CHIP complex promotes proteasomal degradation of apoptosis signal-regulated kinase 1 (ASK1) to inhibit c-Jun N-terminal kinase (JNK) and p38.³⁵ Mitochondrial release of cytochrome c to induce the intrinsic apoptotic pathway requires JNK.³⁶ HSP70 also inhibits apoptosis-inducing factor (AIF), which is required for DNA breakage. HSP70 interacts with TNF-related apoptosis-inducing ligand receptor 1 (TRAIL-R1) and TRAIL-R2 to block the formation of the death-inducing signaling complex (DISC).³⁷ Therefore, HSP70 inhibits apoptosis through caspase-dependent and non-dependent mechanisms in addition to inhibiting JNK, AIF, and interacting with death receptors. HSP70 was found to be present in the lysosomes of cancer cells, so this physiological mechanism can be targeted for relevant drug development.³⁸ HSP70 has two effects on malignant cell necrosis. After necrosis it induces an antitumor response and protects cancer cells from necrotic cell death.³⁹ HSP70 protects against necrotic cell death by inhibiting JNK.³⁰ Furthermore, deletion of HSP70 in cancer can activate an oncogene-induced senescence program. Depending on the expression of different oncogenes, HSP70 inhibits senescence by regulating p53 and the cell cycle kinase Cdc2 as well as HSP70 deletion triggers the activation of p53-dependent or ERK-dependent senescence pathways.^{40,41} In tumor angiogenesis, invasion and metastasis with HIF-1, HSP70 binds and stabilizes HIF-1 α , one of the subunits of HIF-1, in cancer cell lines; furthermore, it has been found that HSP70 binds to the endothelial cell surface to induce angiogenesis via an ERK-dependent mechanism, as well as enhances IL-5-induced angiogenesis through the endothelial-type nitric oxide synthase (eNOS) pathway.^{42,43} The process of cancer cell migration and metastasis is epithelial-mesenchymal transition (EMT), and the effect of HSP70 on cancer metastasis is mainly related to it. Relevant studies have shown that HSP70 induces EMT in hepatocellular carcinoma cells through the p38 MAPK signaling pathway, and the down-regulation of HSP70 destabilizes E-cadherin-catenin complexes, which leads to the migration of tumor cells; moreover, HSP70 not only decreases Smad2 phosphorylation to inhibit TGF- β -induced EMT, but also inhibits phosphorylation of Smad3 and Smad4 as well as the production of reactive oxygen species (ROS) to block high glucose-induced EMT.³⁴

The Function of HSP90 in Carcinogenesis

HSP90 is similar to HSP70 in promoting cancer processes, and in terms of apoptosis, HSP90 is not only involved in the conformational change of Bax and cytochrome c release process, but also interacts with Apaf-1 and thus inhibits the activation of pre-caspase-9 and pre-caspase-3. HSP90 inhibition, on the other hand, downregulates STAT3, survivin, and cyclin D1 and upregulates cytochrome c, caspase-9, and caspase-3.⁴⁴⁻⁴⁶ In addition to apoptosis, HSP90 is associated with necroptosis and autophagy. It has been found that HSP90 inhibitors block necroptosis and affect the stability and function of RIP1 by downregulating MLKL expression and membrane translocation. In KRAS-mutant non-small cell lung cancer cells, HSP90 inhibition not only down-regulates Atg7 and up-regulates caspase 9, but also leads to Beclin 1

proteasome degradation and inhibits TLR3-mediated and TLR4-mediated autophagy.^{47–50} In addition, HSP90 would be involved in focal death by regulating the initiation and activation of the NLRP3 inflammasome and subsequent IL-1 β production.^{5,51,52} HSP90 will lead to tumor cell proliferation by stabilizing mutant p53 in cancer cells. In addition, HSP90 stabilizes epidermal growth factor receptor (EGFR) in tumor cells, thus, HSP90 is essential for promoting the proliferation of cancer cells.^{53,54} It has been found that telomere length is correlated with HSP90, which promotes telomeric DNA binding. In addition, relevant inhibitors of HSP90 down-regulate the phosphorylated form of AKT which in turn leads to apoptosis in senescent cells; these suggest that HSP90 also promotes tumor growth by regulating cellular senescence.^{55,56} It was found that HSP90 stabilizes macrophage migration inhibitory factor (MIF) and thus promotes angiogenesis. It has been reported that the HIF-1 α /VEGF pathway in breast cancer cells under hypoxia is inhibited by HSP90-related inhibitors, thereby suppressing angiogenesis. In addition, HSP90 inhibitors were found to inhibit angiogenesis in triple-negative breast cancer by dysregulating the JAK2/STAT3 pathway and thereby inhibiting angiogenesis.^{57–59} Colon cancer-related studies have found that HSP90 interacts with LRP1 leading to phosphorylation and thus enhanced expression of IKK α /b and NF- κ B, which leads to induction of TCF12, ultimately decreasing E-cadherin and promoting EMT, migration, and invasion. In addition, HSP90 binds to LPR5 and promotes EMT through Akt and Wnt/ β -catenin signaling.^{60,61}

The Function of HSP110 in Different Carcinogenesis

HSP110, being a member of the same family, shares commonalities with HSP70 and HSP90, eg, Hsp110 up-regulation also inhibits cancer cell apoptosis by blocking the release of mitochondrial cytochrome c and inhibiting the activation of caspase 9 and caspase 3 (Figure 1).^{62,63} As studies progressed it was found that HSP110 is upregulated in a variety of malignancies and its overexpression may cause enhancement of Wnt signaling and/or chronic nuclear factor- κ B signaling. In addition, HSP110 is involved in anticancer immunity and, when secreted by cancer cells, promotes macrophage polarization toward the cancer phenotype, whereas its inhibition contributes to macrophage polarization toward the cytotoxic phenotype.^{64–70} Heat shock protein A4 (HSPA4), a member of the HSP110 family, is expressed in many organs and can be induced under different environmental conditions. Reducing the expression of the HSPA4 gene significantly attenuates the migratory, invasive, and transformative activities of tumor cells. HSPA4 is expressed at high levels in malignant tumor cells, and its involvement in tumorigenesis and resistance to chemotherapy may be due to its ability to inhibit tumor cell apoptosis. Overexpression of HSPA4 inhibited apoptosis and prevented the activation of the caspase signaling pathway, leading to the accumulation of misfolded proteins, ROS and DNA damage. HSPA4 (Heat Shock Protein A4) and HSPH1 (Heat Shock Protein H1) are two different heat shock proteins from the same family, which are not the same substance and have some functional differences.⁷¹ A related head and neck squamous cell carcinoma (HNSC) study found that the mutation rate of the HSPH1 gene was about 1.4% in HNSC patients analyzed by the cBioPortal database, the expression level of HSPH1 was significantly higher than that of normal tissues, and there was a significant correlation between the expression of HSPH1 and the tumor stage of HNSC patients. High levels of HSPH1 expression were closely associated with low overall survival in all HNSC patients. In gastric cancer, overexpression of ATF2 resulted in upregulation of HSP110, whereas knockdown of ATF2 resulted in downregulation of HSP110, which, in combination with CHIP-Seq and RNA-Seq, was identified as a target of ATF2. ATF2 gene overexpression promotes the expression of HSP110 thereby inhibiting sorafenib-induced apoptosis of ferroblasts of gastric cancer cells. Knockdown of the HSP110 gene reverses this effect.⁷² HSP110 is exceptionally abundant in colon cancer. Its antiapoptotic properties not only increase the resistance to chemotherapy,⁷³ but also can enhance the activity of STAT3 transcription factor by promoting the activation of STAT3, which directly binds to STAT3, and thus contributes to the phosphorylation of STAT3 by JAK2 and its translocation to the nucleus, thereby triggering the proliferation of colon cancer cells (Figure 1). Notably, induction of HSP110 also activates STAT3, which promotes HSP110 expression by inducing HSP110 transcription. The regulation of STAT3 activity by HSP110 is not limited to intestinal cells. In addition, STAT3 regulates signaling pathways associated with cell proliferation, invasion, and angiogenesis. In malignant hematologic diseases, the expression level of HSPs is significantly elevated, especially in lymphomas, which involves the activation of NF- κ B. HSP110 plays a key role in human non-Hodgkin's lymphoma (NHL). HSP110 stabilizes MyD88 by hindering its proteasomal degradation and stabilizes regulators of the NF- κ B signaling pathway through MyD88. In activated B-cell-like diffuse large B-cell lymphoma (ABC-DLBCL), HSP110 is dependent on

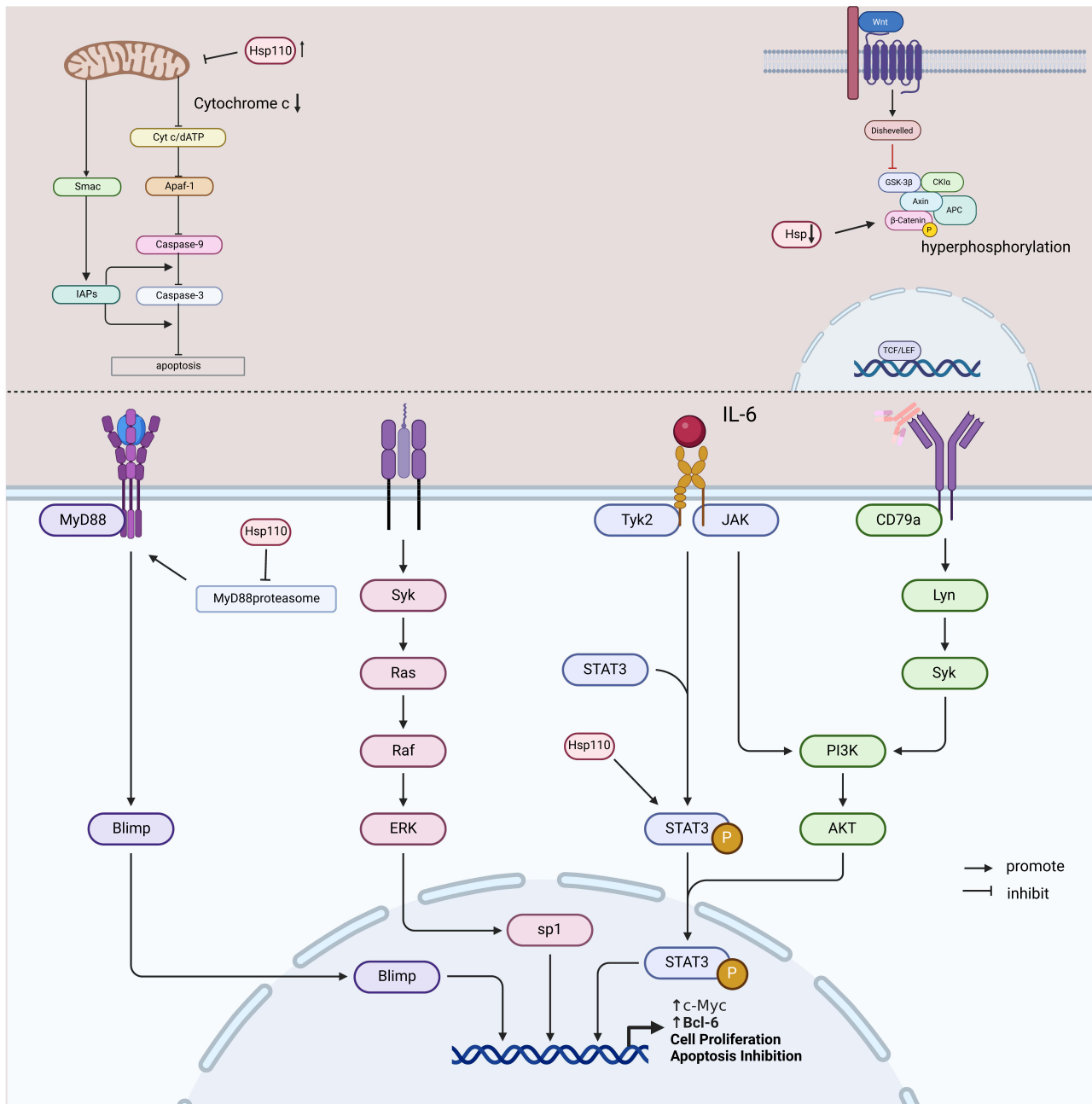


Figure 1 Pathway mechanisms of HSP110 in cancer. Created with BioRender.com.

the NF- κ B signaling pathway to promote growth and survival, and HSP110 may serve as a novel therapeutic target for ABC-DLBCL.⁷⁴ In addition, another study found that HSP110, which displays higher expression levels in non-Hodgkin’s lymphomas, is considered a functional target of aggressive B-NHL, drives growth by promoting the expression of Bcl-6 and c-Myc, and its growth activity is strongly correlated with the presence of c-Myc and/or Bcl-6. In some lymphomas with a higher degree of malignancy, such as diffuse large B-cell lymphoma with a high Ki-67 index and Burkitt’s lymphoma, the expression level of HSP110 is higher. Furthermore, Hsp110 influences the development of malignant meningiomas by regulating the conformational stability of α -synuclein and thereby affecting the development of malignant meningiomas.⁷⁵ Lung cancer studies have found that inhibition of HSP110 expression in non-small cell lung cancer (NSCLC) cells significantly improves the anticancer effect of gefitinib. By decreasing HSP110 levels, β -catenin is destabilized in cancer cells, as this leads to the detachment of PP2A from the β -catenin degradation complex, which in turn promotes

hyperphosphorylation and subsequent degradation of β -catenin. In contrast, upregulation of HSP110 in cancer cells was associated with increased levels of nuclear β -catenin protein, which plays a key role in the development of acquired resistance to EGFR-TKIs in NSCLC (Figure 1).⁷⁶ In healthy oral mucosal epithelium, HSP110 expression is considered weak, whereas oral cancer shows stronger HSP110 expression than healthy oral epithelium.⁷⁷ The expression of HSP110 is significantly higher in melanoma than in normal pigmented nevi.⁷⁸ It has also been found to be significantly increased in thyroid, esophageal, breast, bladder, pancreatic islet cell tumors, gastric malignant lymphomas, pheochromocytomas, and testicular seminomas. In normal human adult tissues, high expression of HSP105 is mainly confined to the testis, more fully emphasizing its potential as a potential diagnostic tool and future immunotherapy target.⁷⁹ In the presence of LPS or IL-6, HSP110 enhances STAT3 phosphorylation in macrophages but does not produce this effect in untreated normal macrophages. The reduction of HSP110 instead inhibited STAT3 phosphorylation in LPS-treated macrophages (Figure 1). HSP110 has a direct interaction with STAT3 in LPS-treated macrophages. In addition, increased KLF2 decreases HSPH1 expression, which reduces LPS-induced STAT3 phosphorylation by inhibiting gene transcription of HSP110.⁸⁰ HSP110 is abundant in the tumor microenvironment, and its presence leads to the polarization of human primary monocytes toward M2-type macrophages, as evidenced by an increase in CD206 expression and a decrease in the expression of the M1 marker HLA-DR, for which HSP110 has emerged as an important target.⁸¹ The following are functions in HSP70, HSP90, and HSP110 cancers (Table 1).

The Therapies of HSP70, HSP90, HSP110 in Carcinogenesis

As research related to HSPs has intensified in recent years, more and more drugs have been developed for the treatment of cancer-related diseases. But most of the drugs have not been subjected to clinical trials and the shortcomings of the drugs are gradually being discovered. Currently, therapeutic studies of HSP70 and HSP90 are focused on molecular inhibitors and immunotherapy, as well as novel therapeutic approaches, but relatively few therapeutic studies have been conducted on HSP110, and the development of drugs for it has been based on similar mechanisms in other family members.

Table 1 HSP70, HSP90, and HSP110 Functions in Cancer

	HSP70	HSP90	HSP110
Inhibition of apoptosis	Inhibition of ASK1, JNK, AIF; interference with TRAIL-R1/R2 prevents DISC formation; inhibition of caspase dependent/non-dependent apoptotic mechanisms	Interferes with Bax conformational changes; inhibits caspase-9/3 activation	Inhibits cytochrome c release and caspase activation to prevent apoptosis
Necrosis and necrotic prolapse	Inhibits JNK and protects cancer cells from necrosis	Influence on necrotic prolapse through regulation of MLKL and RIP1	Influence on macrophage phenotype and necrosis regulation
Immunomodulation	Activates NK cells, T cells, and APCs via exosomes; affects DAMPs	Modulation of NLRP3 inflammasome and induction of IL-1 β release	Polarized macrophages with enhanced M2 phenotype in the tumor microenvironment
Angiogenesis	Stabilization of HIF-1 by binding to HIF-1 α ; enhancement of IL-5-induced angiogenesis via the eNOS pathway	Stabilizes MIF and promotes VEGF pathway; interferes with JAK2/STAT3 to inhibit angiogenesis	Enhancement of STAT3 activity in macrophages to promote angiogenesis
Migration and relocation	Regulation of EMT via p38 MAPK; interference with E-cadherin complexes	Promotion of EMT and invasion through Wnt/ β -catenin signaling	Upregulation of STAT3 enhances cancer cell migration and invasion
Deteriorate with age	Inhibition of senescence through p53, Cdc2 regulation	HSP90 inhibition promotes telomere degradation and activates the AKT pathway	Regulation of STAT3, NF- κ B signaling pathways affecting aging and tumor growth

HSP70

Molecular Inhibitor

There are various inhibitors of the N-terminal ATP-binding structural domain of HSP70, such as 15-deoxytangeretin (15-DSG), VER-155008, MKT-077, etc., which inhibit the ATPase activity of HSP70 thereby blocking cell proliferation or inducing apoptosis. 15-DSG is a natural immunosuppressant but does not work well in tumor cells. The second-generation MAL3-101 and derivatives and VER-155008 are more effective in combination with HSP90 inhibitors. The novel HSP70 inhibitor AZ not only inhibits HSP70 ATPase activity on the lysosomal membrane and induces lysosome-mediated apoptosis in cancer cells, but also attacks the mitochondrial HSP70 molecule mortalin, blocking its interaction with p53, which in turn triggers mitochondria-mediated apoptosis. However, this novel inhibitor has not been tested in patients, so it is not ready for clinical application.^{82,83} ATPase inhibitors have shown efficacy both in vivo and ex vivo due to their ability to target multiple HSP70 isoforms, which is potentially beneficial in multiple HSP70 isoform overexpressing cancer types. However, because different HSP70 family members vary in specific cancer types, subsequent studies will have to take this into account. Understanding the functional cycle of HSP70, including its conformational changes, interactions between structural domains, and the mechanisms of HSP70 in different cancers will be paramount to the development of effective HSP70 inhibitors.^{82,84,85}

Immunotherapy Methods

The development of monoclonal antibodies and vaccines is also a promising immunotherapeutic strategy for HSP70. Monoclonal antibodies, such as cmHSP70.1, which can more accurately target HSP70 by virtue of its high antigenic specificity and has fewer side effects, have already produced results in colon cancer patients. The HSP70 vaccine has also emerged as another option for cancer immunotherapy, and its related vaccine has been tested in clinical trials in patients with cervical intraepithelial neoplasia. In addition, related natural killer (NK) cell immunotherapies are being evaluated.^{6,86,87}

Other Treatments

In recent years, in addition to the above methods, emerging targeted drugs, aptamers, including DNA and RNA aptamers as well as peptide aptamers, can bind target molecules by virtue of their high specificity and affinity, which, although functionally similar to antibodies, have the advantages of small molecular weight and reduced immunogenicity. They are suitable for binding to the N-terminal ATP-binding domain (NBD) or SBD target of HSP70, thereby inhibiting its function and contributing to cancer cell death. A17 is one of the effective aptamers that inhibits the function of HSP70 by virtue of specifically attacking its NBD. A17 in combination with cisplatin enhances apoptosis in HeLa cells and displays antitumor properties, making it a potential cancer treatment option.⁸⁸

HSP90

Molecular Inhibitor

HSP90 inhibitors inhibit the function of the HSP90 molecule primarily by targeting its N-terminal ATP-binding domain, blocking the cycling between ATP- and ADP-bound conformations, and thereby impairing HSP90 function. Geldanamycin (GM) and Radicolol (RD) were early natural inhibitors of HSP90 used in cancer therapy but failed due to structural instability and toxicity issues, whereas the new biotin inhibits cancer cell growth and avoids the compensatory heat shock response by targeting the C-terminus of HSP90, but its clinical efficacy has not yet been validated. In addition to natural inhibitors, synthetic HSP90 inhibitors are under development, such as the purine analogs PU-H71 and PU-DZ8 that bind HSP90 by competing with ADP, but have not been further evaluated; CNF-2024 was found to be effective in lymphoma; SNX-5422 was suspended from development due to ocular toxicity; and KU174 was effective against the C-terminus of HSP90 but was not clinically tested, suggesting that these synthetic inhibitors require further study.^{6,89-94}

Immunotherapy Methods

Due to the ability of HSP90 to activate CD8⁺ and CD4⁺ T cells, several HSP90 vaccines and immunotherapies were born. A team of researchers has identified an innovative ER HSP90-secreted form of Gp96-Ig that mimics the release of HSPs from necrotic cells, which in turn triggers tumor rejection by CD8⁺ T cells. The Gp96-Ig vaccine was effective in clinical trials in patients with non-small cell lung cancer and, in addition, improved survival in patients with PD-L1+ advanced lung cancer

when combined with a PD-1 inhibitor. Multi-chaperone vaccines such as CRCL and mHSP/peptide vaccines contain a variety of HSPs that activate dendritic cells and NK cells, which in turn enhance antitumor immune responses.⁹⁵

HSP110

There are fewer therapeutic studies on HSP110 compared to HSP70 and HSP90, but HSP110, as a chaperone protein, has important targeting potential in cancer therapy. In the same vein as HSP70 and HSP90, small molecule inhibitors can bind to the nucleotide-binding domain (NBD) of HSP110, which in turn inhibits its ATPase activity, but it should be considered that since the enzymatic chaperone function of HSP110 is not regulated by nucleotides, nucleotide mimics may not interfere with their direct chaperone action but may disrupt its nucleotide (NEF) function that in turn affects the folding and function of cancer-related proteins. An alternative approach to develop inhibitors by selectively targeting the SBD of HSP110, such as the drug candidate 2-phenylethylsulfonamide (PES), which targets the Hsp70 SBD, and the TKD motif-directed peptide inhibitor cmHsp70.1 are currently in clinical trials. Since HSP110 synergizes with other HSPs, it may be possible to inhibit the folding of cancer-associated proteins by disrupting the chaperone proteins of HSP110. Thus, HSP110 inhibition shows great promise in cancer therapy.^{74,96}

Possible Future Treatment Options: HSP70, HSP90, and HSP110

Based on the above functional mechanisms of the HSP family, we can envision more anticancer therapies. Personalized therapeutic regimens can be developed based on differences in the expression profiles of HSP family members in different types of cancers, eg, detecting high expression levels of HSP110 or HSP70 can help to screen for groups of patients who are more suitable for targeting these proteins. In addition, the expression levels of HSP70 and HSP90 could also serve as potential biomarkers for predicting patient response to immunotherapy. HSP70 and HSP90 play important roles in the survival, proliferation, and metastasis of tumor cells. Specific inhibitors targeting the HSP70–HSP90–HOP complex can reduce the growth and spread of cancer cells by blocking the function of such complexes. Future studies could further optimize these inhibitors to improve their specificity and therapeutic efficacy while reducing side effects on normal cells. HSP70 is immunogenic and triggers specific immune responses by binding to antigenic peptides of tumor origin. Many human HSP70 vaccines have been developed, such as the HPV16 oE7 fusion protein vaccine,⁹⁷ and a trend has been established that future therapeutic regimens may be developed with more vaccines against HSP70 to enhance the immune response against the tumor. In addition, the property of HSP70 to promote the activation of NK cells and T regulatory cells was utilized to enhance the antitumor immune effect by combining interleukins (eg, IL-2 or IL-15). Multiple post-translational modifications (eg, phosphorylation, acetylation, ubiquitination, etc.) of HSP90 are functionally essential. Development of specific inhibitors targeting these modifications and future therapies may more precisely regulate HSP90 activity in cancer cells, thereby inhibiting tumor progression. HSP110 is highly expressed in a variety of cancers and correlates with chemotherapy resistance, so inhibitors that can interfere with the interaction of HSP110 with key signaling pathways, such as STAT3, may play a key role in anticancer therapy. Combining HSP110 inhibitors with other therapies (eg, drugs targeting STAT3) may enhance treatment efficacy and overcome drug resistance. In addition, HSP110 inhibits antitumor immunity by affecting macrophage polarization, so targeting HSP110 can modulate the direction of macrophage polarization and enhance its antitumor effect, while weakening the tumor's ability to evade the immune system, thus improving the efficacy of immunotherapy. Given that HSP70, HSP90, and HSP110 each play unique roles in different stages and types of tumors, future therapeutic regimens may consider combinations of inhibitors or modulators of these HSPs to achieve broader and synergistic antitumor effects. This multi-targeted therapeutic approach may demonstrate enhanced efficacy in inhibiting the multifaceted growth mechanisms of tumors.

Conclusion

In conclusion, HSP70, HSP90, and HSP110, as core members of the heat shock protein (HSP) family, play critical roles in cancer initiation and progression. Together, these proteins maintain intracellular protein homeostasis, resist apoptosis, support cell proliferation, and promote angiogenesis and metastasis, ensuring the survival and malignant spread of cancer cells. HSP70 affects tumor growth primarily by regulating apoptotic pathways, immune responses, and cell migration, whereas HSP90, by interacting with key molecules in the signaling pathway, in turn inhibits apoptosis and promotes cell

division, and HSP110, as a co-chaperone of HSP70, not only helps maintain protein folding homeostasis but also plays an important role in various cancers by regulating signaling, enhancing drug resistance and influencing the immune microenvironment. Interactions between HSP family members (eg the network of HSP70 and HSP90) not only enhance the adaptive capacity of cancer cells, but are also closely associated with cancer drug resistance. Therefore, inhibitors targeting HSP70, HSP90, and HSP110 have great potential for use in future cancer therapies, and related inhibitors and immunotherapies are beginning to enter clinical trials, promising new opportunities for diagnosis and treatment. These studies lay the foundation for further exploration of new strategies for heat shock proteins in cancer therapy, while highlighting their critical status as multifunctional tumor regulators.

Acknowledgment

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors, and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Nahleh Z, Tfayli A, Najm A, El Sayed A, Nahle Z. Heat shock proteins in cancer: targeting the ‘chaperones’. *Future Med Chem.* 2012;4(7):927–935. doi:10.4155/fmc.12.50
2. Ciocca DR, Calderwood SK. Heat shock proteins in cancer: diagnostic, prognostic, predictive, and treatment implications. *Cell Stress Chaperones.* 2005;10(2):86–103. doi:10.1379/csc-99r.1
3. Kumar S, Stokes J, Singh UP, et al. Targeting Hsp70: a possible therapy for cancer. *Cancer Lett.* 2016;374(1):156–166. doi:10.1016/j.canlet.2016.01.056
4. Youness RA, Gohar A, Kiriacos CJ, El-Shazly M. Heat shock proteins: central players in oncological and immuno-oncological tracks. *Adv Exp Med Biol.* 2023;1409:193–203. doi:10.1007/5584_2022_736
5. Albakova Z, Mangasarova Y. The HSP immune network in cancer. *Front Immunol.* 2021;12:796493. doi:10.3389/fimmu.2021.796493
6. Chatterjee S, Burns TF. Targeting heat shock proteins in cancer: a promising therapeutic approach. *Int J Mol Sci.* 2017;18(9):1978. doi:10.3390/ijms18091978
7. Hagymasi AT, Dempsey JP, Srivastava PK. Heat-Shock Proteins. *Curr Protoc.* 2022;2(11):e592. doi:10.1002/cpz1.592
8. Cornford PA, Dodson AR, Parsons KF, et al. Heat shock protein expression independently predicts clinical outcome in prostate cancer. *Cancer Res.* 2000;60(24):7099–7105. PMID: 11156417.
9. van de Vijver MJ, He YD, Van't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. *N Engl J Med.* 2002;347(25):1999–2009. doi:10.1056/NEJMoa021967
10. Jiang Y, Rossi P, Kalodimos CG. Structural basis for client recognition and activity of Hsp40 chaperones. *Science.* 2019;365(6459):1313–1319. doi:10.1126/science.aax1280
11. Cyran AM, Zhitkovich A. Heat shock proteins and HSF1 in cancer. *Front Oncol.* 2022;12:860320. doi:10.3389/fonc.2022.860320
12. Nitzsche B, Höpfner M, Biersack B. Synthetic small molecule modulators of Hsp70 and Hsp40 chaperones as promising anticancer agents. *Int J Mol Sci.* 2023;24(4):4083. doi:10.3390/ijms24044083
13. Mitra A, Shevde LA, Samant RS. Multi-faceted role of HSP40 in cancer. *Clin Exp Metastasis.* 2009;26(6):559–567. doi:10.1007/s10585-009-9255-x
14. Moses MA, Kim YS, Rivera-Marquez GM, et al. Targeting the Hsp40/Hsp70 chaperone axis as a novel strategy to treat castration-resistant prostate cancer. *Cancer Res.* 2018;78(14):4022–4035. doi:10.1158/0008-5472.CAN-17-3728
15. Pomella S, Cassandri M, Antoniani F, et al. Heat shock proteins: important helpers for the development, maintenance and regeneration of skeletal muscles. *Muscles.* 2023;2:187–203. doi:10.3390/muscles2020014
16. Modrzejewska M, Zdanowska O. The role of heat shock protein 70 (HSP70) in the pathogenesis of ocular diseases-current literature review. *J Clin Med.* 2024;13(13):3851. doi:10.3390/jcm13133851
17. Kampinga HH, Craig EA. The HSP70 chaperone machinery: j proteins as drivers of functional specificity. *Nat Rev Mol Cell Biol.* 2010;11(8):579–592. doi:10.1038/nrm2941
18. Prodromou C. Mechanisms of Hsp90 regulation. *Biochem J.* 2016;473(16):2439–2452. doi:10.1042/BCJ20160005

19. Schopf FH, Biebl MM, Buchner J. The HSP90 chaperone machinery. *Nat Rev Mol Cell Biol.* 2017;18(6):345–360. doi:10.1038/nrm.2017.20
20. Scheuffer C, Brinker A, Bourenkov G, et al. Structure of TPR domain-peptide complexes: critical elements in the assembly of the Hsp70-Hsp90 multichaperone machine. *Cell.* 2000;101(2):199–210. doi:10.1016/S0092-8674(00)80830-2
21. Wang AM, Morishima Y, Clapp KM, et al. Inhibition of hsp70 by methylene blue affects signaling protein function and ubiquitination and modulates polyglutamine protein degradation. *J Biol Chem.* 2010;285(21):15714–15723. doi:10.1074/jbc.M109.098806
22. Mollapour M, Neckers L. Post-translational modifications of Hsp90 and their contributions to chaperone regulation. *Biochim Biophys Acta.* 2012;1823(3):648–655. doi:10.1016/j.bbamcr.2011.07.018
23. Finka A, Mattoo RU, Goloubinoff P. Experimental milestones in the discovery of molecular chaperones as polypeptide unfolding enzymes. *Annu Rev Biochem.* 2016;85:715–742. doi:10.1146/annurev-biochem-060815-014124
24. Mogk A, Bukau B, Kampina HH. Cellular handling of protein aggregates by disaggregation machines. *Mol Cell.* 2018;69(2):214–226. doi:10.1016/j.molcel.2018.01.004
25. Mattoo RUH, Sharma SK, Priya S, Finka A, Goloubinoff P. Hsp110 is a bona fide chaperone using ATP to unfold stable misfolded polypeptides and reciprocally collaborate with Hsp70 to solubilize protein aggregates. *J Biol Chem.* 2013;288(29):21399–21411. doi:10.1074/jbc.M113.479253
26. Zininga T, Achilonu I, Hoppe H, Prinsloo E, Dirr HW, Shonhai A. Plasmodium falciparum Hsp70-z, an Hsp110 homologue, exhibits independent chaperone activity and interacts with Hsp70-1 in a nucleotide-dependent fashion. *Cell Stress Chaperones.* 2016;21(3):499–513. doi:10.1007/s12192-016-0678-4
27. Giuliani C. The flavonoid quercetin induces AP-1 activation in FRTL-5 thyroid cells. *Antioxidants.* 2019;8(5):112. doi:10.3390/antiox8050112
28. Miao W, Yang YY, Wang Y. Quantitative proteomic analysis revealed broad roles of N6-methyladenosine in heat shock response. *J Proteome Res.* 2021;20(7):3611–3620. doi:10.1021/acs.jproteome.1c00191
29. Ray MR, Wafa LA, Cheng H, et al. Cyclin G-associated kinase: a novel androgen receptor-interacting transcriptional coactivator that is overexpressed in hormone refractory prostate cancer. *Int J Cancer.* 2006;118(5):1108–1119. doi:10.1002/ijc.21469
30. Rodriguez-Bravo V. Nuclear pores promote lethal prostate cancer by increasing POM121-Driven E2F1, MYC, and AR nuclear import. *Cell.* 2018;174(5):1200–1215.e20. doi:10.1016/j.cell.2018.07.015
31. Nofrini V, Di Giacomo D, Mecucci C. Nucleoporin genes in human diseases. *Eur J Hum Genet.* 2016;24(10):1388–1395. doi:10.1038/ejhg.2016.25
32. Han ZJ, Feng YH, Gu BH, Li YM, Chen H. The post-translational modification, SUMOylation, and cancer (Review). *Int J Oncol.* 2018;52(4):1081–1094. doi:10.3892/ijo.2018.4280
33. Rosenzweig R. Promiscuous binding by Hsp70 results in conformational heterogeneity and fuzzy chaperone-substrate ensembles. *eLife.* 2017;6:e28030. doi:10.7554/eLife.28030
34. Albakova Z. HSP70 Multi-Functionality in Cancer. *Cells.* 2020;9(3):587. doi:10.3390/cells9030587
35. Gao Y, Han C, Huang H, et al. Heat shock protein 70 together with its co-chaperone CHIP inhibits TNF-alpha induced apoptosis by promoting proteasomal degradation of apoptosis signal-regulating kinase1. *Apoptosis.* 2010;15(7):822–833. doi:10.1007/s10495-010-0495-7
36. Tournier C, Hess P, Yang DD, et al. Requirement of JNK for stress-induced activation of the cytochrome c-mediated death pathway. *Science.* 2000;288:870–874. doi:10.1126/science.288.5467.870
37. Guo F, Sigua C, Bali P, et al. Mechanistic role of heat shock protein 70 in Bcr-Abl-mediated resistance to apoptosis in human acute leukemia cells. *Blood.* 2005;105(3):1246–1255. doi:10.1182/blood-2004-05-2041
38. Nylandsted J, Gyrd-Hansen M, Danielewicz A, et al. Heat shock protein 70 promotes cell survival by inhibiting lysosomal membrane permeabilization. *J Exp Med.* 2004;200(4):425–435. doi:10.1084/jem.20040531
39. Karsch-Bluman A, Feiglin A, Arbib E, et al. Tissue necrosis and its role in cancer progression. *Oncogene.* 2019;38(11):1920–1935. doi:10.1038/s41388-018-0555-y
40. Yaglom JA, Gabai VL, Sherman MY. High levels of heat shock protein Hsp72 in cancer cells suppress default senescence pathways. *Cancer Res.* 2007;67(5):2373–2381. doi:10.1158/0008-5472.CAN-06-3796
41. Gabai VL, Yaglom JA, Waldman T, Sherman MY. Heat shock protein Hsp72 controls oncogene-induced senescence pathways in cancer cells. *Mol Cell Biol.* 2009;29(2):559–569. doi:10.1128/MCB.01041-08
42. Kim TK, Na HJ, Lee WR, Jeoung MH, Lee S. Heat shock protein 70-1A is a novel angiogenic regulator. *Biochem Biophys Res Commun.* 2016;469(2):222–228. doi:10.1016/j.bbrc.2015.11.125
43. Park SL, Chung TW, Kim S, et al. HSP70-1 is required for interleukin-5-induced angiogenic responses through eNOS pathway. *Sci Rep.* 2017;7:44687. doi:10.1038/srep44687
44. Zhao X, Wang J, Xiao L, et al. Effects of 17-AAG on the cell cycle and apoptosis of H446 cells and the associated mechanisms. *Mol Med Rep.* 2016;14(2):1067–1074. doi:10.3892/mmr.2016.5365
45. Peng C, Zhao F, Li H, Li L, Yang Y, Liu F. HSP90 mediates the connection of multiple programmed cell death in diseases. *Cell Death Dis.* 2022;13(11):929. doi:10.1038/s41419-022-05373-9
46. Nimmanapalli R, O'Bryan E, Kuhn D, Yamaguchi H, Wang HG, Bhalla KN. Regulation of 17-AAG-induced apoptosis: role of Bcl-2, Bcl-XL, and Bax downstream of 17-AAG-mediated down-regulation of Akt, Raf-1, and Src kinases. *Blood.* 2003;102(1):269–275. doi:10.1182/blood-2002-12-3718
47. Wu Z, Geng Y, Lu X, et al. Chaperone-mediated autophagy is involved in the execution of ferroptosis. *Proc Natl Acad Sci U S A.* 2019;116(8):2996–3005. doi:10.1073/pnas.1819728116
48. Jacobsen AV, Lowes KN, Tanzer MC, et al. HSP90 activity is required for MLKL oligomerisation and membrane translocation and the induction of necroptotic cell death. *Cell Death Dis.* 2016;7(1):e2051. doi:10.1038/cddis.2015.386
49. Gentle IE, Wong WW, Evans JM, et al. In TNF-stimulated cells, RIPK1 promotes cell survival by stabilizing TRAF2 and cIAP1, which limits induction of non-canonical NF-κB and activation of caspase-8. *J Biol Chem.* 2016;291(5):2547. doi:10.1074/jbc.A110.216226
50. Fearnis C, Pan Q, Mathison JC, Chuang TH. Triad3A regulates ubiquitination and proteasomal degradation of RIP1 following disruption of Hsp90 binding. *J Biol Chem.* 2006;281(45):34592–34600. doi:10.1074/jbc.M604019200
51. Spel L, Hou C, Theodoropoulou K, et al. HSP90β controls NLRP3 autoactivation. *Sci Adv.* 2024;10(9):eadj6289. doi:10.1126/sciadv.adj6289
52. Nizami S, Arunasalam K, Green J, et al. Inhibition of the NLRP3 inflammasome by HSP90 inhibitors. *Immunology.* 2021;162(1):84–91. doi:10.1111/imm.13267
53. Wu H, Dyson HJ. Aggregation of zinc-free p53 is inhibited by Hsp90 but not other chaperones. *Protein Sci.* 2019;28(11):2020–2023. doi:10.1002/pro.3726

54. Ahsan A, Ramanand SG, Whitehead C, et al. Wild-type EGFR is stabilized by direct interaction with HSP90 in cancer cells and tumors. *Neoplasia*. 2012;14(8):670–677. doi:10.1593/neo.12986
55. Grandin N, Charbonneau M. Hsp90 levels affect telomere length in yeast. *Mol Genet Genomics*. 2001;265(1):126–134. doi:10.1007/s004380000398
56. Fuhrmann-Stroissnigg H, Ling YY, Zhao J, et al. Identification of HSP90 inhibitors as a novel class of senolytics. *Nat Commun*. 2017;8(1):422. doi:10.1038/s41467-017-00314-z
57. Kim JY, Cho TM, Park JM, et al. A novel HSP90 inhibitor SL-145 suppresses metastatic triple-negative breast cancer without triggering the heat shock response. *Oncogene*. 2022;41(23):3289–3297. doi:10.1038/s41388-022-02269-y
58. Zhang PC, Liu X, Li MM, et al. AT-533, a novel Hsp90 inhibitor, inhibits breast cancer growth and HIF-1 α /VEGF/VEGFR-2-mediated angiogenesis in vitro and in vivo. *Biochem Pharmacol*. 2020;172:113771. doi:10.1016/j.bcp.2019.113771
59. Klemke L, De oliveira T, Witt D, et al. Hsp90-stabilized MIF supports tumor progression via macrophage recruitment and angiogenesis in colorectal cancer. *Cell Death Dis*. 2021;12(2):155. doi:10.1038/s41419-021-03426-z
60. Wang H, Deng G, Ai M, et al. Hsp90ab1 stabilizes LRP5 to promote epithelial-mesenchymal transition via activating of AKT and Wnt/ β -catenin signaling pathways in gastric cancer progression. *Oncogene*. 2019;38(9):1489–1507. doi:10.1038/s41388-018-0532-5
61. Chen WS, Chen CC, Chen LL, Lee CC, Huang TS. Secreted heat shock protein 90 α (HSP90 α) induces nuclear factor- κ B-mediated TCF12 protein expression to down-regulate E-cadherin and to enhance colorectal cancer cell migration and invasion. *J Biol Chem*. 2013;288(13):9001–9010. doi:10.1074/jbc.M112.437897
62. Yamagishi N, Ishihara K, Saito Y, Hatayama T. Hsp105 family proteins suppress staurosporine-induced apoptosis by inhibiting the translocation of Bax to mitochondria in HeLa cells. *Exp Cell Res*. 2006;312(17):3215–3223. doi:10.1016/j.yexcr.2006.06.007
63. Hatayama T, Yamagishi N, Minobe E, Sakai K. Role of hsp105 in protection against stress-induced apoptosis in neuronal PC12 cells. *Biochem Biophys Res Commun*. 2001;288(3):528–534. doi:10.1006/bbrc.2001.5802
64. Nakatsura T, Senju S, Yamada K, Jotsuka T, Ogawa M, Nishimura Y. Gene cloning of immunogenic antigens overexpressed in pancreatic cancer. *Biochem Biophys Res Commun*. 2001;281(4):936–944. doi:10.1006/bbrc.2001.4377
65. Zappasodi R, Bongarzone I, Ghedini GC, et al. Serological identification of HSP105 as a novel non-Hodgkin lymphoma therapeutic target. *Blood*. 2011;118(16):4421–4430. doi:10.1182/blood-2011-06-364570
66. Ruggiero G, Guarnotta C. HSPH1 inhibition downregulates Bcl-6 and c-Myc and hampers the growth of human aggressive B-cell non-Hodgkin lymphoma. *Blood*. 2015;125(11):1768–1771. doi:10.1182/blood-2014-07-590034
67. Yu N, Kakunda M, Pham V, et al. HSP105 recruits protein phosphatase 2A to dephosphorylate β -catenin. *Mol Cell Biol*. 2015;35(8):1390–1400. doi:10.1128/MCB.01307-14
68. Berthenet K, Bokhari A, Lagrange A, et al. HSP110 promotes colorectal cancer growth through STAT3 activation. *Oncogene*. 2017;36(16):2328–2336. doi:10.1038/onc.2016.403
69. Boudesco C, Verhoeven E, Martin L, et al. HSP110 sustains chronic NF- κ B signaling in activated B-cell diffuse large B-cell lymphoma through MyD88 stabilization. *Blood*. 2018;132(5):510–520. doi:10.1182/blood-2017-12-819706
70. Berthenet K, Boudesco C, Collura A, et al. Extracellular HSP110 skews macrophage polarization in colorectal cancer. *Oncoimmunology*. 2016;5(7):e1170264. doi:10.1080/2162402X.2016.1170264
71. Wu CY, Lin CT, Wu MZ, Wu KJ. Induction of HSPA4 and HSPA14 by NBS1 overexpression contributes to NBS1-induced in vitro metastatic and transformation activity. *J Biomed Sci*. 2011;18(1):1. doi:10.1186/1423-0127-18-1
72. Xu X, Li Y, Wu Y, et al. Increased ATF2 expression predicts poor prognosis and inhibits sorafenib-induced ferroptosis in gastric cancer. *Redox Biol*. 2023;59:102564. doi:10.1016/j.redox.2022.102564
73. Dorard C, de Thonel A, Collura A, et al. Expression of a mutant HSP110 sensitizes colorectal cancer cells to chemotherapy and improves disease prognosis. *Nat Med*. 2011;17(10):1283–1289. doi:10.1038/nm.2457
74. Krause SW, Gastpar R, Andreesen R, et al. Treatment of colon and lung cancer patients with ex vivo heat shock protein 70-peptide-activated, autologous natural killer cells: a clinical Phase I trial. *Clin Cancer Res*. 2004;10(11):3699–3707. doi:10.1158/1078-0432.CCR-03-0683
75. Ge Y, Xu K. Alpha-synuclein contributes to malignant progression of human meningioma via the Akt/mTOR pathway. *Cancer Cell Int*. 2016;16:86. doi:10.1186/s12935-016-0361-y
76. Li Y, Zhang N, Zhang L, et al. Oncogene HSPH1 modulated by the rs2280059 genetic variant diminishes EGFR-TKIs efficiency in advanced lung adenocarcinoma. *Carcinogenesis*. 2020;41(9):1195–1202. doi:10.1093/carcin/bgaa069
77. Arvanitidou S, Martinelli-Kläy CP, Samson J, Lobrinus JA, Dulguerov N, Lombardi T. HSP105 expression in oral squamous cell carcinoma: correlation with clinicopathological features and outcomes. *J Oral Pathol Med*. 2020;49(7):665–671. doi:10.1111/jop.13007
78. Chen KJ, Li FZ, Ye Q, Jia M, Fang S. HSP105 expression in cutaneous malignant melanoma: correlation with clinicopathological characteristics. *PLoS One*. 2021;16(10):e0258053. doi:10.1371/journal.pone.0258053
79. Kai M, Nakatsura T, Egami H, Senju S, Nishimura Y, Ogawa M. Heat shock protein 105 is overexpressed in a variety of human tumors. *Oncol Rep*. 2003;10(6):1777–1782.
80. Liang Y, Luo J, Yang N, Wang S, Ye M, Pan G. Activation of the IL-1 β /KLF2/HSPH1 pathway promotes STAT3 phosphorylation in alveolar macrophages during LPS-induced acute lung injury. *Biosci Rep*. 2020;40(3):BSR20193572. doi:10.1042/BSR20193572
81. Marcion G, Hermetet F, Neiers F, et al. Nanofitins targeting heat shock protein 110: an innovative immunotherapeutic modality in cancer. *Int J Cancer*. 2021;148(12):3019–3031. doi:10.1002/ijc.33485
82. Massey AJ, Williamson DS, Browne H, et al. A novel, small molecule inhibitor of Hsc70/Hsp70 potentiates Hsp90 inhibitor induced apoptosis in HCT116 colon carcinoma cells. *Cancer Chemother Pharmacol*. 2010;66(3):535–545. doi:10.1007/s00280-009-1194-3
83. Park SH, Baek KH, Shin I, Shin I. Subcellular Hsp70 inhibitors promote cancer cell death via different mechanisms. *Cell Chem Biol*. 2018;25(10):1242–1254.e8. doi:10.1016/j.chembiol.2018.06.010
84. Deocaris CC, Widodo N, Shrestha BG, et al. Mortalin sensitizes human cancer cells to MKT-077-induced senescence. *Cancer Lett*. 2007;252(2):259–269. doi:10.1016/j.canlet.2006.12.038
85. Koren J, Miyata Y, Kiray J, et al. Rhodacyanine derivative selectively targets cancer cells and overcomes tamoxifen resistance. *PLoS One*. 2012;7(7). doi:10.1371/annotation/7493e5d2-4c1a-43eb-a83f-16814861ff13

86. Trimble CL, Peng S, Kos F, et al. A phase I trial of a human papillomavirus DNA vaccine for HPV16+ cervical intraepithelial neoplasia 2/3. *Clin Cancer Res.* 2009;15(1):361–367. doi:10.1158/1078-0432.CCR-08-1725
87. Stangl S, Gehrman M, Riegger J, et al. Targeting membrane heat-shock protein 70 (Hsp70) on tumors by cmHsp70.1 antibody. *Proc Natl Acad Sci U S A.* 2011;108(2):733–738. doi:10.1073/pnas.1016065108
88. Rérole A-L. Peptides and aptamers targeting HSP70: a novel approach for anticancer chemotherapy. *Cancer Res.* 2011;71(2):484–495. doi:10.1158/0008-5472.CAN-10-1443
89. Rajan A, Kelly RJ, Trepel JB, et al. A phase I study of PF-04929113 (SNX-5422), an orally bioavailable heat shock protein 90 inhibitor, in patients with refractory solid tumor malignancies and lymphomas. *Clin Cancer Res.* 2011;17(21):6831–6839. doi:10.1158/1078-0432.CCR-11-0821
90. Patel HJ, Modi S, Chiosis G, Taldone T. Advances in the discovery and development of heat-shock protein 90 inhibitors for cancer treatment. *Expert Opin Drug Discov.* 2011;6(5):559–587. doi:10.1517/17460441.2011.563296
91. Fadden P, Huang KH, Veal JM, et al. Application of chemoproteomics to drug discovery: identification of a clinical candidate targeting hsp90. *Chem Biol.* 2010;17(7):686–694. doi:10.1016/j.chembiol.2010.04.015
92. Eskew JD, Sadikot T, Morales P, et al. Development and characterization of a novel C-terminal inhibitor of Hsp90 in androgen dependent and independent prostate cancer cells. *BMC Cancer.* 2011;11:468. doi:10.1186/1471-2407-11-468
93. Okawa Y, Hideshima T, Steed P, et al. SNX-2112, a selective Hsp90 inhibitor, potently inhibits tumor cell growth, angiogenesis, and osteoclastogenesis in multiple myeloma and other hematologic tumors by abrogating signaling via Akt and ERK. *Blood.* 2009;113(4):846–855. doi:10.1182/blood-2008-04-151928
94. Chandarlapaty S, Sawai A, Ye Q, et al. SNX2112, a synthetic heat shock protein 90 inhibitor, has potent antitumor activity against HER kinase-dependent cancers. *Clin Cancer Res.* 2008;14(1):240–248. doi:10.1158/1078-0432.CCR-07-1667
95. Crane CA, Han SJ, Ahn B, et al. Individual patient-specific immunity against high-grade glioma after vaccination with autologous tumor derived peptides bound to the 96 KD chaperone protein. *Clin Cancer Res.* 2013;19(1):205–214. doi:10.1158/1078-0432.CCR-11-3358
96. Hendriks LEL, Dingemans AC. Heat shock protein antagonists in early stage clinical trials for NSCLC. *Expert Opin Investig Drugs.* 2017;26(5):541–550. doi:10.1080/13543784.2017.1302428
97. Zong J, Wang C, Liu B, et al. Human hsp70 and HPV16 oE7 fusion protein vaccine induces an effective antitumor efficacy. *Oncol Rep.* 2013;30(1):407–412. doi:10.3892/or.2013.2445

OncoTargets and Therapy

Dovepress

Publish your work in this journal

OncoTargets and Therapy is an international, peer-reviewed, open access journal focusing on the pathological basis of all cancers, potential targets for therapy and treatment protocols employed to improve the management of cancer patients. The journal also focuses on the impact of management programs and new therapeutic agents and protocols on patient perspectives such as quality of life, adherence and satisfaction. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/oncotargets-and-therapy-journal>