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

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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

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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, SUMOization, 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 SBD-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 SUMOization 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 its 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-1α, 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-1b 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-1a/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 IKKa/b and NF-kB, which leads to induction of TCF12, ultimately decreasing E-calmodulin 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-κB 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 (HSP110), 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-κB. 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-κB signaling pathway through MyD88. In activated B-cell-like diffuse large B-cell lymphoma (ABC-DLBCL), HSP110 is dependent on

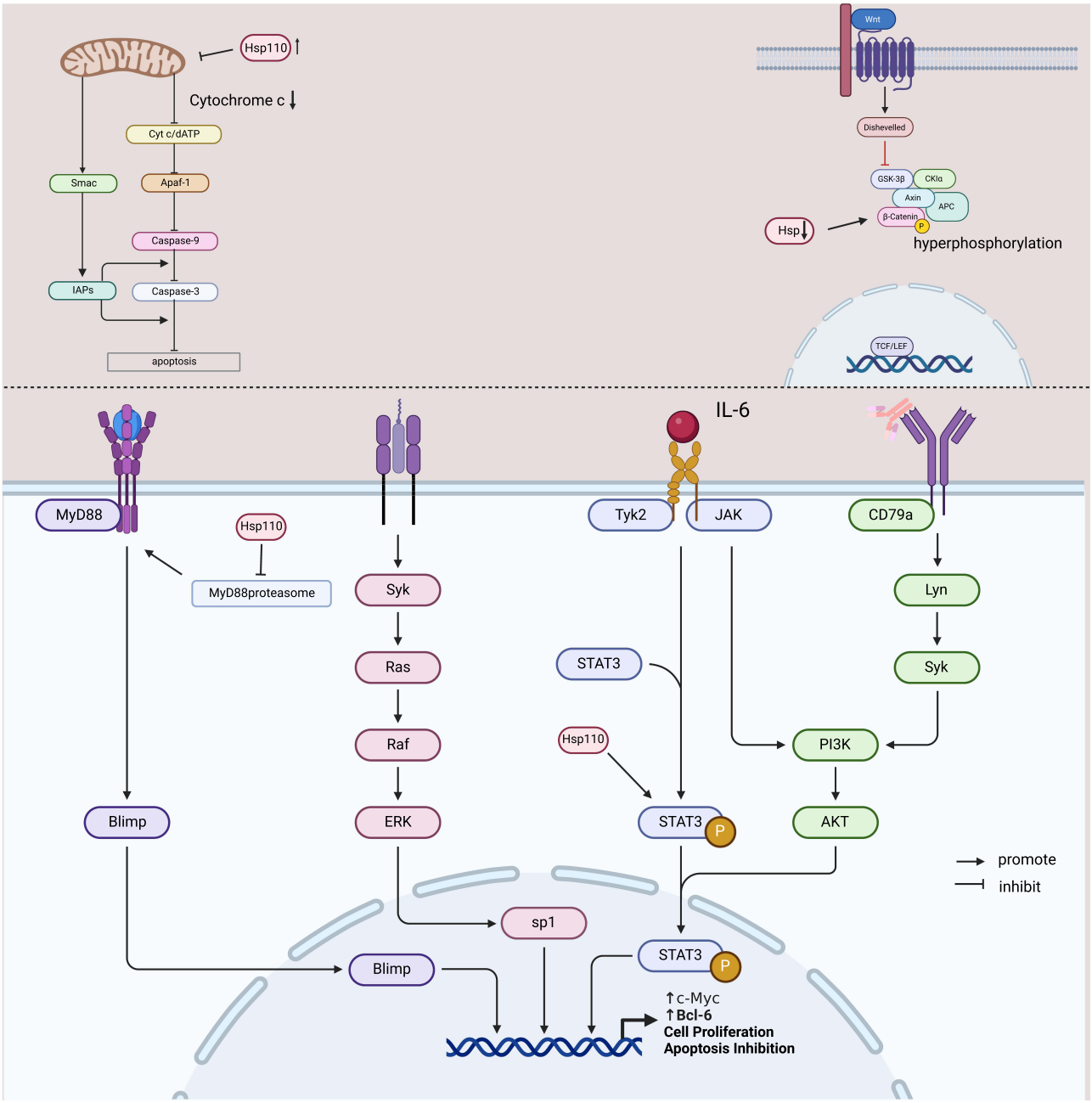

Figure 1 Pathway mechanisms of HSP110 in cancer. Created with BioRender.com.

the NF-κB 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 HSPH1 expression in non-small cell lung cancer (NSCLC) cells significantly improves the anticancer effect of gefitinib. By decreasing HSPH1 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-1β release	Polarized macrophages with enhanced M2 phenotype in the tumor microenvironment
Angiogenesis	Stabilization of HIF-1 by binding to HIF-1α; 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-κB 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 Radicicol (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.

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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.

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