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Heat Shock Protein in Cancer- A Review

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Abstract: Heat shock protein (HSPs) are a highly conserved family of protein chaperones with diverse roles in cellular processes. They are categorized according to their molecular weight, and includes HSP70, HSP40, HSP27, HSP90, and HSP60. These proteins play crucial roles in folding, preventing nonspecific aggregation, and supporting proper protein function. HSPs are implicated in cancer biology, affecting the growth of tumor cells and treatment response. Unusual levels of HSPs have been linked to resistance to treatments and a worse outlook for cancer patients. Heat shock proteins could be useful in clinical settings as biomarkers for diagnosing cancer, monitoring disease progression, and serving as therapeutic targets. Understanding the complex roles of HSPs in cancer could lead to developing novel treatment strategies, including HSP-targeted therapies and immunotherapies. Further research into the precise mechanisms of HSPs in cancer progression and treatment response is essential for advancing cancer therapeutics and improving patient outcomes. This review thoroughly explores the impact of heat shock proteins, specifically HSP27, HSP40, HSP60, HSP70, and HSP90, on different cancer biology and drug research elements. The goal is to offer a detailed summary of what is currently known about the link between HSPs and cancer.

Keywords: Heat shock protein, cancer, HSP27, HSP40, HSP60, HSP70, and HSP90

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1. INTRODUCTION

Heat Shock Proteins (HSPs) constitute an important family of molecular chaperones vital for cellular function, particularly under stress conditions [1]. Classified by molecular weight, major types include HSP27, HSP40, HSP60, HSP70, and HSP90, each with distinct roles in protein folding, preventing aggregation, and regulating cellular processes. In recent years, HSPs have emerged as central players in cancer biology, significantly impacting tumor development, progression, and response to therapy [2]. In cancer research, Hsp70 and small Hsps (sHsps) show elevated levels in various human tumors, epithelial tumors, and gliomas. The increased expression of these chaperones in cancer cells has been associated with suppressing anticancer mechanisms like apoptosis and senescence while promoting the expression of genes related to metastasis [3]. However, Hsp70 and other Hsps also display antitumor effects by aiding tumor rejection by the immune system [4]. Efforts to understand the dual role of Hsp70 and sHsps in cancer have led to investigations into therapeutic strategies targeting these chaperones. Inhibiting or down regulating intracellular Hsp70 has been explored to promote apoptosis or senescence in cancer cells [5]. On the other hand, extracellular and membrane-associated Hsps are being studied for cancer immunotherapy due to their potential to stimulate immune responses against tumors [6]. Recent research suggests HSPs may be valuable biomarkers for cancer diagnosis and prognosis. Their expression levels in tumor tissues and circulating blood cells have been linked to tumor aggressiveness and patient survival rates [7]. This has raised the possibility of using Hsp70 and sHsps as predictive markers for selecting appropriate treatment strategies and monitoring treatment responses in cancer patients. The intricate functions of Hsp70 and sHsps in cancer biology highlight their potential as targets for novel therapeutic approaches. This review gives an indepth examination of the relationship between Hsp70, small heat shock proteins (sHsps), and cancer. We review the targeting of molecular chaperones to influence cell death pathways and explore their use as biomarkers for tailored cancer treatment. Hsp70 and sHsps play a crucial and multifaceted role in cancer biology, influencing tumor development, progression, and response to therapy. Further research into these chaperones could lead to the development of more effective and personalized treatments for cancer patients [8].

1.1 Role of HSPs in Cancer Development

The role of HSPs in Cancer Development sheds light on the pivotal role in various stages of tumorigenesis. Elevated levels of HSPs in cancer cells creates an environment conducive to tumor progression by aiding in the stabilization of overexpressed and mutated cancer genes. HSP90 stabilizes key oncogenic proteins, including mutated forms of EGFR and HER2, which are critical for cancer cell proliferation and survival [9]. This stabilization is essential for the increased growth, survival, and formation of secondary cancers observed in malignant cells. Moreover, HSPs are implicated in the development of treatment resistance, further complicating cancer management strategies. HSP70, for instance, has been Indicated as protective for cancer cells against apoptosis, contributing to resistance against chemotherapeutic agents like cisplatin and doxorubicin [10]. Furthermore, the review explores how the enriched folding environment within tumor cells, resembling thermotolerant cells, contributes to cancer development. HSP27, in particular, has been implicated in promoting cell migration and invasion, key factors in tumor formation and metastasis. A study by *Amina Zoubeidi et al.* ,(2013) revealed that HSP27 promotes epithelial-mesenchymal transition (EMT) in prostate cancer, a critical process in the spread of cancer [11]. The molecular components driving cancer progression primarily consist of proteins that facilitate increased cell accumulation, tumor formation, and metastasis. While HSPs may not directly cause cancer, their elevated levels create an enabling environment for tumor progression to occur. This is particularly crucial in overcoming tissue homeostasis and resuming growth and mobility in cancer, which involves multistep changes to overwhelm the regulatory proteins.

1.2 HSPs in Therapeutic Targeting

Therapeutic targeting of HSP (HSPs) in cancer has emerged as a promising approach to cancer treatment [67]. HSPs play crucial roles in cancer cell survival, proliferation, and resistance to therapy [68]. By targeting HSPs, such as HSP27, HSP70, and HSP90, it is possible to disrupt multiple oncoproteins and signaling pathways essential for tumor progression [79]. HSP70 inhibitors have effectively reduced tumor size in preclinical models, suggesting a direct link between HSPs and tumor survival [70]. In addition to protecting client proteins from degradation and stress, HSPs regulate important signaling pathways in cancer cells. Various HSP inhibitors have been identified as potential therapeutic targets in cancer treatment. For example, targeting HSP70 has been proposed as a druggable strategy due to its role in promoting cancer cell viability by safeguarding lysosomal integrity. Lampros M, et al. (2022) observed that HSP27 overexpression is linked to chemotherapy resistance, reinforcing the significance of HSPs in cancer therapy [71]. Targeting HSP40, another member of the HSP family, has shown promise in the early stages of development, including immunological approaches and small molecule inhibitors. Therapeutic targeting of HSPs in cancer has emerged as a promising strategy for developing effective anti-cancer therapies. Research by Su YH et al. (2015) indicates that HSP90 inhibitors can disrupt multiple oncogenic signaling pathways, pointing to the potential of multi-targeted approaches in cancer treatment [72]. While initially considered challenging due to the high abundance and complexity of HSPs, advances in drug design and targeted therapies have opened new avenues for cancer treatment. Essential functions of HSPs: recent advancements have led to the development of drugs targeting these HSPs, particularly HSP90. The unique structure of the ATPase domain of HSP90 allows for selective inhibition by drugs such as the ansamycin family, leading to the development of a new class of anti-cancer drugs. These HSP90-targeted drugs show promise in targeting overexpressed oncogenes and mutant proteins found in tumor cells, thereby blocking key pathways of autonomous tumor growth. Clinical trials have shown considerable potential for these drugs in inhibiting tumor progression and improving patient outcomes. Efforts to target other HSPs, such as HSP70 and HSP27, are also underway to block their roles in inhibiting programmed cell death and promoting tumor survival. While the high concentrations of these proteins in tumors pose challenges, targeting specific members of the HSP70 family may

offer therapeutic benefits without compromising essential chaperone functions. By harnessing the immunostimulatory properties of HSPs, novel anti-cancer vaccines, and immunotherapy strategies are being explored to enhance the immune response against tumor cells. Therapeutic targeting of HSPs in cancer represents a promising avenue for developing novel anti-cancer treatments. By selectively inhibiting HSPs that promote tumor growth and survival, researchers aim to disrupt key pathways driving malignancy and improve outcomes for cancer patients. Overall, therapeutic targeting of HSPs in cancer holds great potential for disrupting cancer cell survival mechanisms and enhancing the efficacy of cancer therapies. Understanding the intricate interplay between HSPs and cancer development is essential for devising effective therapeutic strategies. Targeting HSPs in cancer treatment holds promise in disrupting the mechanisms that drive tumor growth and progression [12]. By unraveling the role of HSPs in cancer development, researchers and clinicians can explore novel avenues for combating this complex disease and improving patient outcomes. In recent years, HSPs have emerged as potential targets for cancer therapy due to their involvement in cancer cell survival and proliferation [13]. A study by Tsutsumi S *et al*., discusses HSPs emphasizing their role in cancer progression, drug resistance, and metastasis [14]. HSPs are considered promising targets for anti-cancer and anti-metastatic therapies and HSP inhibitors are being studied for their potential to prevent cancer progression and metastasis. Further research is needed to explore more HSP-based therapeutic approaches. HSPs, including Hsp70 and small Hsps, are known to interact with significant proteins that participate in cancer pathways, such as apoptosis, cell cycle regulation, and metastasis [15]. By targeting HSPs, researchers aim to disrupt these pathways and inhibit cancer cell growth. One approach to targeting HSPs is using HSP inhibitors, which block the chaperone activity of HSPs and induce cancer cell death [16]. Several HSP inhibitors, such as geldanamycin and its derivatives, have shown promise in preclinical studies and are being evaluated in clinical trials for various types of cancer. Another approach is the use of HSPs as immunotherapeutic targets. Extracellular HSPs released by cancer cells can act as danger signals, triggering an immune response against the tumor [17]. By targeting these extracellular HSPs, researchers hope to enhance the immune response against cancer cells and improve the efficacy of cancer immunotherapy [18]. The study by Jianxun Song *et al*., reviewed HSPs major roles in cancer progression and resistance to anticancer therapies [19]. They explored HSP-based cancer immunotherapy as a promising approach to target tumors. The potential to use HSPs in innovative immunotherapeutic strategies was a key focus of their research. Understanding the mechanisms underlying the function of HSPs in cancer can lead to developing novel therapeutic approaches and targeting HSP, which ensures a potential treatment approach and improves outcomes for cancer patients in the future [20].

1.3 HSP40

The HSP40 family is a large but relatively understudied group of co-chaperones, with over 41 members encoded by the human genome [21]. These co-chaperones reside in various intracellular locations and regulate the function of HSP70 [22]. The study by Suh WC *et al.*examined the interaction between co-chaperones and HSP70 [23]. It revealed that co-chaperones, through their domains, stimulate HSP70's ATPase activity by influencing the interactions between the nucleotide-binding domain (NBD) and the substrate-binding domain (SBD) [24]. This activation mechanism highlights the key role of cochaperones in regulating HSP70's function in protein processing. Evidence suggests that the HSP40 family and HSP90 enhance the AKT pathway, a key cell survival pathway [25]. Despite ongoing research, the relationship between the HSP40 family and various human cancers remains unclear and subject to debate. Recent research indicates that HSPs, including HSP40, are highly expressed in various human cancers, possibly leading to resistance to chemotherapy [26]. Increased HSP40, HSP70, and HSP90 levels have been detected in brain tumors and lung cancer tissues [27]. The presence of HSP40 in the serum of cancer patients, as detected by specific antibodies, could offer a new method for tumor diagnosis [28]. Studies examining the human genome have identified 41 DnaJ–HSP40 family members, suggesting their significance in vital cellular processes and their distribution across different intracellular locations [29]. The role of the HSP40 family in cancer development and progression remains a subject of debate. Some studies, such as those by Tsai MF *et al*., propose that certain members of the HSP40 family, like hTid1 and HLJ1, might influence tumor growth [30]. Further evidence from studies, including work by Park SK *et al*., suggests that overexpression of certain HSP40s might be linked to increased cancer risk, reinforcing the need to understand these proteins' roles in oncology [31]. Clinical studies by Jones *et al*. have noted that targeting HSP40 could offer new therapeutic strategies in oncology, as they play roles in cancer cell survival and proliferation. The most extensively studied HSP40 family members for their cancer-related roles are HLJ1, Tid1, and MRJ(L). However, further research is essential to understand the functions of the broader HSP40 family in cancer biology, as they likely play various critical roles in malignant processes [32].

1.4 HSP60

HSP60, a heat shock protein, is implicated in various cancers, but its role in brain tumors is unclear. It promotes apoptosis and cell survival, with up-regulated levels in cancers, including glioblastomas [33]. In cervical cancer, HSP60's prognostic relevance is studied, showing a significant contribution to disease development [34]. In advanced prostate cancer, elevated HSP60 correlates with tumor progression and androgen independence, predicting biochemical recurrence [35]. Breast cancer studies show auto antibodies against HSP60, with high-grade tumors exhibiting elevated levels, suggesting potential for early diagnosis [36]. In a study examining the impact of HSP60 on lung cancer, researchers found that, its overexpression was linked to increased cell proliferation and poor prognosis, indicating its potential as a therapeutic target [37]. HSP60 is also identified in liver cirrhosis and hepatocellular carcinoma patients [38]. A recent study investigating pancreatic cancer discovered that HSP60 overexpression not only correlated with tumor aggressiveness but also with resistance to certain chemotherapies, making it a critical factor in treatment outcomes [39]. In colorectal cancer, HSP60 overexpression correlates with tumor differentiation and prognosis [40]. Gastric adenocarcinoma studies revealed high HSP60 expression, with HSP27 and HSP60 correlating with clinico-pathological characteristics. In the context of metastasis, elevated levels of HSP60 appear to drive metastatic characteristics, possibly by activating β -catenin, suggesting an unfavorable prognosis in

cases of metastatic head and neck cancers [41]. Melanoma research has shown that HSP60 is involved in melanoma cell migration and invasion, suggesting its role in the metastatic process and as a potential biomarker for aggressive melanomas[42].

1.5 HSP70

The HSP70 family's eight members play crucial roles in cancer initiation and progression by acting as chaperones and regulating cell signaling, particularly through the co-chaperone bag [43]. High levels of HSP70 in several cancers are associated with greater cell proliferation and malignancy [44]. In medulloblastomas, there's a positive relationship between the Ki-67 index and more aggressive forms of the tumor [45]. Knocking down HSP70 enhances chemosensitivity in different malignancies [46]. High levels of HSP70 can indicate advanced stages and predict a less favorable outcome in melanoma, bladder cancer, colon cancer, and breast cancer [47]. Silencing HSP70 in glioblastoma cells significantly increased their sensitivity to chemotherapy and radiation therapy, suggesting a potential therapeutic approach [48]. HSP70 inhibits programmed cell death at various stages, including Bax activation in the intrinsic pathway and the assembly of the signaling system that causes cell death in the extrinsic pathway [49]. Reducing Hsp72 expression triggers cell senescence through p53-dependent and independent mechanisms [50]. The Hsp70–Bag3 complex modulates various transcription and cell-cycle regulators [51]. HSP70's role in maintaining DNA integrity and its involvement in cancer cell DNA repair make it an ideal target for cancer treatment [52].

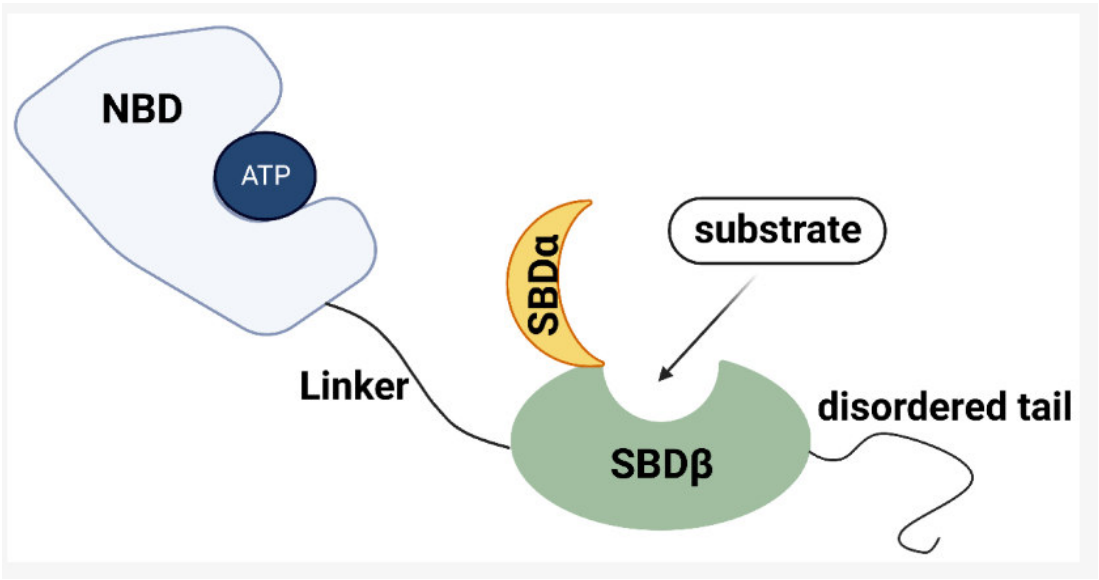

Figure 1: Schematic diagram of HSP70. [53]

1.5 HSP90

HSP90, a crucial anti-apoptotic protein, plays a pivotal role in various signaling pathways and is extensively studied within the HSPs. Elevated levels of HSP90a are found in medulloblastoma and show a positive correlation with HSP70 [54]. In breast cancer, HSP90 expression tends to be higher in ductal carcinomas but lower in lobular carcinomas [55]. Elevated HSP90 levels are also associated with poor prognosis in certain subtypes of breast cancer, suggesting its role in tumor progression [56]. Colorectal cancer's metastasis involves HSP90-regulated epithelial-mesenchymal transition, which, when inhibited, downregulates HIF-1α and NF-κ B, hindering cancer cell invasion and motility [57]. Kryeziu K, *et al.*, demonstrated that, HSP90 inhibition in colorectal cancer could reduce metastasis, reinforcing the protein's significance in cancer spread [58]. The interactions between HSP90 and its co-chaperones, such as Hop, p23, and others, have been extensively researched [59]. HSP90 is considered as a potential therapeutic target for cancer, with inhibitors designed to act on either its N- or C-terminal regions. Combining HSP90 inhibitors with other anticancer agents may overcome chemoresistance, providing a potential strategy for more effective treatment [60]. Retaspimycin hydrochloride and AUY922 are notable inhibitors showing efficacy in preclinical models. However, chemoresistance, often mediated by p-glycoprotein and MRP, poses challenges in HSP90 inhibitor treatment, highlighting the need for further research.

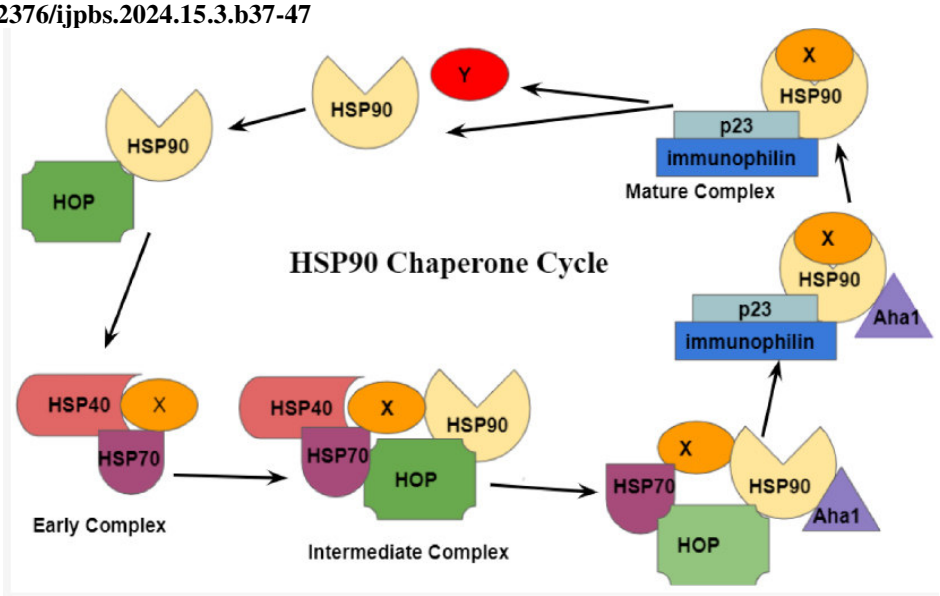

Figure 2: HSP90 chaperone cycle depicting co-chaperones and client proteins interactions with HSP90 [61].

1.6 Significance of Hsp70 and Small Hsps in Cancer

The significance of HSPs, particularly Hsp70 and Small Hsps, in cancer is profound, as they play crucial roles in cancer progression and resistance to treatment. Hsp70 is known to be overexpressed in several malignancies, indicating advanced disease and poor prognosis in certain cancers such as melanoma, bladder cancer, colon cancer, breast cancer, etc [62]. Its involvement in cancer is multifaceted, including the inhibition of apoptosis through multiple pathways, such as the intrinsic and extrinsic pathways, as well as the regulation of senescence and DNA repair mechanisms. Inhibition of Hsp70 has shown promise as a possible target in cancer treatment, with inhibitors like PES-Cl, MKT-077, and Ver-155008 demonstrating significant anticancer activity in preclinical studies [63]. Small Hsps, such as HSP27, have also been linked to cancer progression. HSP27, a small heat shock protein family constituent, acts as an ATP-independent chaperone and has been associated with inhibiting apoptosis through complex interactions with other proteins like Hsp70 and PKR [64]. The overexpression of Small Hsps, including HSP90, HSP27, HSP60, and HSP40, was observed in various human cancers, contributing to treatment resistance [65]. These Small Hsps are being investigated as potential targets for modulating cell death pathways and valuable tumor markers for personalized cancer medicine. The significance of Hsp70 and Small Hsps in cancer lies in their crucial roles in promoting tumor growth, inhibiting programmed cell death, and conferring resistance to therapy [66]. Increased expression of Hsp70 and HSP27 is correlated with resistance to chemotherapy, indicating their role in promoting tumor survival and progression. Furthermore, cancer cells need Hsp70 to survive, emphasizing its importance in maintaining the malignant phenotype. Their increased abundance in tumors offers a tempting target for designing treatments, that can inhibit various aspects of the malignant phenotype, leading to promising approaches in cancer treatment. These proteins mediate a resilient state in cancer cells, allowing them to evade cell death signals and promote tumor progression. Overall, the significance of Hsp70 and small Hsps in cancer lies in their multifaceted roles in promoting tumor growth, inhibiting cell death pathways, and conferring resistance to therapy. Targeting these HSP presents a promising strategy for developing effective anti-cancer therapies. Understanding the intricate interplay between Hsp70 and small Hsps in cancer development is essential for devising effective therapeutic strategies. Targeting HSPs in cancer treatment holds promise in disrupting the mechanisms that drive tumor growth and progression. By unraveling the role of HSPs in cancer development, researchers and clinicians can explore novel avenues for combating this complex disease and improving patient outcomes.

1.7 Mechanisms of HSPs' contribution in Cancer

The functions of HSP in cancer are complex and pivotal in various aspects of tumor biology. Below are key mechanisms illustrating how HSPs contribute to cancer development and progression:

1.8 Protein Folding and Stability

Cancer cells churn out proteins abnormally and often do not fold properly. HSPs act like molecular chaperones, assisting newly created proteins in folding into their proper shapes. They also help existing proteins maintain their structure and function under stress. HSPs are important for normal function in healthy cells, but cancer cells become even more critical [73]. HSPs prevent protein aggregation and ensure cancer cells have the functional proteins to survive and multiply [74]. This makes HSPs a double-edged sword: essential for normal cells but also potentially aiding cancer progression.

1.9 Anti-Apoptotic Effects

Cancer cells pump out proteins at an alarming rate. Often, these proteins fold incorrectly, forming harmful clumps that threaten the cell's survival. Here's where HSP (HSPs) enter the scene, acting as cellular bodyguards. HSPs are molecular chaperones, assisting newly formed proteins in folding correctly and ensuring existing ones maintain their structure

[75]. However, HSPs have another surprising role in cancer: inhibiting programmed cell death or apoptosis [76]. Apoptosis is a natural process where damaged cells self-destruct. However, cancer disrupts this process. HSPs achieve this anti-apoptotic effect by interacting with key players in cell death pathways. They bind to caspases, enzymes essential for dismantling the cell, effectively putting them on hold. HSPs also influence Bcl-2 family proteins, some promoting cell survival while others triggering apoptosis [77]. By tipping the scales in favor of survival proteins, HSPs shield cancer cells from self-destruction. This becomes particularly problematic during cancer treatment. Chemotherapy and radiation aim to induce apoptosis in cancer cells. However, understanding this protective role of HSPs is crucial for developing new cancer therapies that can bypass these cellular shields and effectively eliminate cancer cells.

1.10 Cell Signaling

HSP (HSPs) play a pivotal role in regulating signaling pathways that are fundamental to cell growth, differentiation, and survival [78]. Among them, HSP90 stands out for its ability to bind and stabilize client proteins, including key kinases and transcription factors [79]. This interaction can significantly impact cellular signaling, with downstream effects on processes like cell cycle progression and apoptosis [80]. For instance, HSP90's interaction with kinases can activate pathways that drive tumor cell proliferation, making it a critical factor in cancer development and progression [81]. Likewise, its stabilization of transcription factors can influence gene expression patterns that support tumor survival and resistance to therapy [82]. As a result, HSP90 and other HSP have emerged as attractive targets for cancer treatment, with inhibitors designed to disrupt these protein-protein interactions, potentially leading to the destabilization of oncogenic signaling and the induction of cancer cell death [83].

1.11 Metastasis and Invasion

HSPs in cancer not only do they help cancer cells survive, but some HSPs also act as accomplices in metastasis and the spread of cancer [84]. These HSPs empower cancer cells to become more invasive. For example, HSP60 can work with β - catenin, a protein involved in cell movement [85]. This interaction fuels metastasis in certain cancers. Researchers are discovering how cancer spreads by unraveling these partnerships between specific HSPs and other cellular players. This knowledge could lead to new therapeutic strategies to disrupt these alliances and ultimately hinder metastasis [86].

1.12 Drug Resistance

Cancer's fight against treatment gets a helping hand from HSPs. High HSP levels in cancer cells make them more resistant to chemotherapy and targeted therapies [87]. These molecular chaperones act like repair crews, fixing damaged proteins caused by the drugs. HSPs can also activate pathways within the cancer cells, that promote survival, essentially giving the cell a shield against the intended cell death caused by the treatment. This resistance is a major hurdle in cancer therapy, and researchers are exploring ways to target HSPs alongside traditional treatments. By hindering these cellular repair mechanisms, we can improve the effectiveness of cancer therapies and potentially overcome resistance.

1.13 Tumor Microenvironment

HSPs shape the tumor microenvironment by influencing immune responses, angiogenesis, and inflammation [88]. They can alter the immune system's recognition and response to cancer cells, impacting tumor progression and immune evasion. Understanding these diverse mechanisms through which HSPs contribute to cancer pathogenesis is crucial for developing targeted therapies. Research on HSP inhibitors and their potential to disrupt these pro-tumorigenic functions offers promise for novel cancer treatment strategies [89].

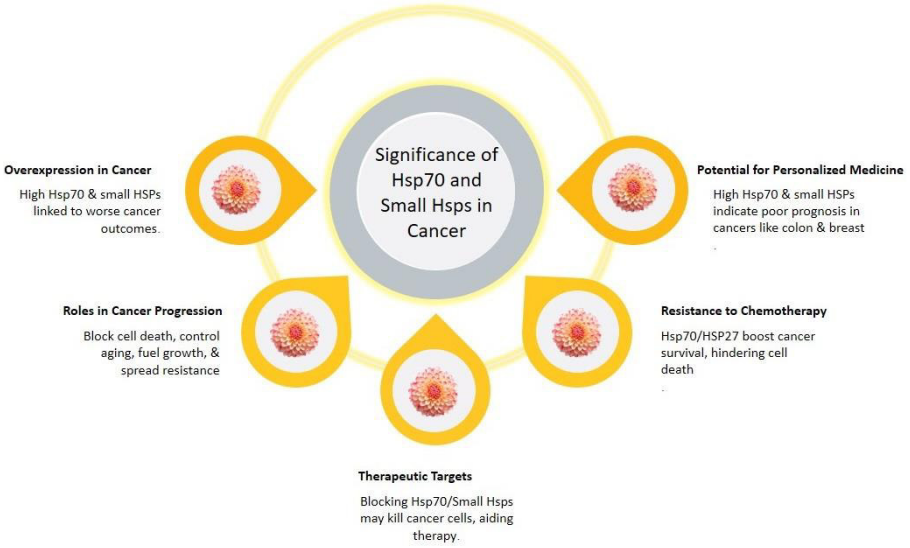

Figure: 3. Roles of Heat Shock Proteins in Cancer Progression and Therapeutic Resistance

1.14 Clinical Implications of Heat shock protein expression in cancer

The clinical implications of HSP expression in cancer are significant, as the overexpression of HSPs has been linked to an unfavorable prognosis, resistance to therapy, and tumor

progression [90]. Increased levels of HSPs, such as HSP27 and Hsp70, have been correlated with resistance to chemotherapy, highlighting their role in promoting tumor survival and evading cell death pathways [91]. Moreover, the upregulation of HSPs in cancer cells can confer a survival advantage by facilitating autonomous tumor growth by accumulating overexpressed and mutated oncogenes and inhibiting programmed cell death. This increased abundance of HSPs in tumors presents a potential target for therapeutic intervention to inhibit key pathways driving tumor progression [92]. HSP expression can affect the tumor microenvironment, potentially leading to increased tumor invasiveness and metastatic potential [93]. The expression of HSPs in cancer also has implications for immunotherapy, as HSPs can function as biological adjuvants and chaperone tumor antigens, potentially enhancing the immune response against tumor cells [94]. Strategies utilizing HSPs in cancer immunotherapy, such as autologous vaccines derived from HSP-bound tumor antigens, hold promise for eliciting specific anti-tumor immune responses and mediating tumor regression. Furthermore, the unique composition and abundance of HSPs in tumors have implications for drug development and treatment response. HSP90 inhibitors can increase the sensitivity of tumors to existing treatments, offering a potential combination therapy route [95]. Preclinical research indicates that targeting HSP90 with specific inhibitors disrupts critical pathways in cancer cells and could enhance the effectiveness of other therapies. The clinical implications of HSP expression in cancer underscore the importance of these proteins in tumor progression, therapy resistance, and immune response modulation. Understanding the role of HSPs in cancer pathogenesis can inform the development of novel treatment strategies aimed at targeting HSPs to improve patient outcomes and overcome therapeutic challenges in cancer management. Recent advances in this field demonstrate that HSP inhibition could serve as a strategy to sensitize tumors to immunotherapy, potentially leading to more effective anti-tumor responses [96,97]."

2. CONCLUSION

In conclusion, the review highlights the critical role of HSP (HSPs) in cancer, emphasizing their overexpression in malignancies and their contribution to tumor progression. HSPs, particularly Hsp27, Hsp70, and Hsp90, are elevated in various cancers and are associated with poor prognosis, influencing cancer cell traits such as uncontrolled growth, reduced tumor suppression, enhanced cell survival, and metastasis. HSPs, especially Hsp90, stabilize oncogenic proteins essential for tumorigenesis, making them attractive targets for cancer therapy. Clinical trials with HSP90 inhibitors have shown promise in treating solid and hematological malignancies, raising questions about their optimal dosing, efficacy in cancer versus normal cells, and pharmacodynamic markers for treatment response. Efforts to target other chaperone machinery components like HSF1 are ongoing to modulate HSP expression and disrupt oncogenic processes. Despite challenges such as drug resistance and organ-specific toxicities, targeting HSPs, especially through combination therapy, advanced molecular biology techniques, and nanomedicine, holds the potential for developing effective anticancer therapies. Utilizing HSP antigens for cancer vaccine development is an emerging field of interest. Understanding the intricate role of HSPs in cancer biology is crucial for developing targeted therapies and improving patient outcomes.

3. AUTHORS CONTRIBUTION STATEMENT

Dr. M. Chandran contributed to the conceptualization and design of the study, data analysis, and manuscript writing. Dr. Ashoka Tiadi assisted with the literature review, data collection, and provided critical revisions of the manuscript. Dr. Priyanka Singh was involved in data interpretation, manuscript drafting, and coordination among authors. Dr. Gurshan Singh Gill contributed to the data verification, and provided important intellectual content. Prof. (Dr.) Nirmali Gogoi supervised the project, provided overall guidance, and approved the final manuscript for submission. All authors have read and approved the final manuscript.

4. CONFLICT OF INTEREST

Conflict of interest declared none.

REFERENCES

1. Grigorova B. Plant Heat Shock Proteins as Molecular Chaperones in Normal and Stress Conditions. Handbook of molecular chaperones: roles, structures and mechanisms.:463.
2. Ciocca DR, Arrigo AP, Calderwood SK. Heat shock proteins and heat shock factor 1 in carcinogenesis and tumor development: an update. Archives of toxicology. 2013 Jan;87:19-48.
3. Kim WS, Ghassemi Nejad J, Roh SG, Lee HG. Heat-shock proteins gene expression in peripheral blood mononuclear cells as an indicator of heat stress in beef calves. Animals. 2020 May 21;10(5):895.
4. Udono H, Levey DL, Srivastava PK. Cellular requirements for tumor-specific immunity elicited by heat shock proteins: tumor rejection antigen gp96 primes CD8+ T cells in vivo. Proceedings of the National Academy of Sciences. 1994 Apr 12;91(8):3077-81.
5. Goloudina AR, Demidov ON, Garrido C. Inhibition of HSP70: a challenging anti-cancer strategy. Cancer letters. 2012 Dec 28;325(2):117-24.
6. Li Y, Subjeck J, Yang G, Repasky E, Wang XY. Generation of anti-tumor immunity using mammalian heat shock protein 70 DNA vaccines for cancer immunotherapy. Vaccine. 2006 Jun 19;24(25):5360-70.
7. Wang J, Cui S, Zhang X, Wu Y, Tang H. High expression of heat shock protein 90 is associated with tumor aggressiveness and poor prognosis in patients with advanced gastric cancer. PloS one. 2013 Apr 26;8(4):e62876.
8. Landriscina M, Amoroso MR, Piscazzi A, Esposito F. Heat shock proteins, cell survival, and drug resistance: the mitochondrial chaperone TRAP1, a potential novel

target for ovarian cancer therapy. Gynecologic oncology. 2010 May 1;117(2):177-82.
9. Tian-wen C, Ya-nan L, Duo F, Lin-yu T, Ke Q, Hao-yun Z, Hong-xian W, Qiu-sheng L, Heng K. Metformin inhibits proliferation and promotes apoptosis of HER2 positive breast cancer cells by downregulating HSP90. J BUON. 2013 Jan 1;18(1):51-6.
10. Asling J, Morrison J, Mutsaers AJ. Targeting HSP70 and GRP78 in canine osteosarcoma cells in combination with doxorubicin chemotherapy. Cell Stress and Chaperones. 2016 Nov 1;21(6):1065-76.
11. Shiota M, Bishop JL, Nip KM, Zardan A, Takeuchi A, Cordonnier T, Beraldi E, Bazov J, Fazli L, Chi K, Gleave M. Hsp27 regulates epithelial mesenchymal transition, metastasis, and circulating tumor cells in prostate cancer. Cancer research. 2013 May 15;73(10):3109-19.
12. Lang BJ, Guerrero-Giménez ME, Prince TL, Ackerman A, Bonorino C, Calderwood SK. Heat shock proteins are essential components in transformation and tumor progression: Cancer cell intrinsic pathways and beyond. International journal of molecular sciences. 2019 Sep 11;20(18):4507.
13. López LA, Gago FE, Tello O. Heat shock proteins and cell proliferation in human breast cancer biopsy samples. Cancer Detect Prev. 1997;21:441-51.
14. Tsutsumi S, Neckers L. Extracellular heat shock protein 90: a role for a molecular chaperone in cell motility and cancer metastasis. Cancer science. 2007 Oct;98(10):1536-9.
15. Sarkars R, Mukherjee S, Roy M. Targeting heat shock proteins by phenethyl isothiocyanate results in cell-cycle arrest and apoptosis of human breast cancer cells. Nutrition and cancer. 2013 Apr 1;65(3):480-93.
16. Kim JA, Kim Y, Kwon BM, Han DC. The natural compound cantharidin induces cancer cell death through inhibition of heat shock protein 70 (HSP70) and Bcl-2-associated athanogene domain 3 (BAG3) expression by blocking heat shock factor 1 (HSF1) binding to promoters. Journal of Biological Chemistry. 2013 Oct 4;288(40):28713-26.
17. Pockley AG, Henderson B. Extracellular cell stress (heat shock) proteins—immune responses and disease: an overview. Philosophical transactions of the royal society B: biological sciences. 2018 Jan 19;373(1738):20160522.
18. Li X, Cai X, Zhang Z, Ding Y, Ma R, Huang F, Liu Y, Liu J, Shi L. Mimetic heat shock protein mediated immune process to enhance cancer immunotherapy. Nano Letters. 2020 May 13;20(6):4454-63.
19. Landriscina M, Amoroso MR, Piscazzi A, Esposito F. Heat shock proteins, cell survival and drug resistance: the mitochondrial chaperone TRAP1, a potential novel target for ovarian cancer therapy. Gynecologic oncology. 2010 May 1;117(2):177-82.
20. Chatterjee S, Burns TF. Targeting heat shock proteins in cancer: a promising therapeutic approach. International journal of molecular sciences. 2017 Sep 15;18(9):1978.
21. Chen MS, Roti JR, Laszlo A. Hsc40, a new member of the hsp40 family, exhibits similar expression profile to that of hsc70 in mammalian cells. Gene. 1999 Oct 1;238(2):333-41.
22. Schmidt S, Strub A, Röttgers K, Zufall N, Voos W. The two mitochondrial heat shock proteins 70, Ssc1 and Ssq1, compete for the cochaperone Mge1. Journal of molecular biology. 2001 Oct 12;313(1):13-26.
23. Suh WC, Burkholder WF, Lu CZ, Zhao X, Gottesman ME, Gross CA. Interaction of the Hsp70 molecular chaperone, DnaK, with its cochaperone DnaJ. Proceedings of the National Academy of Sciences. 1998 Dec 22;95(26):15223-8.
24. Fewell SW, Smith CM, Lyon MA, Dumitrescu TP, Wipf P, Day BW, Brodsky JL. Small molecule modulators of endogenous and co-chaperone-stimulated Hsp70 ATPase activity. Journal of Biological Chemistry. 2004 Dec 3;279(49):51131-40.
25. Chatterjee M, Andrulis M, Stühmer T, Müller E, Hofmann C, Steinbrunn T, Heimberger T, Schraud H, Kressmann S, Einsele H, Bargou RC. The PI3K/Akt signaling pathway regulates the expression of Hsp70, which critically contributes to Hsp90-chaperone function and tumor cell survival in multiple myeloma. Haematologica. 2013 Jul;98(7):1132.
26. Kunachowicz D, Król-Kulikowska M, Raczycka W, Sleziak J, Błażejewska M, Kulbacka J. Heat Shock Proteins, a Double-Edged Sword: Significance in Cancer Progression, Chemotherapy Resistance and Novel Therapeutic Perspectives. Cancers. 2024 Apr 14;16(8):1500.
27. Mittal S, Rajala MS. Heat shock proteins as biomarkers of lung cancer. Cancer biology & therapy. 2020 Jun 2;21(6):477-85.
28. Korneeva I, Bongiovanni AM, Girotra M, Caputo TA, Witkin SS. Serum antibodies to the 27-kd heat shock protein in women with gynecologic cancers. American journal of obstetrics and gynecology. 2000 Jul 1;183(1):18-21.
29. Carper SW, Duffy JJ, Gerner EW. Heat shock proteins in thermotolerance and other cellular processes. Cancer Research. 1987 Oct 15;47(20):5249-55.
30. Tsai MF, Wang CC, Chang GC, Chen CY, Chen HY, Cheng CL, Yang YP, Wu CY, Shih FY, Liu CC, Lin HP. A new tumor suppressor DnaJ-like heat shock protein, HLJ1, and survival of patients with non–small-cell lung carcinoma. Journal of the National Cancer Institute. 2006 Jun 21;98(12):825-38.
31. Park SK, Arslan F, Kanneganti V, Barmada SJ, Purushothaman P, Verma SC, Liebman SW. Overexpression of a conserved HSP40 chaperone reduces toxicity of several neurodegenerative disease proteins. Prion. 2018 Jan 2;12(1):16-22.
32. Babi A, Menlibayeva K, Bex T, Doskaliev A, Akshulakov S, Shevtsov M. Targeting heat shock proteins in Malignant brain tumors: from basic research to clinical trials. Cancers. 2022 Nov 4;14(21):5435.
33. Tang H, Li J, Liu X, Wang G, Luo M, Deng H. Down-regulation of HSP60 Suppresses the Proliferation of Glioblastoma Cells via the ROS/AMPK/mTOR Pathway. Scientific reports. 2016 Jun 21;6(1):28388.
34. Hwang YJ, Lee SP, Kim SY, Choi YH, Kim MJ, Lee CH, Lee JY, Kim DY. Expression of heat shock protein 60 kDa is upregulated in cervical cancer. Yonsei medical journal. 2009 Jun 6;50(3):399.
35. So A, Gleave M, Hurtado-Col A, Nelson C. Mechanisms of the development of androgen independence in prostate cancer. World journal of urology. 2005 Feb;23:1-9..

36. Shi L, Gehin T, Chevolot Y, Souteyrand E, Mangé A, Solassol J, Laurenceau E. Anti-heat shock protein autoantibody profiling in breast cancer using customized protein microarray. Analytical and bioanalytical chemistry. 2016 Feb;408:1497-506.
37. Cappello F, Angileri F, Conway de Macario E, JL Macario A. Chaperonopathies and chaperonotherapy. Hsp60 as therapeutic target in cancer: potential benefits and risks. Current pharmaceutical design. 2013 Jan 1;19(3):452-7.
38. Zhang J, Zhou X, Chang H, Huang X, Guo X, Du X, Tian S, Wang L, Lyv Y, Yuan P, Xing J. Hsp60 exerts a tumor suppressor function by inducing cell differentiation and inhibiting invasion in hepatocellular carcinoma. Oncotarget. 2016 Oct 10;7(42):68976.
39. Kunachowicz D, Król-Kulikowska M, Raczycka W, Sleziak J, Błażejewska M, Kulbacka J. Heat Shock Proteins, a Double-Edged Sword: Significance in Cancer Progression, Chemotherapy Resistance and Novel Therapeutic Perspectives. Cancers. 2024 Apr 14;16(8):1500.
40. He Y, Wu Y, Mou Z, Li W, Zou L, Fu T, Zhang A, Xiang D, Xiao H, Wang X. Proteomics- based identification of HSP60 as a tumor- associated antigen in colorectal cancer. PROTEOMICS–Clinical Applications. 2007 Mar;1(3):336-42.
41. Tsai YP, Yang MH, Huang CH, Chang SY, Chen PM, Liu CJ, Teng SC, Wu KJ. Interaction between HSP60 and β -catenin promotes metastasis. Carcinogenesis. 2009 Jun 1;30(6):1049-57.
42. Miao W, Li L, Wang Y. A targeted proteomic approach for heat shock proteins reveals DNAJB4 as a suppressor for melanoma metastasis. Analytical chemistry. 2018 May 3;90(11):6835-42.
43. Zhao K, Zhou G, Liu Y, Zhang J, Chen Y, Liu L, Zhang G. HSP70 family in cancer: Signaling mechanisms and therapeutic advances. Biomolecules. 2023 Mar 27;13(4):601.
44. Turturici G, Geraci F, Candela ME, Cossu G, Giudice G, Sconzo G. Hsp70 is required for optimal cell proliferation in mouse A6 mesoangioblast stem cells. Biochemical Journal. 2009 Jul 15;421(2):193-200.
45. Zhao F, Zhang J, Li P, Zhou Q, Zhang S, Zhao C, Wang B, Yang Z, Li C, Liu P. Prognostic value of Ki-67 index in adult medulloblastoma after accounting for molecular subgroup: a retrospective clinical and molecular analysis. Journal of Neuro-Oncology. 2018 Sep;139:333-40.
46. Yoshidomi K, Murakami A, Yakabe K, Sueoka K, Nawata S, Sugino N. Heat shock protein 70 is involved in malignant behaviors and chemosensitivities to cisplatin in cervical squamous cell carcinoma cells. Journal of Obstetrics and Gynaecology Research. 2014 May;40(5):1188-96.
47. Seier S, Bashiri Dezfouli A, Lennartz P, Pockley AG, Klein H, Multhoff G. Elevated levels of circulating Hsp70 and an increased prevalence of CD94+/CD69+ NK cells is predictive for advanced stage non-small cell lung cancer. Cancers. 2022 Nov 21;14(22):5701.
48. Pasi F, Paolini A, Nano R, Di Liberto R, Capelli E. Effects of single or combined treatments with radiation and chemotherapy on survival and danger signals expression in glioblastoma cell lines. BioMed research international. 2014 Oct;2014.
49. Rowarth NM, Dauphinee AN, Denbigh GL, Gunawardena AH. Hsp70 plays a role in programmed cell death during the remodelling of leaves of the lace plant (Aponogeton madagascariensis). Journal of experimental botany. 2020 Jan 23;71(3):907-18.
50. Thompson SL, Compton DA. Proliferation of aneuploid human cells is limited by a p53-dependent mechanism. Journal of Cell Biology. 2010 Feb 8;188(3):369-81.
51. Meriin AB, Narayanan A, Meng L, Alexandrov I, Varelas X, Cissé II, Sherman MY. Hsp70–Bag3 complex is a hub for proteotoxicity-induced signaling that controls protein aggregation. Proceedings of the National Academy of Sciences. 2018 Jul 24;115(30):E7043-52.
52. Causse SZ, Marcion G, Chanteloup G, Uyanik B, Boudesco C, Grigorash BB, Douhard R, Dias AM, Dumetier B, Dondaine L, Gozzi GJ. HSP110 translocates to the nucleus upon genotoxic chemotherapy and promotes DNA repair in colorectal cancer cells. Oncogene. 2019 Apr 11;38(15):2767-77.
53. Zhao, K.; Zhou, G.; Liu, Y.; Zhang, J.; Chen, Y.; Liu, L.; Zhang, G. HSP70 Family in Cancer: Signaling Mechanisms and Therapeutic Advances. *Biomolecules* 2023, *13*, 601. https://doi.org/10.3390/biom13040601
54. Alexiou GA, VArtholoMAtos G, Stefanaki K, Patereli A, Dova L, Karamoutsios A, Lallas G, Sfakianos G, Moschovi M, Prodromou N. Expression of heat shock proteins in medulloblastoma. Journal of Neurosurgery: Pediatrics. 2013 Nov 1;12(5):452-7.
55. Dimas DT, Perlepe CD, Sergentanis TN, Misitzis I, Kontzoglou K, Patsouris E, Kouraklis G, Psaltopoulou T, Nonni A. The prognostic significance of Hsp70/Hsp90 expression in breast cancer: a systematic review and meta-analysis. Anticancer research. 2018 Mar 1;38(3):1551-62.
56. Simpson NE, Lambert WM, Watkins R, Giashuddin S, Huang SJ, Oxelmark E, Arju R, Hochman T, Goldberg JD, Schneider RJ, Reiz LF. High levels of Hsp90 cochaperone p23 promote tumor progression and poor prognosis in breast cancer by increasing lymph node metastases and drug resistance. Cancer research. 2010 Nov 1;70(21):8446-56.
57. Subramanian C, Grogan PT, Wang T, Bazzill J, Zuo A, White PT, Kalidindi A, Kuszynski D, Wang G, Blagg BS, Cohen MS. Novel C- terminal heat shock protein 90 inhibitors target breast cancer stem cells and block migration, self- renewal, and epithelial–mesenchymal transition. Molecular oncology. 2020 Sep;14(9):2058-68.
58. Kryeziu K, Bruun J, Guren TK, Sveen A, Lothe RA. Combination therapies with HSP90 inhibitors against colorectal cancer. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2019 Apr 1;1871(2):240-7.
59. Riggs DL, Cox MB, Cheung-Flynn J, Prapapanich V, Carrigan PE, Smith DF. Functional specificity of co-chaperone interactions with Hsp90 client proteins. Critical reviews in biochemistry and molecular biology. 2004 Jan 1;39(5-6):279-95.
60. Lu X, Xiao L, Wang L, Ruden DM. Hsp90 inhibitors and drug resistance in cancer: the potential benefits of combination therapies of Hsp90 inhibitors and other anti-cancer drugs. Biochemical pharmacology. 2012 Apr 15;83(8):995-1004.

61. Birbo, B.; Madu, E.E.; Madu, C.O.; Jain, A.; Lu, Y. Role of HSP90 in Cancer. *Int. J. Mol. Sci.* 2021, 22, 10317. https://doi.org/10.3390/ijms221910317
62. Jagadish N, Agarwal S, Gupta N, Fatima R, Devi S, Kumar V, Suri V, Kumar R, Suri V, Sadasukhi TC, Gupta A. Heat shock protein 70-2 (HSP70-2) overexpression in breast cancer. Journal of experimental & clinical cancer research. 2016 Dec;35:1-4.
63. Goloudina AR, Demidov ON, Garrido C. Inhibition of HSP70: a challenging anti-cancer strategy. Cancer letters. 2012 Dec 28;325(2):117-24.
64. Singh MK, Sharma B, Tiwari PK. The small heat shock protein Hsp27: Present understanding and future prospects. Journal of thermal biology. 2017 Oct 1;69:149-54.
65. Richards EH, Hickey E, Weber L, Masters JR. Effect of overexpression of the small heat shock protein HSP27 on the heat and drug sensitivities of human testis tumor cells. Cancer Research. 1996 May 15;56(10):2446-51.
66. Qi Y, Wang H, Zou Y, Liu C, Liu Y, Wang Y, Zhang W. Over-expression of mitochondrial heat shock protein 70 suppresses programmed cell death in rice. FEBS letters. 2011 Jan 3;585(1):231-9.
67. Ikwegbue PC, Masamba P, Mbatha LS, Oyinloye BE, Kappo AP. Interplay between heat shock proteins, inflammation and cancer: a potential cancer therapeutic target. American journal of cancer research. 2019;9(2):242.
68. Landriscina M, Amoroso MR, Piscazzi A, Esposito F. Heat shock proteins, cell survival and drug resistance: the mitochondrial chaperone TRAP1, a potential novel target for ovarian cancer therapy. Gynecologic oncology. 2010 May 1;117(2):177-82.
69. Blagosklonny MV. Hsp-90-associated oncoproteins: multiple targets of geldanamycin and its analogs. Leukemia. 2002 Apr;16(4):455-62.
70. Abel EJ, Culp SH, Tannir NM, Tamboli P, Matin SF, Wood CG. Early primary tumor size reduction is an independent predictor of improved overall survival in metastatic renal cell carcinoma patients treated with sunitinib. European urology. 2011 Dec 1;60(6):1273-9.
71. Lampros M, Vlachos N, Voulgaris S, Alexiou GA. The role of hsp27 in chemotherapy resistance. Biomedicines. 2022 Apr 14;10(4):897.
72. Su YH, Tang WC, Cheng YW, Sia P, Huang CC, Lee YC, Jiang HY, Wu MH, Lai IL, Lee JW, Lee KH. Targeting of multiple oncogenic signaling pathways by Hsp90 inhibitor alone or in combination with berberine for treatment of colorectal cancer. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2015 Oct 1;1853(10):2261-72.
73. Treweek TM, Meehan S, Ecroyd H, Carver JA. Small heat-shock proteins: important players in regulating cellular proteostasis. Cellular and molecular life sciences. 2015 Feb;72:429-51.
74. Navarro-Zaragoza J, Cuenca-Bermejo L, Almela P, Laorden ML, Herrero MT. Could small heat shock protein HSP27 be a first-line target for preventing protein aggregation in Parkinson's disease?. International Journal of Molecular Sciences. 2021 Mar 16;22(6):3038.
75. Hartl FU, Martin J, Neupert W. Protein folding in the cell: the role of molecular chaperones Hsp70 and Hsp60. Annual review of biophysics and biomolecular structure. 1992 Jun;21(1):293-322.
76. Mailhos C, Howard MK, Latchman DS. Heat shock protects neuronal cells from programmed cell death by apoptosis. Neuroscience. 1993 Aug 1;55(3):621-7.
77. Fu YF, Fan TJ. Bcl-2 family proteins and apoptosis. Sheng wu hua xue yu sheng wu wu li xue bao Acta biochimica et biophysica Sinica. 2002 Jul 1;34(4):389-94.
78. Daugaard M, Jäättelä M, Rohde M. Hsp70-2 is required for tumor cell growth and survival. Cell Cycle. 2005 Jul 2;4(7):877-80.
79. Riggs DL, Cox MB, Cheung-Flynn J, Prapapanich V, Carrigan PE, Smith DF. Functional specificity of co-chaperone interactions with Hsp90 client proteins. Critical reviews in biochemistry and molecular biology. 2004 Jan 1;39(5-6):279-95.
80. Wang Z. Regulation of cell cycle progression by growth factor-induced cell signaling. Cells. 2021 Nov 26;10(12):3327.
81. Kancha RK, Bartosch N, Duyster J. Analysis of conformational determinants underlying HSP90-kinase interaction. PLoS One. 2013 Jul 2;8(7):e68394.
82. Chandrashekar DS, Bashel B, Balasubramanya SA, Creighton CJ, Ponce-Rodriguez I, Chakravarthi BV, Varambally S. UALCAN: a portal for facilitating tumor subgroup gene expression and survival analyses. Neoplasia. 2017 Aug 1;19(8):649-58.
83. Su YH, Tang WC, Cheng YW, Sia P, Huang CC, Lee YC, Jiang HY, Wu MH, Lai IL, Lee JW, Lee KH. Targeting of multiple oncogenic signaling pathways by Hsp90 inhibitor alone or in combination with berberine for treatment of colorectal cancer. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2015 Oct 1;1853(10):2261-72.
84. Tsutsumi S, Neckers L. Extracellular heat shock protein 90: a role for a molecular chaperone in cell motility and cancer metastasis. Cancer science. 2007 Oct;98(10):1536-9.
85. Tsai YP, Yang MH, Huang CH, Chang SY, Chen PM, Liu CJ, Teng SC, Wu KJ. Interaction between HSP60 and β -catenin promotes metastasis. Carcinogenesis. 2009 Jun 1;30(6):1049-57.
86. El-Tanani M, Rabbani SA, Babiker R, Rangraze I, Kapre S, Palakurthi SS, Alnuqaydan AM, Aljabali AA, Rizzo M, El-Tanani Y, Tambuwala MM. Unraveling the Tumor Microenvironment: Insights into Cancer Metastasis and Therapeutic Strategies. Cancer Letters. 2024 Apr 16:216894.
87. Musiani D, Konda JD, Pavan S, Torchiaro E, Sassi F, Noghero A, Erriquez J, Perera T, Olivero M, Di Renzo MF. Heat-shock protein 27 (HSP27, HSPB1) is up-regulated by MET kinase inhibitors and confers resistance to MET-targeted therapy. The FASEB Journal. 2014 Sep;28(9):4055.
88. Shi K, Wang Y, Zhou X, Gui H, Xu N, Wu S, He C, Zhao Z. Tumor microenvironment targeting with dual stimuli-responsive nanoparticles based on small heat shock proteins for antitumor drug delivery. Acta Biomaterialia. 2020 Sep 15;114:369-83.
89. Gao C, Peng YN, Wang HZ, Fang SL, Zhang M, Zhao Q, Liu J. Inhibition of heat shock protein 90 as a novel platform for the treatment of cancer. Current Pharmaceutical Design. 2019 Mar 1;25(8):849-55

90. Landriscina M, Amoroso MR, Piscazzi A, Esposito F. Heat shock proteins, cell survival and drug resistance: the mitochondrial chaperone TRAP1, a potential novel target for ovarian cancer therapy. Gynecologic oncology. 2010 May 1;117(2):177-82.
91. Lampros M, Vlachos N, Voulgaris S, Alexiou GA. The role of hsp27 in chemotherapy resistance. Biomedicines. 2022 Apr 14;10(4):897.
92. Yun CW, Kim HJ, Lim JH, Lee SH. Heat shock proteins: agents of cancer development and therapeutic targets in anti-cancer therapy. Cells. 2019 Dec 24;9(1):60.
93. Poggio P, Sorge M, Seclì L, Brancaccio M. Extracellular HSP90 machineries build tumor microenvironment and boost cancer progression. Frontiers in Cell and Developmental Biology. 2021 Oct 14;9:735529.
94. Das JK, Xiong X, Ren X, Yang JM, Song J. Heat shock proteins in cancer immunotherapy. Journal of oncology. 2019 Oct;2019.
95. Holmes JL, Sharp SY, Hobbs S, Workman P. Silencing of HSP90 cochaperone AHA1 expression decreases client protein activation and increases cellular sensitivity to the HSP90 inhibitor 17-allylamino-17-demethoxygeldanamycin. Cancer research. 2008 Feb 15;68(4):1188-97.
96. Matsumoto Y, Machida H, Kubota N. Preferential sensitization of tumor cells to radiation by heat shock protein 90 inhibitor geldanamycin. Journal of radiation research. 2005 Jun;46(2):215-21.
97. Ghosh S, Ts DP, Chourasia RK, Mahmood AA. CANCER STEM CELLS: Cancer Stem Cells: Potential For Treatment. International Journal of Trends in OncoScience. 2023 Oct 3:1-2.
98. Mallu MR, Kotikalapudi SR, Agaarapu RV, Golamari SR. Clinical and Therapeutic Significance of Various Heat Shock Proteins.(2021). Int. J. Life Sci. Pharma Res.;11(4):L112-119.