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HSP70 and HSP90 in Cancer: Cytosolic, Endoplasmic Reticulum and Mitochondrial Chaperones of Tumorigenesis

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HSP70 and HSP90 are two powerful chaperone machineries involved in survival and proliferation of tumor cells. Residing in various cellular compartments, HSP70 and HSP90 perform specific functions. Concurrently, HSP70 and HSP90 homologs may also translocate from their primary site under various stress conditions. Herein, we address the current literature on the role of HSP70 and HSP90 chaperone networks in cancer. The goal is to provide a comprehensive review on the functions of cytosolic, mitochondrial and endoplasmic reticulum HSP70 and HSP90 homologs in cancer. Given that high expression of HSP70 and HSP90 enhances tumor development and associates with tumor aggressiveness, further understanding of HSP70 and HSP90 chaperone networks may provide clues for the discoveries of novel anti-cancer therapies.

Keywords: heat shock proteins, HSP70, HSP90, GRP78, GRP94, TRAP1, mortalin, cancer

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INTRODUCTION

Heat shock protein 70 kDa (HSP70) and HSP90 are two powerful ATPase-dependent chaperone machineries involved in protein folding, degradation, maturation of client proteins and protein trafficking (1–4). Over the last decade, HSP90 and HSP70 have gained a lot of attention due to their critical roles in cancer (5–7). Currently, a large number of preclinical and clinical studies assess various ways of exploiting HSP70 and HSP90 machineries for the discovery of effective anti-cancer therapies (8).

HSP90 family is composed of four members: two in cytosol (HSP90AA1&HSP90AB1), one in endoplasmic reticulum (ER) (GRP94/HSP90B1) and one in mitochondria (TRAP1) (9, 10). Even though conformational states are conserved in all HSP90 members, each HSP90 homolog has its own kinetics and equilibria, suggesting specific functions in the relevant subcellular compartment (11). Cytosolic HSP90 members require co-chaperones for their functional cycles, though no co-chaperones have been yet identified for mitochondrial and ER HSP90 chaperones (11, 12).

HSP70 family is composed of 13 members and the most well-studied are: cytosolic HSP70/HSPA1A and HSC70/HSPA8, mitochondrial HSP70 homolog known as mortalin/glucose-regulated protein 75 (GRP75), and an ER HSP70 member- HSPA5/GRP78 also known as binding immunoglobulin protein (BiP) (10, 13). Similar to HSP90, HSP70s require co-chaperones for the regulation of their functional cycles (5).

HSP90 and HSP70 play essential role in proteome homeostasis (14). HSP70 binds to virtually all unfolded or misfolded proteins while HSP90 interacts with specific set of clients [reviewed in (13, 15, 16)] (17). Both chaperones undergo conformational changes to facilitate the binding and release of client proteins (13, 17). HSP70 is composed of N-terminal nucleotide-binding domain (NBD) and C –terminal substrate-binding domain (SBD), comprising an α-helical lid (SBDα) and a β-sandwich core (SBDβ) (13). HSP90 is composed of three domains, such as N-terminal (NTD) and middle domains (MD), required for ATP binding and hydrolysis, and C-terminal domain (CTD), which is essential for dimerization (18). HSP70 typically acts early in the folding process, while HSP90 functions later (17). HSP70 functional cycle is tightly regulated by HSP40 co-chaperone and nucleotide-exchange factors (NEFs) (13). Upon release from HSP70, newly synthesized polypeptides will either fold spontaneously or will be transferred to HSP90 for further folding or targeted for proteasomal degradation (5, 13). The function of HSP90 and its co-chaperones is also regulated by various post-translational modifications. Acetylation and phosphorylation may affect ATPase activity, client and co-chaperone binding (15). Furthermore, HSP90 can also be ubiquitinated by the C- terminus of HSC70-interacting protein (CHIP) [reviewed in (15)]. CHIP is an E3 ubiquitin - protein ligase, which binds to the C terminal EEVD motif of HSP70 and HSP90 chaperones *via* its tetratricopeptide repeat (TPR) domain (13, 19). Additionally, HSP90 and HSP70 folding activity can also be affected by reactive aldehydes generated from lipid peroxidation (20).

HSP70 and HSP90 molecular chaperones collaborate with each other in the process of protein remodeling. Several studies have demonstrated that HSP70, HSP90 and co-chaperones regulate the tumor suppressor protein p53 (21, 22). In a recent study, Boysen and colleagues have reported that stress-inducible HSP70 isoform (HSPA1A) and DNAJB1 co-chaperone unfold the p53 DNA binding domain (DBD) while HSP90 protects the p53 DBD from unfolding (23). Similar HSP90 and HSP70 functional antagonism has also been observed for other client proteins. Wang and colleagues reported that HSP70 binds and inactivates the glucocorticoid receptor (GR) ligand-binding domain and loads it onto HSP90 *via* HSP70 and HSP90 organizing protein (HOP), leading to the formation of GR-maturation complex (17).

Several research groups reported the presence of HSPs in extracellular milieu. Specifically, HSP70 family members (HSP70/HSPA1A and mortalin), HSP90 family members (GRP78, HSP90α and HSP90β), HSP60 and HSP27 were identified on the cell surface of tumor cells (24–26). Along this line, the majority of HSP70 and HSP90 members and their co-chaperones were identified in extracellular vesicles derived from various liquid biopsies of cancer patients (27–31) [reviewed in (8)]. Furthermore, HSP70 and HSP90 family members and co-chaperones have been shown to be released by immune cells in extracellular vesicles (8, 32–36). It is also worth mentioning that extracellular HSP70 and HSP90 homologs modulate various components of the immune system [reviewed in (37)]. Currently, various studies are aimed at exploiting extracellular HSPs as a diagnostic tool and as therapeutic targets (8, 38–43). This review will focus on functions of the cytosolic, mitochondrial and ER members of HSP70 and HSP90 chaperone machineries in cancer (**Figure 1**). Further understanding of HSP70 and HSP90 functions may provide clues on their roles in cancer progression and open new perspectives for the development of novel anti-cancer therapies.

CYTOSOLIC HSP90 AND HSP70 IN CANCER

HSP90α/HSP90AA1 and HSP90β/HSP90AB1

HSP90α and HSP90β are the two main cytosolic HSP90 isoforms encoded by two different genes, namely *HSP90AA1* and *HSP90AB1*, respectively (44, 45). HSP90α is induced upon inflammation, proteotoxic and other stress conditions, whereas HSP90β is constitutively expressed (44, 45). Even though the two isoforms share a high degree of identity (85%), they have distinct functions (44, 45). Taipale and colleagues predicted that HSP90 interacts with 7% of the transcription factors, 60% of the protein kinases and 30% of mammalian E3-ubiquitin ligases in the human genome (46). In this regard, Prince and collaborators compared relative interaction strength for both isoforms and demonstrated that HSP90α binds hypoxia-inducible factor 1α (HIF-1α) with higher relative interaction strength than to the heat shock factor 1 (HSF-1) (45). By contrast, HSP90β had higher relative interaction strength towards HSF-1 than to HIF-1α (45). This was further supported by the finding that HSP90α-knockout cells are more prone to hypoxia-induced cell death, while addition of purified recombinant extracellular HSP90α prevented cell death under hypoxia (47). Along this line, downregulation of HIF-1α resulted in decreased HSP90α expression in metastatic breast cancer cells (48).

Recently, Ono and colleagues have shown that triple deletion of HSP90α/β and CDC37 co-chaperone reduced epithelial-mesenchymal transition (EMT), attenuated extracellular vesicle (EV)-driven tumorsphere formation and EV-driven macrophage M2 polarization in metastatic oral cancer (49). Results also showed that a high HSP90α-positive cancer cell rate correlated with high-grade tumors, whereas HSP90β-positive cancer cell rate associated with low-grade tumors (49). Furthermore, in contrast to low-grade tumors, HSP90β was highly expressed in infiltrating tumor-associated macrophages in metastatic oral cancer (49).

Interestingly, Li and colleagues have reported that cytosolic HSP90 together with its co-chaperone CDC37 are important for the regulation of necroptosis (50). Mechanistically, receptor-interacting protein kinase 3 (RIP3) binds to HSP90-CDC37 while HSP90 inhibition disrupts RIP3 activation, thus blocking necroptosis (50).

HSP90α also interacts with B-cell lymphoma 2 (Bcl-2) –associated transcription factor 1 (Bclaf1) (51). Zhou and co-workers reported that HSP90 CTD domain inhibitor novobiocin

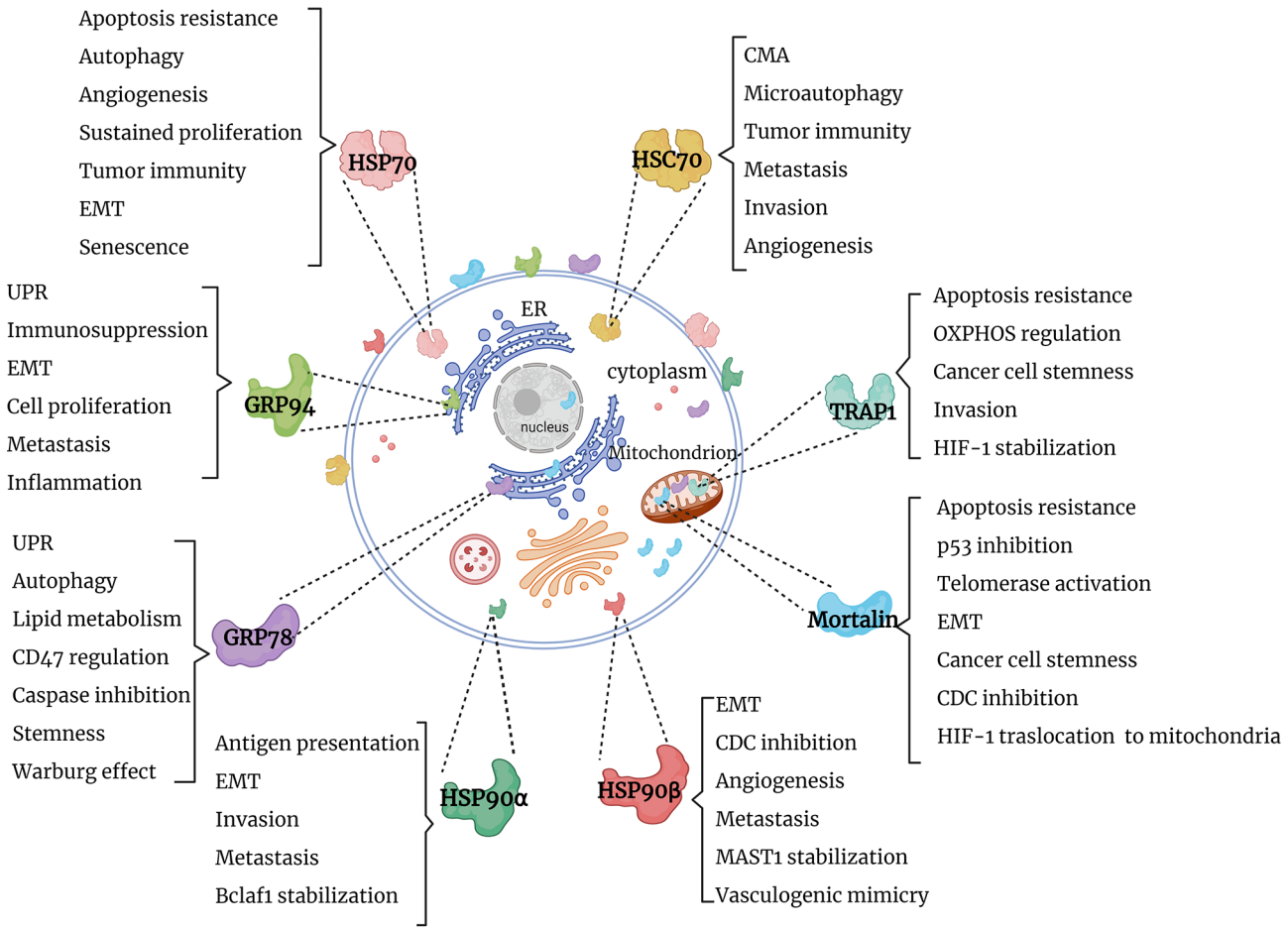

FIGURE 1 | Graphical summary of HSP90 and HSP70 functions in cancer. HSP90 and HSP70 homologs are distributed in cytosol, nucleus, ER and mitochondria, where they perform specific functions, supporting tumor survival and growth. EMT, epithelial-mesenchymal transition; UPR, unfolded protein response; OXPHOS, oxidative phosphorylation; CMA, chaperone-mediated autophagy; CDC, complement-dependent cytotoxicity; Bclaf1, B-cell lymphoma 2 -associated transcription factor 1; HIF-1, hypoxia-inducible factor 1; MAST1, microtubule-associated serine/threonine kinase 1.

resulted in proteasomal degradation of Bclaf, reduced *c-Myc* mRNA and inhibited hepatocellular carcinoma growth, suggesting that targeting HSP90 CTD domain may be a promising strategy for tumors with Bclaf upregulation (51). Cooper and colleagues showed that HSP90α/β also interacts with GSK3β/axin1/β-catenin (52). In another study, Wang and colleagues demonstrated that overexpression of HSP90β leads to growth, invasion and migration of gastric cancer cells (53). Mechanistically, HSP90β interacts with LRP5, leading to EMT, *via* activation of Akt and Wnt/β-catenin signaling pathways in gastric cancer cells (53). Taken together, HSP90α and HSP90β act through multiple signaling pathways, including c-Myc, Akt and Wnt/β-catenin (54).

Intriguingly, inactivation of ubiquitin-specific protease 22 (USP22), member of gene expression signature known as "death-from-cancer", associates with lower HSP90β expression in mammary and colorectal cell lines (55). USP22-depleted tumor cells exhibited a high sensitivity to HSP90 inhibitor ganetespib, suggesting that targeting USP22 and HSP90β may prove effective for the treatment of breast and colorectal cancer (55). Recently, Pan and co-workers have shown that HSP90β stabilizes microtubule-associated serine/threonine kinase 1 (MAST1), a molecule associated with cisplatin resistance (56). Mechanistically, HSP90β binds to MAST1 and prevents its ubiquitination by CHIP and the ensuing degradation *via* proteasome (56). In this regard, HSP90 inhibitor 17-AAG has been shown to sensitize cells to cisplatin (56).

HSP90α and HSP90β also interact with HSP70 family members. Specifically, Moriya and co-workers demonstrated that HSP90α together with HSP70 ER member GRP78/BiP interact with PRDM14, a member of PR domain-containing family overexpressed in many tumors (57). In another study, Rozenberg and colleagues reported that HSP90β interacts with mortalin during complement activation (58). Results also showed that HSP90β competes with mortalin for binding to complement C9 (58). It appears that the interaction of HSP90β

with mortalin protects tumor cells from complement-dependent cytotoxicity (CDC) (58).

Taking into account the important roles of HSP90α and HSP90β in tumor development, it is critical to identify HSP90 isoform-specific inhibitors. In this regard, Huck and colleagues demonstrated that protein-scaffold inhibitors preferentially bind HSP90α rather than HSP90β (59). In another study, Khandelwal and co-workers have designed a selective HSP90β inhibitor, which resulted in specific degradation of HSP90β clients (60). Collectively, HSP90α and HSP90β play a critical role in angiogenesis, invasion, metastasis, EMT and CDC, however, further studies are needed to identify the distinct functions of HSP90α and HSP90β in cancer development.

HSP70/HSPA1A/1B and HSC70/HSPA8

HSP70 and the heat shock cognate protein 70 (HSC70) are stress-inducible and constitutive cytosolic isoforms encoded by *HSPA1A/1B* and *HSPA8*, respectively (61). HSP70 chaperone function involves co-chaperones, such as HOP, CHIP, HSP40, HSP70-interacting protein (Hip) and NEFs (13, 62–66). Co-chaperones assist HSP70 throughout its functional cycle in folding and degradation of its client proteins (13).

HSP70 is a multi-functional chaperone which has been implicated in various hallmarks of cancer [reviewed in (5)]. Mechanistically, HSP70 blocks apoptosis *via* inhibiting c-Jun N-terminal kinase (JNK), p38, apoptosis-inducing factor (AIF) and formation of death-inducing signaling complex (DISC) (67–70). Apart from apoptosis, HSP70 also regulates both necrosis by inhibiting JNK and autophagy by stabilizing lysosomal membranes (71–74). Furthermore, HSP70 is essential for survival of malignant cells as HSP70 protects tumor cells from oncogene-induced senescence program by regulating p53 and cyclin-dependent kinase Cdc2 (5, 72).

HSP70 also interacts with aminoacyl-transfer RNA synthetase-interacting multifunctional protein 2 (AIMP2) lacking exon 2 (AIMP-DX2) and HIF-1α, leading to angiogenesis, metastasis and tumor aggressiveness (75–78). Along this line, overexpression of HSP70 correlates with metastatic tumors (79). HSP70-peptide complexes isolated from hepatocellular carcinoma tissues promote EMT *via* p38 mitogen-activated protein kinase (MAPK) pathway (80). Additionally, HSP70 stabilizes E-cadherin/catenin complexes and Wiskott-Aldridge syndrome family member 3 (WASF3), thus regulating the metastatic process (81–84).

HSP70 plays critical role in tumor immunity. Several studies have shown that HSP70-peptide complexes induce cytotoxic T lymphocyte (CTL) response (85–87). In addition, Multhoff and colleagues reported that HSP70s on the tumor cells are recognized by NK cells (88). Moreover, HSP70-derived peptide TKD together with IL-2 or IL-15 can stimulate NK cells (89–91). This was further translated into a phase II clinical trial, where TKD peptide was used to pre-stimulate autologous NK cells for their adoptive transfer into patients with non-small cell lung carcinoma (92).

HSC70 is also involved in chaperone-assisted selective autophagy and endosomal microautophagy (eMI) (93–95). Li and colleagues reported that mitochondrial outer membrane protein FUNDC1 associates and delivers HSC70-peptide complex to mitochondria for its further ubiquitination by CHIP (96). HSC70 also interacts with Rab1A, a critical molecule for cancer cell survival (97). HSC70 inhibition downregulates Rab1A expression, while Rab1A inactivation leads to cell death *via* inhibition of autophagosome formation, suggesting that HSC70 promotes tumor survival by stabilizing Rab1A (97). HSC70-intreacting partners also include ASIC2, mutant forms of p53 and p73, proto-oncogenic form of Dbl and cell surface nucleolin (98–101).

Several studies reported that upon heat shock or oxidative stress HSC70 translocates from the cytoplasm into the nucleus (102, 103). Wang and colleagues reported that inhibition of nuclear HSC70 reduces cell growth upon heat shock (103). High expression of HSC70 has been observed in various tumors (104, 105). HSC70 was also identified as one of the proteins secreted by neuroblastoma cell lines in the conditioned media (106). Shan and colleagues illustrated that HSPA8 silencing dampens the cell proliferation and induces apoptosis in endometrial cancer cells (107). In another study, HSC70 depletion increased the expression of integrin β1, suggesting that HSC70 may promote invasion (108).

Mizukami and colleagues reported that fusion of HSC70 with $CD4^+$T and $CD8^+$ T cell epitopes elicited anti-tumor response (109). In another study, Zhang and colleagues demonstrated that fusion of HSC70-derived ATPase domain with tyrosinase-related protein 2 (TRP2) mounted CTL response in B16 melanoma, suggesting that HSC70-based immunotherapy approaches might prove effective for anti-cancer treatment (105, 110).

MITOCHONDRIAL HSP90 AND HSP70 IN CANCER

TRAP1

Tumor necrosis factor receptor-associated protein 1 (TRAP1) was initially discovered as a protein associated with the cytoplasmic domain of type 1 Tumor necrosis Factor Receptor-1 (TNFR1) (111, 112). The 75-kDa molecular chaperone, designated as HSP75, showed the ability to form complexes with the retinoblastoma protein (113). It then became clear that TRAP1 and HSP75 are identical molecules (112). TRAP1 functions as homodimer and requires ATP for its chaperone activity (114). TRAP1 has N-terminal mitochondrial targeting sequence that directs TRAP1 to mitochondrial matrix and is cleaved upon the import (115–117).

TRAP1 is highly expressed in mitochondria isolated from tumor cells compared to normal cells (3). Long lines of experimental evidence suggest that TRAP1 is involved in tumor metabolism and cytoprotection of cancer cells. Masuda and colleagues reported that induction of apoptosis by β-hydroxyisovalerylshikonin (β-HIVS) and topoisomerase II inhibitor VP16 in tumor cell lines is associated with the reduction in TRAP-1 expression (118). Moreover, inactivation of *TRAP1* by small interfering RNA (siRNA) in tumor cells treated with β-HIVS or VP16 induced the release of cytochrome *c*,

pointing out an important role of TRAP1 in intrinsic apoptotic pathway (112, 118). In a subsequent study, Hua and colleagues demonstrated that granzyme M, a serine protease stored in granules of NK cells, acts on mitochondria and causes swelling, loss of transmembrane potential, production of reactive oxygen species (ROS) and cytochrome *c* release (119). Mechanistically, granzyme M cleaves TRAP1 leading to ROS accumulation and cell death (119). Kang and colleagues reported that TRAP1 and HSP90 in mitochondria interact with cyclophilin D and antagonize the mitochondrial permeability transition process (3, 112).

TRAP1 showed to be a critical regulator of mitochondrial metabolism. Sciacovelli and co-workers demonstrated that high expression of TRAP1 in tumor cells enhances neoplastic transformation (120). Specifically, TRAP1 forms complexes with succinate dehydrogenase (SDH) and inhibits its activity, contributing to Warburg phenotype (120). Warburg phenotype is characterized by preferential conversion of glucose to lactate, so that tumor cells mainly rely on glycolysis, an anaerobic metabolism for ATP production, even in the presence of oxygen (121). TRAP1 inhibits oxygen consumption rate and ATP synthesis by oxidative phosphorylation (OXPHOS) (120). Results also showed that TRAP1-expressing tumor cells have a high level of succinate, resulting in HIF-1α stabilization (120, 122). Along this line, Chae and co-workers reported that TRAP1 together with SDHB regulate HIF1α-dependent tumorigenesis (123). In another study, Yoshida and colleagues found that *TRAP1* knockout (KO) enhances mitochondrial respiration and suppresses glycolysis (124). Furthermore, *TRAP1* KO cells exhibited high levels of ATP, ROS production and cytochrome *c* oxidase (complex IV), a terminal enzyme in electron transport chain required for ATP production (124). Authors also showed that TRAP1 associates with c-Src and downregulates its activity (124). In addition, Park and colleagues demonstrated that interaction of TRAP1 with sirtuin-3 enhances mitochondrial respiration and reduces ROS production in glioma stem cells, thus supporting stemness (125).

Taking into account that full-length of TRAP1 is required for OXPHOS regulation, it has been suggested that TRAP1, similarly to HSP90, requires other chaperones for its OXPHOS function (117). In a recent study, Joshi and colleagues demonstrated that TRAP1 interacts with other mitochondrial chaperones, including HSPA9/GRP75, HSP60 and prohibitin as well as with OXPHOS-associated molecules, such as complex IV, complex II and ATP synthase (117). Interestingly, most of TRAP1 interactors, except for GRP75 and HSP60, had a preference for ATP-bound state (117).

Inactivation of TRAP1 showed to enhance invasion (124). Agliarulo and co-workers demonstrated that TRAP1 silencing promotes cell motility while simultaneously compromising the ability of cells to cope with stress, and this effect showed to be mediated *via* the AKT pathway (126). It is also interesting to point out that TRAP1 expression varies in different types of cancer. For example, low expression of TRAP1 correlated with high-grade cervical and bladder cancer, while high TRAP1 expression was found in colorectal carcinomas (124, 127). Therefore, further studies are required to understand the role of TRAP1 in mitochondrial bioenergetics, apoptotic mechanisms and its expression in specific types of cancer.

GRP75/HSPA9/Mortalin/mtHSP70

Mortalin is found in mitochondria, ER, nucleus, cytosol, extracellular vesicles and on the cell surface (24, 128, 129). Mortalin shares 52% and 65% homology with stress-inducible isoform HSP70/HSPA1A and yeast mitochondrial HSP70 – SSC1, respectively (130). Similar to TRAP1, mortalin has a 46-amino acid mitochondrial targeting sequence that allows GRP75 to be localized in mitochondria (131). Mortalin is highly expressed in tumor tissues, leading to tumor growth, metastasis, angiogenesis and apoptosis resistance (132, 133). Ryu and co-workers used mutant mortalin, lacking the mitochondrial targeting sequence, to identify the presence of mortalin in the nucleus and, hence, they called it nuclear mortalin (129). Nuclear mortalin inhibits p53 and activates telomerase and heterogeneous nuclear ribonucleoprotein K (hnRNP-K) (129, 132, 134–136). Importantly, Lu and colleagues demonstrated that mortalin interacts with p53 in cancer cells under stress (136). Targeting mortalin-p53 interaction has resulted in p53-dependent apoptosis in tumor cells, suggesting that disruption of mortalin-p53 complex may be a promising strategy for anti-cancer therapy (136, 137).

Another strategy by which mortalin protects cancer cell from apoptosis involves HIF-1α (138). Recently, Mylonis and colleagues have reported that mortalin binds and mediates targeting of HIF-1α to the outer mitochondrial membrane, where HIF-1α blocks apoptosis when ERK is inactivated (138). HIF-1α release from the mitochondria under ERK inactivation resulted in induction of apoptosis (138).

Mortalin plays a critical role in epithelial-mesenchymal transition (EMT) (139). High expression of proteins involved in focal adhesion, PI3K-AKT and JAK-STAT signaling has been observed in mortalin - positive tumor cells (139). Furthermore, these cells exhibited high expression of mesenchymal markers, including vimentin, fibronectin, β-catenin and CK14, while the expression of epithelial markers (E-cadherin, CK8 and CK18) was reduced (139).

In a recent study, Yun and colleagues have reported that cells that overexpress mortalin had increased expression of cancer cell stemness markers, such as ABCG2, OCT-4, CD9, MRP1, ALDH1 and CD133 (132). Results had also shown that inactivation of mortalin by short hairpin RNA (shRNA) suppresses migration and invasion (132). Moreover, high expression of mortalin has correlated with resistance to therapies while mortalin silencing sensitized tumor cells to chemotherapeutic agents (132). In a recent study, Li and colleagues have demonstrated that NF-κB binds to mortalin promoter, leading to ovarian cancer cell proliferation (140). Conversely, NF-κB downregulation leads to reduction in mortalin expression (140).

Similar to TRAP1, mortalin plays an important role in mitochondrial bioenergetics (141). Mortalin is a major mitochondrial protein involved in mitochondrial import of proteins (142). Mortalin, bound to the translocase of the inner membrane-44 (TIM-44), imports the preprotein into the mitochondrial matrix, where mortalin refolds or transfers the

preprotein to HSP60 chaperone (142–144). Inactivation of mortalin leads to a loss of mitochondrial membrane potential, reduction of oxygen consumption and induction of oxidative stress in medullary thyroid carcinoma (145).

ER HSP90 AND HSP70 IN CANCER

GRP94/HSP90B1/gp96/ERp99/ Endoplasmin

The HSP90 member that resides in ER is GRP94 (146). GRP94 is targeted to ER by its N-terminal signal sequence that is cleaved upon GRP94 entry into the ER lumen where GRP94 resides due to its C-terminal KDEL sequence (146, 147). Another location where GRP94 has been identified is the cell surface (146). Several studies reported the presence of GRP94 on the surface of tumor cells and a small portion of immature thymocytes during early development, though the role of membrane-bound GRP94 is not yet clear (148, 149). Additionally, GRP94 functions as a dimer and unlike cytosolic HSP90s, has no known co-chaperones (146).

Unlike cytosolic HSP90 homologs, GRP94 is not upregulated in response to a high temperature, but rather is induced in response to ER stress, including glucose deprivation, hypoxia, B cell differentiation and perturbations of calcium or redox homeostasis (146, 150–154). Stress in ER machinery leads to cascades of signals known as unfolded protein response (UPR), which subsequently restores homeostasis or induces growth arrest and apoptosis (146, 155, 156).

Proper folding of proteins and quality control require collaboration between GRP94 and mitochondrial HSP70 family member GRP78 (146). Similar to HSP70-HSP90 collaboration, GRP78 binds to immunoglobulin (Ig) chains followed by GRP94 Ig folding in ER (146, 157, 158). Furthermore, GRP78-GRP94 forms ternary complex with client proteins in ER presumably for handling over the clients from GRP78 to GRP94 (146, 158).

GRP94 functions are not restricted to UPR, as GRP94 showed to be a critical immune chaperone [reviewed in (37)] (159). It has been shown that GRP94 is a chaperone for integrins and leucine-rich repeats domain 32 (LRRC32), also known as GARP, a docking protein for the membrane expression of transforming growth factor - β (TGF-β) (159, 160). Zhang and colleagues showed that GRP94 deletion in T regulatory cells leads to the loss of FOXP3, increased expression of interferon - γ (IFN-γ) and reduced bioavailability of TGF-β (160, 161). Since TGF-β plays critical roles in oncogenic processes, including EMT, angiogenesis, proliferation, metastasis and immune evasion, targeting GRP94 may prove effective for the development of anticancer therapies through the control of the expression of TGF-β (159).

Melendez and colleagues demonstrated GRP94 is expressed on the surface of breast cancer cells, whereas no expression of GRP94 was observed on the surface of non-malignant cells (162). Zheng and co-workers reported that GRP94 surface expression on tumor cells induces DC maturation and primes T cells, suggesting that GRP94 is a potent DC stimulator (163).

Besides immunologic functions, GRP94 regulates maturation of insulin-like growth factors (IGFs), which are essential prosurvival factors for tumor cells (159, 164). Hua and colleagues demonstrated that inactivation of GRP94 resulted in apoptosis of multiple myeloma cells *via* disruption of the Wnt-LRP6-survivin pathway (165). Results also showed that GRP94 inhibition blocked multiple myeloma growth in mouse xenograft model, suggesting that GRP94 may be a promising target for the treatment of multiple myeloma (165).

With the use of GRP94-selective inhibitor PU-WS13, Patel and colleagues demonstrated that GRP94 plays an important role in plasma membrane HER2 stability, and inactivation of GRP94 resulted in reduction of HER2-overexpressing tumor cell viability (166). Mechanistically, inhibition of GRP94 leads to the translocation of HER2 to early endosomes and plasma-membrane adjacent lysosomes (166). Along this line, membrane GRP94 interacts with HER2 and facilitates its dimerization, contributing to cell proliferation (167). Targeting GRP94 with a monoclonal antibody reduced growth and increased apoptosis in breast cancer cells (167). In another study, targeting GRP94 with the W9 monoclonal antibody sensitized $BRAF^{V600E}$ melanoma cells to BRAF inhibitors (168). Taken together, GRP94 plays crucial role in UPR, tumor immunity and promotes cancer *via* its client network. GRP94-based immunotherapy approaches represent promising strategies for anti-cancer therapy, however, this requires further investigation.

GRP78/HSPA5/BiP

GRP78 performs various cellular functions, including folding, degradation, transport of peptides across ER membrane and regulation of calcium homeostasis (169, 170). Similar to cytosolic HSP70 homologs, GRP78 is composed of N-terminal ATPase domain and C-terminal substrate-binding domain (SBD) (168). Due to its ER retention motif, GRP78 primarily resides in ER, but it has also been observed in mitochondria, cytoplasm, cell surface, nucleus and extracellular vesicles (8, 171, 172). Similar to GRP94, GRP78 chaperone plays critical role in UPR, initiated upon ER stress (171). GRP78 inactivation results in spontaneous activation of UPR, expansion of ER lumen and induction of GRP94 expression (173).

Another process that is activated upon ER stress and involves GRP78 is autophagy. High expression of GRP78 increased autophagosome formation in estrogen receptor-positive breast cancer cells (174, 175). Mechanistically, elevated expression of GRP78 activates AMP-activated protein kinase (AMPK) and tuberous sclerosis 2 (TSC2), both of which inhibit mechanistic target of rapamycin (mTOR), resulting in initiation of autophagy (174, 175). Silencing of GRP78 leads to inhibition of autophagosome formation (173). Furthermore, Li and colleagues demonstrated that high expression of GRP78 activates the Class III phosphatidylinositol 3-kinase (PI3K)-mediated autophagy pathway and induces degradation of IKKβ, leading to inhibition of the NF-κB pathway, at the same time altering expression of pyruvate kinase M2 and HIF-1α (176). Along this line, under stress conditions, GRP78 binds to cytosolic misfolded proteins and SQSTM1/p62 (171, 177, 178). Interaction with p62 leads to SQSTM1/p62 conformational change, favoring cargo delivery into autophagosome for its further degradation into amino acids

(171, 177, 178). Malek and co-workers reported that treatment with the proteasome inhibitor bortezomib induces GRP78 and GRP78-mediated autophagy in myeloma cells (179). Inhibition of GRP78 followed by bortezomib treatment disrupted autophagy and enhanced anti-tumor effect (179). In a recent study, Wu and colleagues have demonstrated that the GRP78 inhibitor HA15 promoted apoptosis which was accompanied with UPR and autophagy in lung cancer cells (180).

ER stress and UPR induce GRP78, resulting in its translocation to mitochondrial compartments, including intermembrane space, inner membrane and matrix (181). Hayashi and colleagues demonstrated that GRP78 forms complex with sigma-1 receptor (Sig-1R), ER calcium-sensitive co-chaperone in mitochondrion-associated membrane (182). Under ER stress, Sig-1R dissociates from GRP78 and binds to inositol 1,4,5- trisphosphate receptors, promoting a prolonged calcium influx from ER into mitochondria (182).

Recently, Ni and co-workers have identified a novel cytosolic GRP78 isoform (GRP78va) generated by alternative splicing (183). Results showed that GRP78va is upregulated in human leukemia cell lines, as well as in primary leukemia cells obtained from patients (183). GRP78va lacks ER retention signaling peptide and specifically activates ER kinase PERK (183). Mechanistically, GRP78va interacts with P58IPK, an inhibitor of PERK, and antagonizes its inhibitory activity (183). Inactivation of GRP78va decreased survival, whereas overexpression promoted survival of leukemia cells, suggesting that high expression of the cytosolic GRP78 isoform protects cancer cells from cell death (183). GRP78 may also translocate to cytosol through the ER-associated degradation (ERAD) pathway and *via* Bax/Bak-dependent changes, affecting ER permeability upon ER stress-induced apoptosis (184, 185).

GRP78 has also been detected in the nucleus (186–188). Matsumoto and colleagues used gilvocarcin V (GV), anti-tumor antibiotic that promotes protein-DNA cross-linking when photoactivated by near UV-light, to show that GRP78 lacking hydrophobic leader sequence was selectively cross-linked to DNA in human fibroblasts (189). In another study, Zhai and co-workers demonstrated that inactivation of GRP78 sensitizes cells to UVC-induced cell death, suggesting a protective role of GRP78 against DNA damage (186, 190).

High expression of GRP78 was observed in various types of cancer such as colon, lung, prostate, myeloma, leukemia and breast cancer and showed to correlate with unfavorable clinical outcome (179, 191, 192). Biallelic inactivation of both *PTEN* and *GRP78* inhibited AKT activation and tumorigenesis in prostate epithelium (193). This was further supported by the finding that antibody directed against COOH-terminal domain of GRP78 inhibited growth and AKT activity in prostate cancer cell lines (194). In another study, Cook and colleagues demonstrated that GRP78 inactivation inhibits *de novo* fatty acid synthesis in breast cancer cells (195). Combination of tamoxifen and GRP78-targeting morpholino antisense oligonucleotides resulted in increased ROS production and cell death (195). Intriguingly, GRP78 inactivation downregulated the expression of innate immune checkpoint CD47 in breast cancer cells, whereas reduction of GRP78 in normal mammary tissue increased the expression of CD47 and macrophage infiltration (195). Recently, the same research team has demonstrated that co-expression of CD47 and GRP78 associated with a poor outcome in breast cancer patients (196).

Induction of UPR affects sensitivity of cells to chemotherapeutic agents (197). In this regard, Reddy and co-workers demonstrated that elevated GRP78 expression inhibits apoptosis in cells treated with topoisomerase inhibitors (187). Mechanistically, etoposide treatment leads to the activation of caspase-7, while elevated expression of GRP78 inhibits caspase-7 activation (187). Along this line, several studies showed that GRP78 forms a complex with caspase-7 and caspase -12 and prevents release of caspase-12 from ER, suggesting that one of the mechanisms by which GRP78 blocks cell death is by inhibiting caspase activation (187, 198). In another study, Lee and colleagues observed elevated expression of GRP78 in 5-fluorouracil (5-FU)-resistant colorectal cancer cells (180). GRP78 inhibition in cells treated with 5-FU led to apoptosis through the activation of caspase-3 (180). Furthermore, GRP78 promoted cell survival *via* the activation of PI3K-AKT-mTOR signaling pathway (180).

Recently, Dauer and colleagues have demonstrated that GRP78 silencing leads to a slower proliferation rate, reduction in colony formation and downregulation of genes involved in self-renewal in pancreatic cancer cells (199). Furthermore, GRP78 silencing affected the redox balance leading to lipid-peroxidation and higher ROS production (199). Chang and co-workers reported that overexpression of GRP78/p-PERK signaling pathway activates nuclear factor-erythroid 2-related factor (NRF2), leading to enhanced expression of glycolytic enzymes and stemness markers in head and neck squamous cell carcinoma, thus, supporting Warburg phenotype and cancer cell stemness (200). Taken together, GRP78s may change its location and mediate various processes, including UPR, Warburg phenotype, stemness, apoptosis, autophagy and innate immune responses.

DISCUSSION

Residing in various cellular compartments, HSP70 and HSP90 isoforms perform distinct functions within a cancer cell. HSP70 and HSP90 homologs are critical regulators of UPR, mitochondrial bioenergetics, lipid metabolism, apoptosis, innate and adaptive immune responses. Apart from their primary locations, HSP70 and HSP90 isoforms may translocate and accumulate in specific locations inside the cell under various stress conditions, thus supporting tumorigenesis. Furthermore, HSP homologs may be released into extracellular space and acquire different functions. HSP90 and HSP70 cytosolic, ER and mitochondrial isoforms support tumor growth and development *via* different signaling pathways (**Figure 2**). Concurrently, different HSP homologs may also act through the same mechanism. For example, inhibiting the interaction between HSP90α and Bclaf1 leads to the downregulation of mature *c-Myc* mRNA, while *Myc* silencing decreases *TRAP1* mRNA (51,

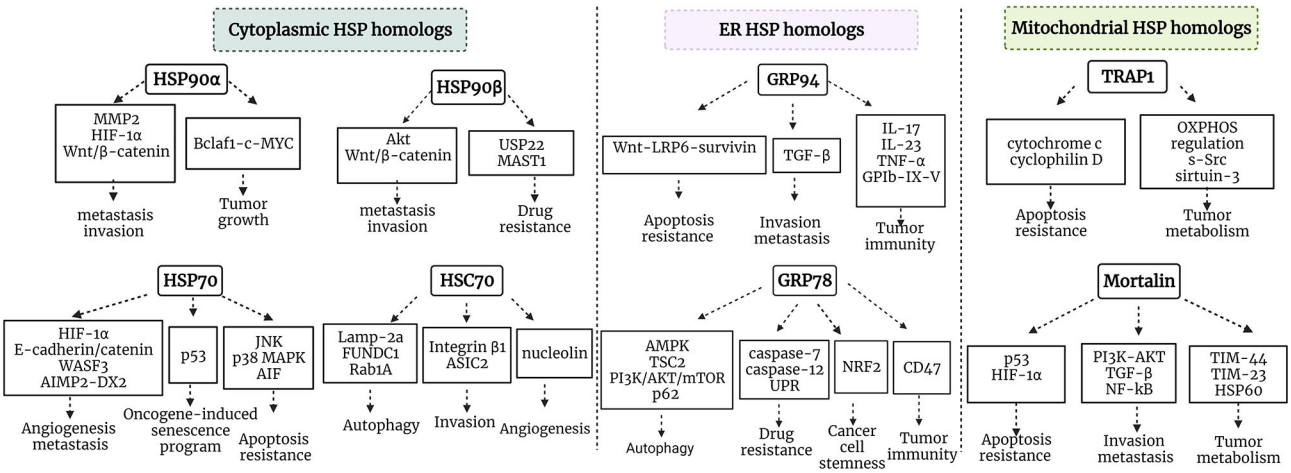

FIGURE 2 | Schematic representation of HSP90/HSP70 signaling pathways in cancer. HSP90α and HSP90β are cytosolic stress-inducible and constitutive members of HSP90 family, respectively, which support tumor development *via* multiple signaling pathways. HSP70 and HSC70 are two main cytosolic stress-inducible and constitutive members of HSP70 family, respectively, which play critical roles in the regulation of apoptosis, autophagy, oncogene-induced senescence program, angiogenesis, invasion and metastasis. GRP94 and GRP78 are ER HSP90 and HSP70 members, which play an important role in the regulation of apoptosis, invasion, metastasis, autophagy, drug resistance, cancer cell stemness and tumor immunity. TRAP1 is a mitochondrial HSP90, which plays critical role in tumor metabolism and cytoprotection of cancer cells. Mortalin is a mitochondrial HSP70 family member playing an important role in tumor metabolism, regulation of apoptosis, invasion and metastasis. MMP9, matrix metalloproteinase 9; OXPHOS, oxidative phosphorylation; Bclaf1, B-cell lymphoma 2 -associated transcription factor 1; HIF-1, hypoxia-inducible factor 1; MAST1, microtubule-associated serine/threonine kinase 1; TGF-β, transforming growth factor β; PI3K, phosphatidylinositol 3-kinase; WASF3, Wiskott-Aldridge syndrome family member 3; TIM-44, translocase of inner membrane-44; NRF2, nuclear factor-erythroid 2-related factor; AIMP-DX2, aminoacyl-transfer RNA synthetase-interacting multifunctional protein 2 (AIMP2) lacking exon 2; MAPK, mitogen-activated protein kinase; TSC2, tuberous sclerosis 2; mTOR, mechanistic target of rapamycin.

201). Furthermore, Zavareh and colleagues demonstrated that HSP90 inhibition downregulates the expression of immune checkpoint PD-L1 on the surface of tumor cells *via* the regulation of c-Myc (202). HSP105 inhibition also downregulates c-Myc (203). Therefore, targeting specific molecular pathways by inhibiting HSP homologs may be effective against tumors with the dysregulation of specific signaling pathways, however, it should be taken into account that blocking a specific HSP isoform may have an effect on other HSP homologs, and this requires further investigation.

Even though considerable progress has been made in assessing intracellular and extracellular functions of HSP70 and HSP90 in cancer, a lot is still unclear. For example, the effect of various HSP70 and HSP90-based therapies on the distribution of HSP70 and HSP90 homologs across cellular compartments and their release in extracellular space is unknown and requires further investigation. It is also important to differentiate between two HSP90 cytosolic isoforms and assess their individual functions in cancer. Furthermore, since HSP90 and HSP70 play critical roles in innate and adaptive immune responses, it is important to understand intracellular HSP70 and HSP90 immune functions in cancer. Elucidating intracellular and extracellular roles of individual HSP70 and HSP90 homologs may provide further clues on the release of HSP70 and HSP90 in the tumor microenvironment and help in the development of more effective HSP70 and HSP90-based therapies.

CONCLUSION

HSP90 and HSP70 are two powerful chaperone machineries involved in almost all stages of tumor development. HSP90 and HSP70 homologs are implicated in the regulation of apoptosis, UPR, lipid metabolism, metastasis, angiogenesis, autophagy, innate and adaptive immune responses, acting *via* different signaling pathways. Further understanding of molecular mechanisms of specific HSP90 and HSP70 homologs inside and outside the cell may provide clues for the discovery of novel anti-cancer therapies.

AUTHOR CONTRIBUTIONS

ZA wrote and revised the manuscript. AA contributed to editing and revision of the manuscript. YM and LG provided an administration support. All authors contributed to the article and approved the submitted version.

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