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Review

Functions and Therapeutic Use of Heat Shock Proteins in Hepatocellular Carcinoma

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Abstract: Heat shock proteins are intracellular proteins expressed in prokaryotes and eukaryotes that help protect the cell from stress. They play an important role in regulating cell cycle and cell death, work as molecular chaperons during the folding of newly synthesized proteins, and also in the degradation of misfolded proteins. They are not only produced under stress conditions like acidosis, energy depletion, and oxidative stress but are also continuously synthesized as a result of their housekeeping functions. There are different heat shock protein families based on their molecular weight, like HSP70, HSP90, HSP60, HSP27, HSP40, etc. Heat shock proteins are involved in many cancers, particularly hepatocellular carcinoma, the main primary tumor of the liver in adults. Their deregulations in hepatocellular carcinoma are associated with metastasis, angiogenesis, cell invasion, and cell proliferation and upregulated heat shock proteins can be used as either diagnostic or prognostic markers. Targeting heat shock proteins is a relevant strategy for the treatment of patients with liver cancer. In this review, we provide insights into heat shock proteins and heat shock protein-like proteins (clusterin) in the progression of hepatocellular carcinoma and their use as therapeutic targets.

Keywords: chaperones; protein folding; heat shock protein; hepatocellular carcinoma

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1. Introduction

Hepatocellular carcinoma (HCC) is the most common type of liver cancer, which mainly originates from chronic liver diseases and cirrhosis mediated by viral infection, alcohol consumption abuse, and toxic agents. HCC is the second-leading cause of cancer-related deaths in males worldwide, especially in Asian countries [1,2]. HCC is caused by the uncontrolled proliferation of altered hepatocytes and is characterized by a high rate of recurrence, chemoresistance, and metastatic affection. Despite technological advances in cancer therapy, the prognosis for HCC remains very poor. Therefore, new therapeutic targets and strategies for the treatment of this malignancy are needed.

Chaperones are a family of proteins that play a key role in protein folding, post-translational modifications, and the stabilization of unfolded proteins. This stabilization aids in many biological processes, such as protein translocation, degradation, and folding [3]. They are found in all organisms, from bacteria to human beings, and are essential to cell survival [4]. Some of them harbor ATPase or protease activity [4,5]. Chaperones are also involved in the regulation of their genes and the presentation of proteins designed for degradation by proteases through the proteasome. Molecular chaperones interact with unfolded or partially folded protein subunits, stabilize non-native conformations,

and participate in the correct folding of the protein. They do not interact with native proteins, nor do they form a part of the final folded structures. They often couple with ATP binding/hydrolysis for the folding process [6]. Chaperones assist in protein folding by binding to nascent or denatured polypeptides through hydrophobic interactions, hydrogen bonding, and electrostatic forces. They use ATP-driven molecular machinery to carry out their functions [7]. Essential for cell viability, their expression is often increased by cellular stress. They prevent inappropriate association or aggregation of exposed hydrophobic surfaces and their substrates into productive folding, transport, or degradation pathways. Protein misfolding causes aggregation and build-up in a variety of diseases like Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, and Huntington's disease [8], which share a common feature of the accumulation of misfolded or abnormal proteins. It has been found that when misfolded proteins prove resistant to protein quality control systems, their accumulation reaches critical levels, causing hazards. In Parkinson's disease, the involvement of α synuclein, Parkin, causes the formation of Lewy bodies. Various heat shock proteins, such as HS27, HSP70, HSP90, and BiP, are likely to be involved in maintaining protein homeostasis and thereby reducing the aggregation of α-synuclein [9,10]. In Alzheimer's disease, an alteration in the amyloid precursor protein causes the production of the amyloid β peptide and the hyperphosphorylation of Tau proteins. These changes result in the formation of amyloid plaques and cause activation of HSP40, HSP60, HSP70, HSP90 [11–13]. Amyotrophic lateral sclerosis (ALS) is linked to a mutation in the Superoxide dismutase 1 (SOD1) gene. To mitigate the impact of misfolded proteins, HSP25, HSP27, HSP40, HSP70, and HSP90 are involved [14,15]. In Huntington's disease, the presence of mutant Huntingtin causes the accumulation of intracellular amyloid fibrils. The cellular defense mechanisms involve the participation of HSP40, HSP70, HSP104, HSP84, sHSPB6, and GRP78 [16–19]. The level of chaperones is relatively high in most types of human cancer compared to their normal tissues of origin because of the high neo-protein demands of the malignant cells [20].

The concept of "addiction to chaperons" has gained popularity in oncology as a hypothesis that could explain the increased level of heat shock proteins (HSPs) in cancerous cells. Cancerous cells experience an array of stresses viz., the presence of genetic mutations, increased ploidy, and increased protein synthesis to combat hypoxia, acidosis, nutrient deprivation, and a hostile tumor microenvironment. This ultimately demands the augmentation of the level of HSPs for proper protein folding inside the cells [21]. Cells have developed a quality management system that ensures that the whole cell proteome works correctly and retains only folded proteins with a correct, definitive and functional conformation.

Under stress conditions, like high temperatures, cellular protein homeostasis becomes disturbed, which causes the activation of cellular defense mechanisms to restore it. The protein-folding cellular machinery has the remarkable ability to specifically recognize misfolded proteins and supports folding to its original state. Some classes of molecular chaperones evolved independently and are both structurally and mechanically different, like HSPs, which are highly conserved molecules.

Many of the small proteins likely fold at a very fast rate in the dilute buffer solutions. The larger the protein is, the longer it takes to fold it. However, some proteins may fail to properly fold and reach their native state. In a cellular environment, the efficient folding of such proteins in a biologically appropriate time frame requires molecular chaperons so that the protein maintains its soluble configuration. Due to point gene mutation or deletion, the ability of the related protein to fold could be disrupted, and the stable and definitive state could not be attained by mutated proteins. In this case, the chaperon system provides a crucial buffered environment, allowing mutated proteins to fold and (may) acquire new functions [22].

The mechanism of chaperones can be categorized into three stages: substrate recognition and binding, protein folding or unfolding, and release of the substrate. First, chaperones bind misfolded proteins as substrates and identify those that require assistance by

recognizing exposed hydrophobic areas on the polypeptide chain. This type of interaction helps to prevent the proteins from forming aggregates, which can lead to cellular toxicity. Chaperones bind to the exposed hydrophobic sites with low affinity to prevent aggregation, and once bound, they form a tight complex [23]. Second, chaperones use ATP hydrolysis to perform their protein folding or unfolding functions. Once bound to the substrate, chaperones use their ATP-driven machinery to facilitate protein folding. At this stage, chaperones can either facilitate the refolding of a partially denatured protein or prevent the misfolding of a newly synthesized protein. ATP hydrolysis-dependent cycles provide the energy to overcome kinetic barriers and enable proteins to reach their stable, native conformation. Finally, once the protein recognized as a substrate has reached its native conformation, the chaperone releases it. In some cases, chaperones can assist in the release of the protein from a complex by recruiting other accessory proteins, which can perform subsequent folding and assembly steps.

Several classes of chaperones, including HSP60, HSP70, and HSP90 chaperones, have been identified. These chaperones differ in their affinity for the substrates and their mechanisms of action. HSP70, for instance, prevents protein aggregation by binding to denatured proteins and assisting in refolding. HSP90 is essential for stabilizing large proteins [24], while HSP60 (also known as GroEL) forms a barrel-shaped complex with GroES to function as a molecular chaperone. Small heat shock proteins with a low molecular mass of 15 to 30 kDa are also molecular chaperones. They are highly conserved and ubiquitously expressed in biological tissues and cells [25]. They interact with misfolded or partially folded proteins through multiple interactions and use ATP hydrolysis-dependent machinery to fold proteins and prevent aggregations [26].

Chaperones have emerged as attractive therapeutic targets for cancer therapy as they are involved in the expression and activity of numerous oncogenes and tumor suppressor genes. The role of chaperones in HCC has been the focus of extensive research in recent years. The involvement of chaperones in the pathogenesis of HCC and their potential as therapeutic targets have gained strong interest from the scientific community. Our review articles explore the diverse functions and potential of heat shock proteins in the context of hepatocellular carcinoma. This article provides an integrated and global view of existing literature to elucidate the roles of HSPs in HCC progression and their emerging significance as potential therapeutics. A systematic literature search was conducted using online databases like PubMed and Scopus. This review will summarize the involvement of the molecular chaperone HSPs in HCC progression (Figure 1) and the description of different molecular chaperones as therapeutic targets for the treatment of this deadly cancer (Figure 2).

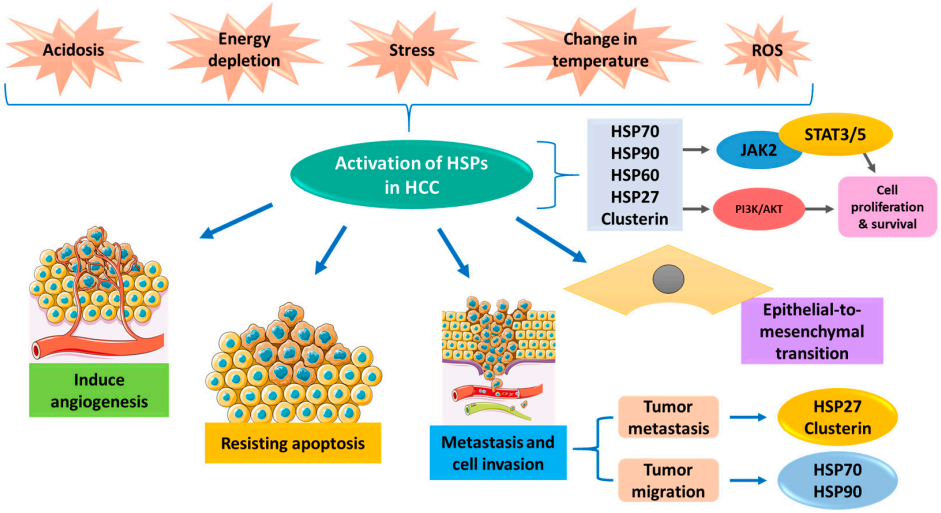

Figure 1. Involvement of different heat shock proteins in hepatocellular carcinoma progression following various stresses.

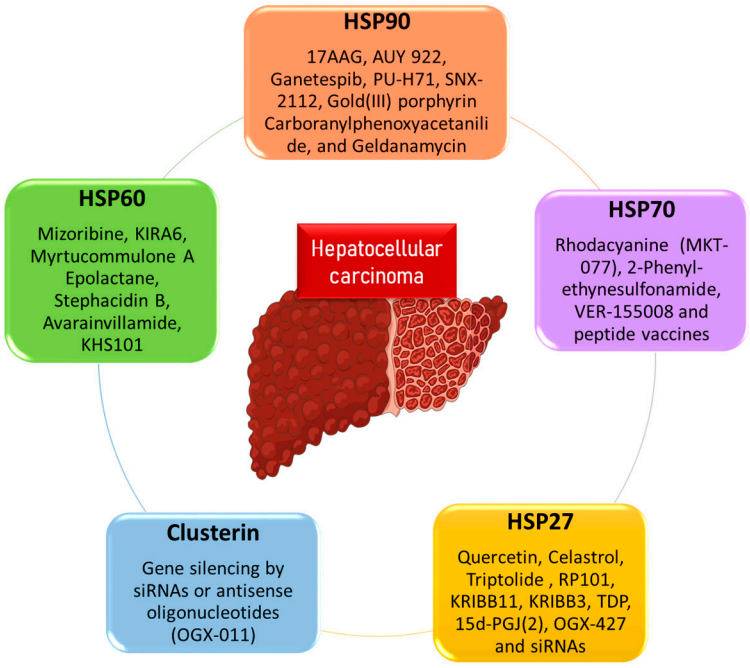

Figure 2. Heat-shock protein-derived targeted therapies for hepatocellular carcinoma treatment.

2. Chaperones in Hepatocellular Carcinoma

2.1. HSP110 Family

HSP110, previously known as HSP105, belongs to a group of high-molecular-weight HSPs, and it controls protein homeostasis [27]. The human genome encodes seventeen HSP70s, with four of these being Hsps, which are protein homologs of HSP110, forming a non-canonical clade within the HSP70 family [28]. As compared to the canonical HSP70, HSP110 is considerably more efficient in recognizing denatured proteins, and thereby, during stress, it can efficiently rescue the misfolded proteins [29]. HSP110 is involved in the phosphorylation of STAT3 in the cytosol, cell proliferation, tumor growth, angiogenesis, and metastasis [30]. HSP110 forms a multiprotein complex with HSP70 and HSP40 to enhance the folding of nascent polypeptides in tumor cells and is involved in stabilizing heat-denatured proteins [31]. HSP110 also modulates metastasis in cancer by interacting with VEGF and, thereby, is responsible for abnormal angiogenesis. It associates with pro-inflammatory cytokines and mediates EMT. Moreover, HSP110 upregulates the expression of proinflammatory cytokines such as IL-6, IL-12, and TNF-α by stimulating the dendritic cells [32]. Both IL-6 and TNF-α are involved in the process of EMT. Under stress conditions, HSP110 is associated with HSPB5 and suppresses the aggregation of proteins [33]. HSPB5 is a member of the small Hsp family and is known to control the activity of the proangiogenic factor, vascular endothelial growth factor (VEGF) [34]. Hence, HSP110 indirectly serves as a promoter of angiogenesis.

2.2. HSP90 Family

HSP90 is a molecular chaperone involved in the folding and stabilization of various proteins, including oncogenic, mutated, or truncated proteins [35]. The HSP90 family comprises four isoforms with a molecular weight close to 90-kD: HSP90α, HSP90β, GRP94, and tumor necrosis factor (TNF) receptor-associated proteins 1 (TRAP1), which are highly conserved and ubiquitously expressed molecules. They are found in all living organisms except archaea [36]. The HSP90 proteins function in the stabilization of signal transduction proteins, transcription factors, and other macromolecular protein complexes. HSP90 is involved in several cellular processes, including the folding, assembly, and maturation of diverse proteins, the degradation of misfolded proteins, and the regulation of protein–protein interactions. Clients of HSP90 include kinases, transcription factors, steroid hormone

receptors, immune receptors, and other signaling molecules. HSP90 is also critical for cellular stress responses and the maintenance of proteostasis. The HSP90 family has a modular structure comprising three domains: the N-terminal domain (NTD), the middle domain (MD), and the C-terminal domain (CTD). The NTD and MD are responsible for ATP binding and are involved in client-protein interaction, while the CTD regulates HSP90 ATP site activity and client release [37–39]. HSP90 is regulated by multiple co-chaperones, including p23, Aha1, and Hop/Sti1, which modulate its ATPase activity and client-binding affinity [40].

Several studies have reported an overexpression of HSP90 in HCC tissues and cell lines compared to normal liver tissue. Upregulation of HSP90 is associated with tumor growth, invasion, and resistance to chemotherapy in HCC. Radiofrequency ablation also increased cellular expression of HSP90 in HCC tissues [41]. Inhibition of HSP90 has been shown to induce apoptosis and impede HCC cell proliferation [42]. Phosphatidylinositol-3-kinase-like kinases (PIKK) constitute a family of Ser/Thr kinases that comprise six members in humans, namely, ATM, ATR, DNA PKCs, TRAPP, SMG1, and mTOR. PIKK family members play an essential role in DNA damage and repair signaling among other functions. Correct folding assembly of the PIKK complex also requires an HSP90 chaperone in association with a heterotrimeric co-chaperone called the Tel2-Tti1-Tti2 (TTT) complex [43]. B-cell lymphoma 2 (Bcl-2)-associated transcription factor 1 (Bclaf1) upregulation is associated with a poor prognosis and reduced survival in HCC. Its functional impact relies on its interaction with HSP90α in this cancer [44], and there is a critical relationship between HSP90 and the PI3K-AKT-mTOR signaling pathway [43]. HSP90 is a chaperone protein that plays an important role in folding and stabilizing client proteins involved in HCC cell proliferation, survival, and migration, making it an attractive target for cancer therapy [45,46]. The PI3K-AKT-mTOR signaling pathway is often deregulated in HCC, resulting in increased proliferation, decreased apoptosis, and increased migration and invasion [47]. HSP90 interacts with several components of this pathway (i.e., AKT, MTOR, and PTEN) to stabilize their activity [48]. The inhibition of HSP90 by small-molecule inhibitors such as geldanamycin and 17-AAG induced the degradation of several client proteins of the PI3K-AKT-mTOR signaling pathway and suppressed HCC cell proliferation and invasion. Additional studies showed that HSP90 inhibition improves the efficacy of sorafenib-based targeted therapy in HCC cells [44]. Combination therapy with an HSP90 inhibitor and sorafenib has shown higher efficacy compared to sorafenib alone in preclinical HCC models [44,49]. Therefore, targeting HSP90 in combination with other therapeutics may be a promising strategy for the treatment of HCC by blocking the PI3K-AKT-MTOR signaling pathway.

2.3. HSP70 Family

HSP70 is a 70 kDa conserved protein that plays an essential role in maintaining cellular homeostasis. These proteins also help in the folding, stabilization, and degradation of proteins inside the cell at the time of cellular stress. Hsp70 also plays an important role in cancer development and progression. It is usually upregulated in HCC. It acts as a hallmark of tumor cell invasion and migration, which support angiogenesis and metastasis by promoting the folding and functions of proteins involved in these processes. HSP70 has two major domains, namely the N-terminal nucleotide-binding domain (NBD) and the C-terminal substrate-binding domains (SBD), connected by a linker. NBD is 45 kDa and carries ATPase activity, while (SBD) is required for peptide binding [42].

HSP70 is strongly induced in response to various cellular stresses, such as heat shock, hypoxia, and oxidative stress. HSP70 is involved in many cellular processes, including protein folding and degradation, intracellular trafficking, and apoptosis regulation [42]. An elaborate network of chaperones is present in organisms across all domains of life to oversee the health of the cellular proteome [50]. The HSP70 family of molecular chaperones occupies a central node in this network, steering proteins synthesized on the ribosome to their native conformations as well as cooperating with the machinery of protein disaggregation, refolding, and proteolysis to control the fate of improperly folded and aggregated

cellular proteins [21,24,51,52]. HSP70 interacts with client substrates via an ATP-dependent chaperone cycle that is tightly regulated by HSP40 co-chaperone and nucleotide exchange factors (NEFs) [24,50,51].

HSP70 activates the PI3K/AKT/mTOR signaling pathway to promote cell survival and proliferation. HSP70 may also promote cell migration and invasion by regulating epithelial-to-mesenchymal transition (EMT) and extracellular matrix (ECM) by stabilizing the Wiskott-Aldrich syndrome family member 2 (WASF2) [53–55]. HSP70 has been reported to modulate the sensitivity of HCC cells to chemotherapy and radiotherapy. HSP70 can inhibit apoptosis and autophagy and, thereby, participate in cell death resistance. HSP70 is also involved in inducing angiogenesis by stabilizing the accumulation of hypoxia-inducible factor-1 (HIF-1). This transcriptional factor is responsible for sensing even a small amount of oxygen, which is required for tumor angiogenesis and tumor cell migration [56,57]. HSP70 is upregulated in HCC tissues compared to non-tumor tissues, and its expression correlates with tumor progression and a poor prognosis [58]. Inhibiting HSP70 can disturb the stability of oncogenes, resulting in tumor growth inhibition. Anti-cancer treatments like chemotherapy and immunotherapy, along with HSP70 chaperone inhibitors, can enhance treatment efficiency [59]. HSP70 can also promote the expression of drug resistance-associated genes such as MDR1, conferring or reinforcing chemoresistance. Finally, various HSP70 inhibitors have been shown in preclinical studies to suppress HCC cell proliferation, migration, and invasion and to sensitize HCC cells to chemotherapy and radiotherapy [60]. In conclusion, targeting HSP70 chaperones, alone or in combination with other anti-cancer approaches, could be a relevant therapeutic strategy in HCC treatment [48].

2.4. HSP60

HSP60, also known as chaperonin 60 or GroEL, is another important member of the HSP family. It is encoded by the nuclear gene *HSPD1*, located on chromosome 2. The N-terminal region of HSP60 contains a mitochondrial targeting signal, which is essential to its import into mitochondria [61]. Once in the mitochondria, the mitochondrial targeting sequence gets cleaved by protease, yielding its mature form. Hence, the majority of HSP60 is found in mitochondria, where, along with HSP10, it helps in the proper folding of newly synthesized proteins and the maintenance of mitochondrial protein homeostasis [62,63]. It also has a crucial function in preserving the integrity and functionality of the mitochondrial respiratory chain and cell survival. As a consequence, HSP60 is much less abundant in the cytoplasm and at the cell membrane [64,65].

HSP60 is a key component of the mitochondrial unfolding protein response reaction (UPRmt). Upon UPRmt activation, several transcription factors, including activating transcription factor 4 (ATF4), activating transcription factor 5 (ATF5), and C/EBP homologous protein (CHOP), are activated and mobilized. In the absence of stress, ATF5 is found in mitochondria; however, when exposed to stresses, like reactive oxygen species or mitochondrial DNA damage, ATF5 gets translocated into the nucleus along with CHOP and ATF4, where they jointly upregulate the expression of HSP60.

Several studies have shown that HSP60 expression is upregulated in HCC tissues compared to normal liver tissues [66,67] and used as an advanced biomarker in its early detection [68]. Moreover, high levels of HSP60 protein in HCC are associated with poor prognosis and increased rates of tumor recurrence and metastasis. At the molecular level, it has been found that HSP60 stimulates the differentiation of HCC-derived SMMC7221 [69]. HSP60 also plays a role in promoting inflammation, a key factor in the development of adult liver diseases including cirrhosis and HCC. HSP60 has been reported to activate immune cells, contribute to liver injury, and trigger the release of pro-inflammatory cytokines that promote the development of HCC [70]. HSP60 exerts an anti-apoptotic effect by interacting with survivin and cyclophilin D (CypD) and a pro-apoptotic effect by interacting with procaspase 3 and fragile histidine triad protein (FHIT) [71–73]. HSP60 is also involved in tumor metastasis by interacting with β-catenin [74]. Despite the benefit of these previous studies in the treatment of HCC patients, further investigations are needed to fully un-

derstand the cellular functions of HSP60 and the mechanisms by which this chaperone contributes to this liver malignancy.

2.5. HSP27

HSP27 belongs to the family of small HSPs and possesses a molecular weight of approximately 27 kDa [75]. The human HSP27 protein contains 205 amino acids, which are encoded by *HSPB1* genes located on chromosome 7q11.23 [76]. The gene gets activated in response to stress through phosphorylations of HSP27 on Ser-15, Ser-78, and Ser-82 [77]. This protein is responsible for modulating various client proteins like cytochrome C, caspase-3, and translationally controlled tumor proteins (TCTP), which are responsible for cancer initiation and development [77,78]. HSP27 is also required for cytoskeleton organization, DNA repair, and RNA splicing. The numerous functions of HSP27 are the consequence of its interaction with many client proteins [79].

Because of its multiple roles, HSP27 is deeply involved in cancer development and progression, as well as metastasis and angiogenesis. It regulates cellular apoptosis and drug resistance and serves as a prognostic factor for poor disease outcomes in melanoma and glioma. HSP27 is involved in the folding, unfolding, and stabilization of proteins, as well as the protection of cells from stressors such as heat, toxins, and reactive oxygen species [25,77]. It acts as a protein chaperone and an antioxidant and plays a role in the inhibition of apoptosis and actin cytoskeletal remodeling [75,80]. HSP27 is overexpressed in various types of cancer, including HCC. In this cancer, HSP27 promotes cell growth, migration, survival, and invasion by regulating different pro-oncogenic pathways [81,82]. For instance, HSP27 promotes HCC by activating the PI3K/Akt and MAPK/ERK pathways, both of which are involved in regulating cell growth and survival. Moreover, HSP27 has been shown to regulate the metastatic potential of HCC cells by promoting EMT, a process that allows cancer cells to migrate and invade surrounding tissues [83]. HSP27 also facilitates the neo-formation of blood capillaries (angiogenesis), which are essential for HCC growth and progression.

2.6. HSP20

HSP20 is one of the low-molecular-weight HSPs. It is found in various tissues, but its specific role in cancer is poorly understood. A study was conducted using human HCC-derived HuH7 cell lines, and the team showed that the introduction of HSP20 in HCC cells caused an inhibition of cell proliferation [84,85]. HSP20 acts as a suppressor of HCC cell growth through MAPKs and AKT-dependent signaling, making HSP20 a novel therapeutic target in HCC [84].

2.7. Clusterin

Clusterin is an ATP-independent molecular chaperon with properties similar to HSPs. It has been found that clusterin is highly expressed in cancer cells and is involved in inhibiting apoptosis [86]. The level of clusterin is found to be upregulated in the case of HCC patients, and glycosylation of clusterin is used as a biomarker of early diagnosis [87]. A study on clusterin and liver cancer prognosis showed that high levels of clusterin are linked to worse tumor characteristics and patients with poor prognosis [88]. Another study also showed that clusterin is more expressed in metastatic tissues compared to primary tumors. Table 1 and Figure 3 describe the functions of HSP family members.

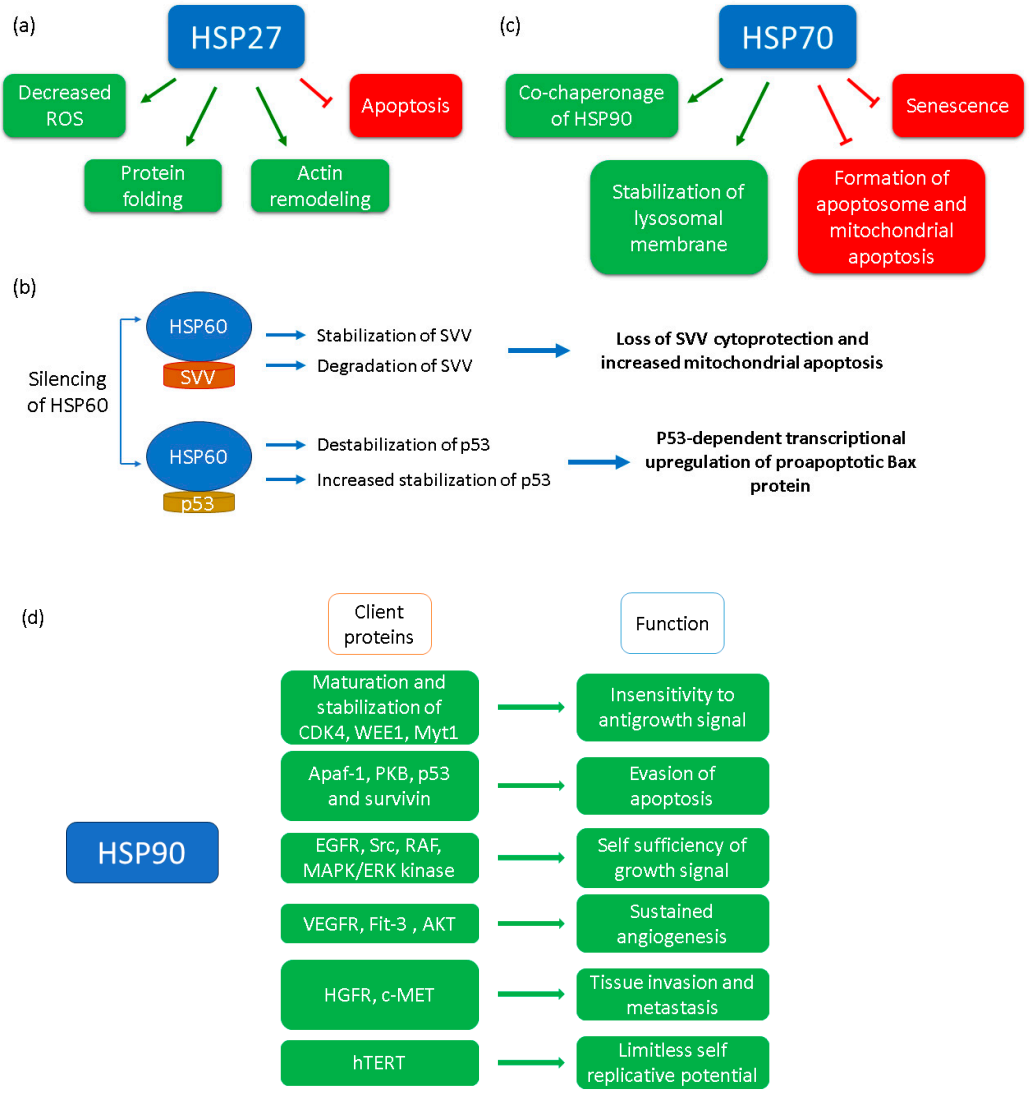

Figure 3. (**a**–**d**) Diagram representing biological functions of major Chaperons in Cancer.

Table 1. Describes the classification and role of heat shock family members.

S. N°	HSP Family	Members of the HSP Family	Function	References
1	Small HSP	HSP10 and HSP27	Molecular chaperon, HSP10 acts as a cofactor for HSP60.	[89,90]
2	HSP40/DNAJ	HSP40	Molecular chaperon, HSP40 acts as a cofactor for HSP70.	[91]
3	HSP60	HSP60	Chaperonin	[92]
4	HSP70	HSP70, HSC70, GRP75, GRP78	Molecular chaperone	[93]
5	HSP90	HSP90A, HSP90B, GRP94, TRAP1	Molecular chaperone	[93]
6	Large HSPs	HSP110, GRP170	Molecular chaperone, Holdase	[93]

3. Role of Chaperones in HCC Treatment and Therapeutics

Chaperones play a crucial role in the development and progression of HCC; therefore, stand as relevant therapeutic targets. They help in protein folding and prevent the formation of abnormal protein aggregates. In HCC, chaperones are involved in the regulation of various signaling pathways that promote tumor growth, proliferation, and survival. Under physiological conditions, the expression of HSPs is negligible, which increases drastically in stressed conditions as well as in cancer cells. With the help of elevated levels of HSPs, cancer cells can evade anti-growth signals and apoptosis while promoting cell proliferation [20]. Targeting HSPs like HSP90 can cause targeted damage, specifically to tumor cells, but is less toxic to normal cells [94]. Therefore, many HSP inhibitors have entered clinical trials to treat malignancies. Targeting chaperones in HCC therapy involves the use of drugs that inhibit their activity or promote their degradation (Figure 2). The names of the inhibitors of various HSPs and their modes of action have been listed in Table 2. For instance, HSP90 inhibitors have been shown to reduce the growth of HCC cells by inducing cell cycle arrest and apoptosis. Owing to similar effects in various malignancies, these inhibitors have multifaceted anti-tumor effects and can act against breast cancer, brain cancer, and melanoma [94]. Similarly, HSP27 inhibitors sensitize HCC cells to chemotherapy and radiation therapy [95]. Moreover, targeting chaperones in combination with other therapies, such as immunotherapy and targeted therapy, has shown promising results in preclinical studies. For instance, combining an HSP70 inhibitor with an immune checkpoint inhibitor enhanced the anti-tumor activity of the latter [96].

HSPs are being investigated as potential prognostic and diagnostic biomarkers in HCC [97]. Blood circulating levels of HSP70 and HSP90 are associated with HCC progression and poor prognosis [20]. Other chaperones, such as protein disulfide isomerase A3 (PDIA3), glucose-regulated protein 78 (GRP78), and calreticulin (CRT), are also implicated in HCC development and progression [98–101]. Elevated PDIA3 levels are associated with HCC metastasis, while increased expression of GRP78 and CRT is associated with HCC cell proliferation and invasion [102].

Targeting chaperones as a therapeutic strategy is of great interest in cancer research, including HCC. However, targeting chaperones in HCC therapy presents some challenges. One of the major challenges is the lack of specificity of chaperone inhibitors. Many chaperone inhibitors also target other chaperones and proteins and are known to cause side effects and toxicity. Therefore, the development of selective chaperone inhibitors is critical to minimize toxicity and improve therapeutic efficacy. Another challenge is the complex network of chaperones and co-chaperones involved in protein folding. HCC cells have been shown to rely on specific chaperone networks for survival, making it difficult to identify specific proteins to target. Moreover, chaperones have been found to have overlapping functions, further complicating the development of targeted chaperone inhibitors. In addition, the role of chaperones in promoting protein degradation and autophagy has also been implicated in cancer cell survival and resistance to therapy. Therefore, targeting the chaperone alone may not be sufficient to treat HCC effectively, and combination therapy may be required. Despite these challenges, the potential benefits of targeting chaperones in HCC therapy cannot be ignored. Further research is needed to better understand the role of chaperones in HCC and to develop targeted and effective therapies.

3.1. HSP90 as a Therapeutic Target

HSP90 is a highly conserved and ubiquitously expressed molecular chaperone that plays an essential role in maintaining cellular proteostasis, especially under stress conditions. It empowers the folding, stabilization, and function of numerous proteins, known as HSP90 client proteins, several of which are implicated in cellular signal transduction, proliferation, differentiation, and apoptosis. Interestingly, many of these client proteins are frequently overexpressed or functionally dysregulated in various cancers, including HCC. Considering the compelling preclinical basis of HSP90 in HCC, there have been ongoing advancements and preclinical trials in this area [58,103]. Researchers have developed

several pharmacologic strategies to exploit its vulnerabilities (Table 2, Figure 2). These primarily include the development of small-molecule inhibitors that selectively dock into the HSP90's ATP-binding pocket, thereby precluding ATP binding, impairing HSP90's chaperone activity, and instigating the degradation of its client proteins. So far, several HSP90 inhibitors have been investigated in preclinical studies and early phase clinical trials for HCC with promising results. Several HSP90 inhibitors, such as geldanamycin, 17-allylamino17demethoxygeldanamycin (17-AAG), and Ganetespib, have shown efficacy in preclinical studies and stand as potential treatments for HCC [42,104]. Among these, AUY922, a novel resorcinol-derived HSP90 inhibitor, has been found to disrupt the EGFR-STAT3 signaling axis, significantly suppressing HCC cell proliferation, inducing apoptosis, and impairing angiogenesis in vitro and in vivo. In a recent phase II clinical trial involving patients with advanced HCC, AUY922 demonstrated a 9.1% partial response rate and an acceptable safety profile [68]. Similarly, ganetespib, a triazolone-containing HSP90 inhibitor, has been reported to inhibit AKT and VEGF signaling in preclinical HCC models, causing tumor growth arrest and reduced microvessel density. In phase I clinical trials in advanced HCC patients, ganetespib showed biological activity, with 1 out of 12 patients experiencing a partial response that lasted for 14 weeks [105]. Further basic and translational research is required to elucidate the molecular mechanisms underlying the antitumor actions of HSP90's inhibitors, to develop robust predictive biomarkers for patient selection guidance, and to rationalize novel combination strategies that effectively exploit HSP90s vulnerabilities while minimizing the risk of toxicity and resistance. SNX-2112 and PU-H71 are HSP90 inhibitors that cause a decrease in cancer growth by inactivating the unfolded protein response. PU-H71 causes antitumor activity in HCC cell lines [106,107]. 17 dimethoxy 17-allylamino geldanamycin (17-AAG) has a greater binding affinity with the N-terminal domains of HSP90, thereby preventing ATP binding. It causes apoptotic cell death and has also shown the downregulation of HSP90 by upregulating GRP75 in HCC cells [104,105]. Summarizing the above, we can say that HSP90-based therapeutic strategies are a promising tool for the management of the progression of HCC. HSP inhibitors have been designed as a part of HCC therapy, and their effects on cancer are summarized in Table 2.

3.2. HSP70 as a Therapeutic Target

HSP70 is a chaperone protein that plays a critical role in protein folding, trafficking, and degradation. It is involved in several biological pathways, including stress response, apoptosis, and cellular proliferation. Several studies have demonstrated that the inhibition of HSP70 can sensitize HCC cells to chemotherapy and induce cell death. One approach for targeting HSP70 in HCC is through the use of small-molecule inhibitors that block its chaperone activity (Table 2, Figure 2). One such inhibitor is called VER-155008, which has been shown to inhibit HSP70 function and induce cell death in HCC cells. Additional HSP70 inhibitors include 2-phenylethynesulfonamide or pifithrin-μ and rhodacyanine, also called MKT-077 [71,108,109]. 2-phenylethynesulfonamide binds to the C-terminal peptide binding domain of HSP70, resulting in disruption of its association with client proteins including p53 and proapoptotic APAF-1. This results in the aggregation of misfolded proteins and ultimately apoptosis [110]. MKT-077 disrupts the ATPase domain of HSP70 and impacts its function [111]. Another study evaluated the potential of HSP70 peptide vaccines as a therapeutic approach for HCC [112]. Overall, these findings suggest that HSP70 is a relevant therapeutic target for cancer. Further studies and clinical trials will be needed to assess the safety and efficacy of targeting HSP70 in HCC patients.

3.3. HSP60 as a Therapeutic Target

Several studies are being conducted to develop HSP60-specific drugs for HCC (Table 2, Figure 2). These inhibitors are categorized into two main categories, depending on their actions. The first group works by binding directly with HSP60, while the second acts on the post-translational modifications of HSP60 [113]. Some inhibitors of HSP60 are mi-

zoribine, myrtucommulone A, KIRA 6, epolactaene, streptavidin B, avarainvillamide, and KHS101 [114–116]. Some synthetic HSP60 inhibitors are o-carboranylphenoxyacetanilide and gold [III] porphyrin [117]. The therapeutic potential of HSP60 using extraneous delivery of JetPE1/shHSP60 complexes destabilizes cytoplasmic survivin in HCC and hence can inhibit the growth of HCC [56]. Interestingly, HSP60 inhibitors can be used as combination therapy or tumor-targeted therapy. An Imidazole nucleoside antibiotic named mizoribine also has the potential to inhibit the folding capacity of HSP60. It is derived from *Eupenicillium brefeldianum*, which is used as a potent immunosuppressive agent in very minute quantities [114]. It has also been found that it shows cytotoxicity against cells derived from the malignant lymphoma of the mouse. Myrutucommulone A is a non-prenylated acylophloroglucinol derived from *Myrtus communis* [101]. It inhibits chaperone activity by directly binding HSP60. This chemical compound is used in anti-bacterial, and anti-inflammatory applications and also has anti-tumor properties [101,103,104]. It also causes apoptosis in malignant cells [118]. Stephacidin B is obtained by *Aspergillus ochraceus* and avrainvillamide is isolated from *Aspergillus* sp. CNC358. They both have in vitro anticancer activities [119,120]. Epolactaene inhibits HSP60 by alkylating cys442 [115]. KIRA6 has been tested on multiple cancer cell lines and is directly interacting with HSP60 and reducing its ATP folding capacity [121]. Thus, HSP 60 is a potential candidate that can be targeted to treat HCC.

3.4. HSP27 as a Therapeutic Target

As seen above, HSP27 regulates different pro-oncogenic pathways like activation of PI3K/AKT and MAPK/ERK and also plays a role in the remodeling of the actin cytoskeleton, promotion of EMT, and inhibition of apoptosis. Due to its critical role in HCC progression and aggressivity, current data support the idea that HSP27 is a relevant and attractive therapeutic target for HCC. However, blocking its activity is challenging since HSP27 is involved in many cellular functions and protein–protein interactions [79]. Several approaches have been investigated to target HSP27, including small molecule inhibitors, siRNA, and peptides. Additional pre-clinical investigations are needed to determine the safety and efficacy of such approaches in clinical settings. Several HSP27 inhibitors have been developed and tested in preclinical studies for their potential to treat HCC patients [76]. For example, a nucleoside analog bromovinyldeoxyuridine, also known as RP101, can bind HSP27, weaken its binding to pro-caspase3, Akt1, and cytochrome C and inhibit its anti-apoptotic function [122,123]. Another inhibitor, KRIBB3, has been shown to significantly suppress the growth and proliferation of HCC cells in vitro and in vivo [124]. Another HSP27 inhibitor, 15-deoxy-Delta (12,14)-prostaglandin J(2) (15d-PGJ(2)), J2, has demonstrated potent antitumor effects in HCC by inducing apoptosis and inhibiting cell migration and invasion [125]. Other compounds such as quercetin, celastrol, and triptolide have also shown promising results in HCC cell lines by inhibiting HSP27 expression and activity [95,126–128]. Despite these promising findings, these different HSP27 inhibitors are still in the early stages of development, and additional pre-clinical studies and clinical trials are needed to evaluate their safety and efficacy in humans. Using a gene-silencing siRNA-based strategy, an anti-metastasis and proapoptotic effect of HSP27 down-regulation in HCC cells has been shown [58]. A study suggested that a second-generation antisense oligonucleotide, OGX-427, suppresses the expression of HSP27 and downregulates the metastasis in HCC through AKT-MMP2 signaling [58,129]. 1,3,5-trihydroxy-13,13- dimethyl-2H-pyran [7,6-b] xanthone (TDP), a natural compound isolated from the plant *Garcinia oblongifolia*, directly interacts with HSP27 and stimulates it to form aggregates, followed by its degradation by ubiquitin-mediated proteasomes, thereby suppressing the chaperone activity of HSP27, which ultimately results in apoptosis [130,131].

In conclusion, the potential of HSP27 inhibition as a therapeutic target for HCC treatment is a very exciting and dynamic area of research that should lead to the development of new and effective treatments for this disease in a decade.

3.5. Clusterin as a Therapeutic Target

It is highly challenging to inhibit clusterin as it works in an ATP-independent manner. Silencing clusterin expression using siRNA or antisense oligodeoxynucleotide improves the efficiency of drugs like gemcitabine, oxaliplatin, and doxorubicin in HCC treatments [131,132]. A second-generation antisense oligonucleotide, OGX-011, which targets the mRNA of clusterin, can suppress the metastatic process in many HCC cell lines [91]. Reducing clusterin levels increases the sensitivity of cells to chemotherapy and radiotherapy in some cancers [86,133]. It has also been found that silencing the levels of clusterin increases the expression of MMP-2 and decreases the level of E-cadherin expression, which is associated with cell adhesion [86,134]. Overexpression of clusterin leads to chemotherapy drug resistance by activating AKT pathways, which play an important role in cell survival and proliferation [134].

Table 2. Inhibitors targeting various chaperons and their functions in the management of HCC.

Chemicals/Inhibitors	Tested on	Functions	References
HSP27 Inhibitors			
KRIBB11	Mouse model	Inhibit tumor growth	[124,135]
KRIBB3		Inhibit growth and proliferation of HCC cells	[124]
15-deoxy-Delta (12,14)-prostaglandin J (2)		Antitumor effects in HCC	[125,136]
Quercetin Celastrol Triptolide	HCC cell lines Phase 2	Inhibit HSP27 expression.	[126,127,137–139]
OGX-427		Suppress metastasis.	[95]
RP101	Phase II trial	Bind with HSP27 and inhibits its interaction with other proteins	[122,123,140]
1,3,5-trihydroxy-13,13-dimethyl-2H-pyran [7,6-b] xanthone (TDP)		Directly binds HSP60 and stimulates it to form aggregates followed by its ubiquitin-mediated proteolysis	[124,125,130,141]
HSP90 inhibitors			
17AAG	Phase I/II/III clinical trial	Tumor growth arrest and reduce microvessels.	[142,143]
Ganetespib	Phase I/II/III clinical trials	Suppress HCC cell proliferation.	[105,144,145]
AUY 922	Phase I/II Clinical Trial	Inhibit expression of HSP90	[146]
SNX 2112	HCC cell lines	Induce apoptosis.	[107,147,148]
PU-H71	Phase I clinical trial	Decrease cancer growth by inactive UPR.	[106,149]
Geldanamycin (GA)	Phase I clinical trial	Prevent cell growth by binding to the ATP-binding site of HSP90.	[150–153]
Carboranylphenoxyacetanilide	Multiple cancer cell lines	Directly interacts with HSP60 to inhibit its function	[154,155]
Gold(III) porphyrin	Multiple cancer cell lines	Directly interacts with HSP60 to inhibit its function	[156,157]
17-DMAG	Phase I clinical trial	Analogue of GA, Prevent cell growth by binding to the ATP-binding site of HSP90.	[158]

Table 2. *Cont.*

Chemicals/Inhibitors	Tested on	Functions	References
HSP70 inhibitors			
VER155008		Inhibit expression of HSP70 and cause cell death.	[159,160]
2-Phenylethynesulfonamide		Binds C terminal PBD of HSP70, resulting in aggregation of misfolded protein and finally apoptosis	[110,161]
MKT-077 Peptide vaccine	Phase I clinical trial Mouse model	disrupts ATPase domain of HSP70	[111]
HSP60 inhibitors			
Mizoribine	HCC cell lines	inhibit the folding capacity of HSP60.	[128,162]
Myrtucommulone A	HCC cell lines	anti-bacterial, anti-inflammatory, anti-tumor property	[163–165]
Epolactaene		inhibits HSP60 by alkylating cys442	[115,166]
Stephacidin B, Avarainvillamide		in vitro anticancer activities	[119,167]
KIRA6	Multiple cancer cell lines	interacts with HSP60 and decreases its ATPase and folding ability.	[121]
KHS101		Inhibits HSP60-dependent substrate refolding activity	[168,169]
Clusterin inhibitor OGX-011	HCC cell lines	Suppress metastasis.	[95,170]

4. Conclusions

The role of chaperones and HSPs in HCC is an important area of research that should have significant implications for clinical practice. It has been found that elevated levels of HSPs are associated with increased aggressiveness of tumors and a poor prognosis in patients suffering from HCC. Increased levels of HSP are correlated with vascular invasion and a decrease in overall survival. HSPs play a vital role in modulating the immune response and, hence, can be used for immunotherapeutic approaches. Several HSPs can be used as immunogenic molecules that aim to stimulate the immune system. Altered expression of HSPs has been used as a prognostic biomarker, is a sign of cellular stress, and can be used for the early detection of HCC. Several studies have unequivocally explained the active participation of chaperons in the progression of HCC. In clinical settings, healthcare professionals may take on the role of chaperons in deciding treatment plans for HCC patients by considering the use of HSP inhibitors [20].

Many studies have clearly shown the involvement of chaperones in HCC development and progression and their relevance as targets for the design of effective therapeutic strategies. Further research is needed to fully understand the complex mechanisms involved in the regulation of chaperones in HCC and to design new compounds. Therefore, the potential for chaperones to serve as diagnostic and prognostic biomarkers, as well as therapeutic targets, cannot be ignored. In clinical practice, healthcare professionals should consider the role of chaperones in HCC and the use of HSP inhibitors approved by health agencies when setting up treatment plans for patients. In addition, the development of targeted therapies that focus on chaperones could lead to more effective treatments for HCC patients that have previously been difficult to treat. Targeting chaperones as a therapeutic strategy is thus highly relevant and needed in cancer research, including HCC, but presents some challenges to overcome. One of them is the lack of specificity of chaperone inhibitors for their protein targets. Many chaperone inhibitors target several chaperones and proteins without making a difference between tumor cells and normal cells, thus causing side effects and toxicity. Therefore, the development of selective chaperone inhibitors is crucial to minimize toxicity and improve therapeutic efficacy. Another challenge is the complex

network of chaperones and co-chaperones involved in protein folding and homeostasis. HCC cells have been shown to rely on specific chaperone networks for survival, making it difficult to identify which chaperones to target in tumor cells. Moreover, chaperones have been found to have overlapping functions, further complicating the development of targeted therapies. In addition, the role of chaperones in promoting protein degradation and autophagy has also been implicated in cancer cell survival and resistance to therapy. Therefore, targeting the chaperones alone may not be sufficient to treat HCC effectively, and combination therapy may be required. The data about the therapeutic response of inhibitors of HSPs is not well known, so more clinical trials are needed to validate the antitumor activity of HSPs in HCC patients. Along with this, validation of the enhanced efficacy of inhibition of HSPs with targeted drugs such as rapamycin is still needed. Lastly, novel HSP inhibitors with high specificity towards cancer cells are yet to be developed, so that the non-cancerous cells should not undergo deleterious effects. Despite these challenges, the potential benefits of targeting chaperones in HCC therapy cannot be overlooked. Further research is needed to better understand the role of chaperones in HCC and to develop targeted and effective therapies.

Overall, the study of chaperones in HCC represents an exciting area of research with significant potential for improving patient outcomes. Scientists and healthcare professionals must continue to explore this area of research and work towards developing new and innovative treatments for HCC patients. The role of chaperones in HCC therapy is an exciting area of research with tremendous potential for the development of new and effective treatments for this deadly disease [79].

Cases of hepatocellular carcinoma (HCC) are highly prevalent in developing and underdeveloped countries, especially in the context of the rise of non-alcoholic fatty liver disease. It requires comprehensive public health strategies. Awareness about this disease should be raised for widespread health education programs about the risk factors, symptoms, and consequences. Cost-effective screening programs should be established for early detection and management. Vaccination programs should be promoted. Nutritional interventions should be developed to improve healthy eating habits. Individuals should be empowered with knowledge about liver health to encourage regular check-ups.

In summary, chaperones play an important role in the development and progression of HCC. Further research is needed to fully investigate their potential as diagnostic and prognostic biomarkers for HCC [171], and their use as targets may open new, promising avenues for the treatment of this deadly malignancy.

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Abbreviations

HSP	Heat shock protein
HCC	Hepatocellular carcinoma
ATP	Adenosine triphosphate
PIKK	Phosphatidylinositol-3 kinase-related kinases
Bcl2	B-cell lymphoma 2
Bclaf	Bcl2 associated transcription factor1
mTOR	Mammalian target of rapamycin
PI3K	*P*hosphoinositide 3-kinase
17-AAG	17-N-Allylamino-17-demethoxygeldanamycin
NBD	Nucleotide-binding domain
SBD	Substrate binding domain
NTD	N-terminal domain
CTD	C-terminal domain
TNF	Tumor necrosis factor
TRAP1	TNF receptor-associated protein 1
NEF	Nucleotide exchange factor
EMT	Epithelial to mesenchymal transition
ECM	Extracellular matrix
WASF2	Wiskott-Aldrich syndrome family member 2
HIF1	Hypoxia-inducible factor 1
MDR	Multiple drug resistance
ATF	Activating transcription factor
CHOP	C/EBP homologous protein
CypD	Cyclophilin D
FHIP	Fragile histidine triad protein
VEGF	Vascular endothelial growth factors
MMPs	Metalloproteinases
TCTP	Translationally controlled tumor proteins
MAPK	Mitogen-activated protein kinase
ERK	Extracellular signal-regulated kinase
PDIA3	Protein disulfide isomerase A3
GRP78	Glucose-regulated protein 78
CRT	Calreticulin

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