Tumor Biol. (2015) 36:4923–4931
DOI 10.1007/s13277-015-3674-x

REVIEW

Multifaceted roles of HSF1 in cancer

Sufang Jiang[1] · Kailing Tu[1] · Qiang Fu[1] · David C. Schmitt[2] · Lan Zhou[3] · Na Lu[4] · Yuhua Zhao[1]

Received: 17 March 2015 / Accepted: 15 June 2015 / Published online: 25 June 2015

Abstract Heat shock transcription factor 1 (HSF1) is the master regulator of the heat shock response. Accumulating evidence shows that HSF1 is overexpressed in a variety of human cancers, is associated with cancer aggressiveness, and could serve as an independent diagnostic or prognostic biomarker. In this review, we will provide an overview of the multifaceted roles of HSF1 in cancer, with a special focus on the four underlying molecular mechanisms involved. First, HSF1 regulates the expression of heat shock proteins (HSPs) including HSP90, HSP70, and HSP27. Second, HSF1 regulates cellular metabolism, including glycolysis and lipid metabolism. Third, HSF1 serves as a regulator of different signaling pathways, such as HuR-HIF-1, Slug, protein kinase C (PKC), nuclear factor-kappaB (NF-κB), PI3K-AKT-mTOR, and mitogen-activated protein kinase (MAPK) pathways. Finally, HSF1 regulates microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). Overall, HSF1 plays many important roles in cancer via regulating cell proliferation, anti-apoptosis, epithelial-mesenchymal transition (EMT), migration, invasion, and metastasis and may be a potential therapeutic target for human cancers.

Keywords HSF1 · HSPs · Metabolism · Signaling pathways · Cancer

✉ Yuhua Zhao
zhaoyh@scu.edu.cn

[1] Department of Biochemistry and Molecular Biology, West China School of Preclinical and Forensic Medicine, Sichuan University, Chengdu 610041, Sichuan, People's Republic of China

[2] Mitchell Cancer Institute, University of South Alabama, Mobile, AL 36604, USA

[3] Department of Anatomy, West China School of Preclinical and Forensic Medicine, Sichuan University, Chengdu 610041, Sichuan, People's Republic of China

[4] Second Affiliated Hospital of Chongqing Medical University, Chongqing 400010, People's Republic of China

Introduction

The heat shock response is one of the most efficient and conserved cellular protective mechanisms. Heat shock transcription factor 1 (HSF1) is the master regulator of the heat shock response [1] that protects cells, and ultimately organisms, from heat, ischemia, inflammation, oxidative stress, and other noxious conditions [2]. Inactive monomeric HSF1 is located in the cytoplasm. Once activated, HSF1 forms a phosphorylated trimer in the nucleus. Active trimerized HSF1 binds to the heat shock elements (HSEs) within the promoters of heat shock protein (HSP) genes such as HSP90, HSP70, and HSP27 and triggers their transcription [3]. HSPs are important chaperone proteins that have proven to be essential for cell survival under conditions of cell stress. The main function of HSPs is to aid in the process of normal protein folding and protect the proteome from the dangers of misfolding and aggregation [4].

Recently, a number of clinical studies have indicated that HSF1 is overexpressed in a variety of human tumors such as hepatocellular carcinoma (HCC) [5, 6], breast cancer [7], endometrial carcinoma [8], oral squamous cell carcinoma (OSCC) [9], prostate cancer [10], and sporadic colorectal cancer [11] (Table 1). Elevated levels of HSF1 correlate with the clinical aggressiveness of HCC, breast cancer, and endometrial carcinoma (Table 1), implicating the importance of HSF1 in invasion, metastasis, and poor prognosis. Moreover, HSF1 may serve as an independent diagnostic or prognostic

Table 1 The clinical relevance and significance of HSF1 in cancer

Cancer types	Clinical relevance	Clinical significance	References
Hepatocellular carcinoma (HCC, *n*=226)	1. HSF1 protein level in HCC tissues is higher than non-cancerous liver tissues. 2. HSF1 protein expression is associated with tumor size, number of tumor nodules, TNM stage, BCLC stage, and histological grade. 3. HSF1 expression is positively correlated with BAG3 expression. 4. Higher HSF1 protein level is associated with shorter overall survival.	HSF1 could be an independent prognostic factor for overall survival in HCC patients.	[5]
HCC (*n*=213)	1. HSF1 level is highly elevated in HCC tissues. 2. High HSF1 level is correlated with multiple nodules, venous invasion, absence of capsular formation, and high Edmondson-Steiner grade. 3. High HSF1 expression is associated with poor overall survival and disease-free survival.	HSF1 may serve as a prognostic marker and therapeutic target for HCC.	[6]
Breast cancer (*n*=1841)	1. Nuclear HSF1 level is increased in situ and invasive tissues. 2. HSF1 expression was associated with high histologic grade, larger tumor size, and nodal involvement at diagnosis. 3. High HSF1 expression is associated with reduced survival in ER-positive patients.	HSF1 could be an independent prognostic indicator in ER-positive patients and a useful therapeutic target for breast cancer.	[7]
Endometrial carcinoma (*n*=823)	High HSF1 protein level is associated with aggressive disease and poor survival.	HSF1 may be an independent prognostic marker in ER-positive patients.	[8]
Oral squamous cell carcinoma (OSCC) (*n*=50)	1. HSF1 mRNA expression was greater in cancer tissues than in normal tissues. 2. Higher nuclear HSF1 expression was closely related to tumor size and histopathologic types.	HSF1 might be a potential diagnostic biomarker and a therapeutic target for OSCC.	[9]
Prostate cancer (*n*=22)	HSF1 is overexpressed in cancer sections compared to normal sections.		[10]
Sporadic colorectal cancer (*n*=35)	HSF1 mRNA levels was increased in cancer tissues compared to normal tissues.		[11]
Early stage breast cancer (*n*=46)	Stromal HSF1 activation is associated with reduced disease-free and overall survival.	Stromal HSF1 could be an independent prognostic indicator in breast cancer.	[12]
Stage I non-small cell lung adenocarcinoma (*n*=72)	1. Stromal HSF1 activation is correlated with reduced disease-free survival. 2. Stromal HSF1 activation is associated with reduced disease-free survival in patients with KRAS mutant tumors.	Stromal HSF1 could serve as an independent prognostic marker in lung cancer.	[12]

BAG3 Bcl-2-associated athanogene domain 3; *BCLC* Barcelona Clinic Liver Cancer; *TNM* tumor node metastasis

biomarker and therapeutic target for cancer patients (Table 1). Additionally, a study on the role of stromal HSF1 in tumor biology has recently been reported and shows that HSF1 is frequently activated in the stromal cells, where it is a potent enabler of malignancy [12] (Table 1).

In 2007, Dai et al. established the powerful role of HSF1 in carcinogenesis for the first time [13]. Since then, the elucidation of the many roles of HSF1 in cancer has become a popular area of cancer research. HSF1 contributes to HCC development by promoting invasion and metastasis both in vitro and in vivo [6]. In mammary tumors, HSF1 has a critical role in angiogenesis [14] and in ErbB2-induced cellular transformation, tumorigenesis, and metastasis [15, 16]. Therefore, the transcription factor HSF1 has a powerful influence on HCC and breast cancer development and progression.

Increasing evidence has demonstrated that HSF1 plays a critical role in tumorigenesis and tumor development and also functions as a powerful multifaceted modifier of carcinogenesis. However, the molecular mechanisms underlying these alterations are complex. Mendillo et al. proposed two possible mechanisms: HSF1 facilitates the expression of HSPs to protect proteins from degradation that are essential for tumorigenesis and survival, and HSF1 also modulates the expression of genes regulating cell cycle, signaling, metabolism, adhesion, and protein translation [17]. Dai et al. suggest that HSF1 supports malignant transformation by orchestrating a network of core cellular functions, including proliferation, survival, protein translation, and glucose metabolism [13].

In summary, investigation of the mechanisms by which HSF1 is activated and determination of the roles of HSF1 in malignant transformation are important areas of study. Therefore, this review will focus on discussing the multifaceted roles of HSF1 in cancer, including regulation of HSPs, metabolism, signaling pathways, and microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) (Fig. 1), with a focus on the underlying mechanisms through which HSF1 exerts its effects.

HSF1 regulates the expression of HSPs

One of the most important mechanisms by which HSF1 is activated is through regulation of the expression of HSPs. HSPs are important chaperone proteins. Molecular chaperones participate in protein folding, in normal cellular metabolism, and in the induction of the HSP subset of chaperones, which assist in the repair and refolding of damaged polypeptides under stress conditions [18]. However, studies indicate that HSPs are overexpressed in breast, colon, prostate, endometrial, and lung cancer cells [11, 19–23]. HSF1 is the primary factor responsible for the transcription of HSPs and is therefore the major regulator of the expression of HSPs. HSF1 facilitates the expression of HSPs as well as the resulting accumulation of HSPs, and it also supports the malignant phenotype through many important signaling pathways [19]. In support of this evidence, HSF1 deficiency produces reduced levels of HSPs, leading to inhibition of important signaling molecules and suppression of tumorigenesis [15]. In this review, we will discuss how HSF1 regulates HSP90, HSP70, and HSP27 in tumorigenesis and tumor progression.

HSP90 and its client proteins may have important roles in supporting tumorigenesis and tumor development [20]. The absence of the HSF1 gene in $Hsf1^{-/-}/Her2^{+}$ mice reduces mammary tumorigenesis, and a reduction of HSF1 expression level in $Hsf1^{+/-}/Her2^{+}$ mice reduces lung metastasis. One mechanism proposed to explain this phenomenon is that HSF1 deficiency reduces the levels of HSP90, HSP70, and other chaperones as well as their client proteins. The reduction of HSPs and their clients leads to reduced signaling through receptor tyrosine kinases resulting in reduced tumor growth or metastasis. Reduction in HSF1 levels also leads to a baseline reduction in multiple chaperones, including HSP90. Therefore, reduced HSP90 forms altered complexes with its client proteins, such as ras-associated factor 1 (RAF1), leading to inefficient activation of RAS/RAF/MEK/ERK signaling [15]. Another study in breast cancer also showed the importance of HSP90 clients by demonstrating that HER2

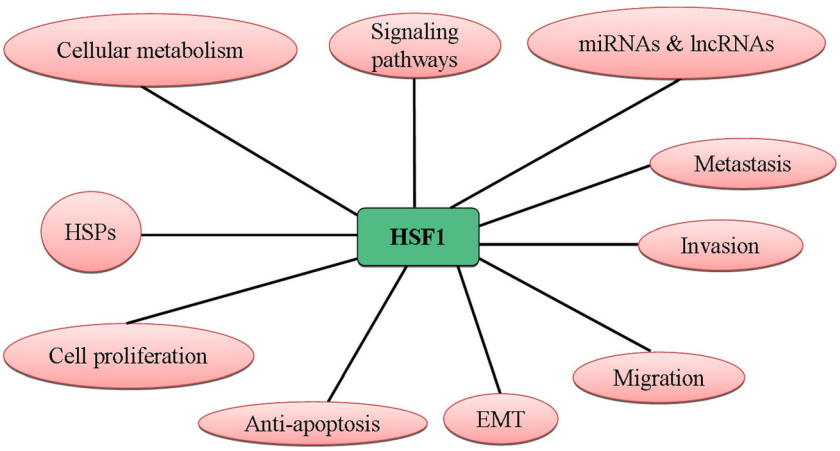

Fig. 1 Multifaceted roles of HSF1 in cancer. HSF1 regulates HSPs, cellular metabolism, signaling pathways, miRNAs, and lncRNAs and plays important roles in cancer by affecting many critical cellular processes, such as cell proliferation, anti-apoptosis, EMT, migration, invasion, and metastasis

overexpression controls HSF1 activity, subsequently stabilizing numerous tumor-promoting HSP90 clients such as MIF, AKT, and HSF1 itself, thereby strongly promoting tumor growth [20].

Among all HSPs, HSP70 plays a central role in the promotion of anti-apoptosis under stress, such as nitric oxide and UV exposure [21, 22]. The first mechanism for the anti-apoptotic effect of HSPs, including HSP70, may be attributed to their functions as chaperones, through which they can protect cells from death [23]. HSP70 interacts with p53 [24, 25] and is able to modulate the p53-dependent apoptosis of tumor cells. Specifically, HSP70 binding to mutated p53 may result in stabilization of the mutant p53 protein, thereby abrogating the pro-apoptotic function of normal wild-type p53 and contributing to tumorigenesis [26].

In addition to HSP90 and HSP70, the level of HSP27 is also frequently elevated in human tumors and cancer cell lines [23]. High levels of HSP27 correlate closely with metastasis, resistance to anti-cancer drugs, and poor prognosis in human cancers [27]. HSF1 promotes HCC cell migration and invasion in vitro and in vivo in an HSP27-dependent manner. HSF1 induces the expression and phosphorylation of HSP27, which regulates actin reorganization and cell migration. This is an important molecular mechanism through which HSF1 promotes HCC invasion and metastasis [6].

Meng et al. reported that in HER2-positive breast cancer cells, HSF1 deficiency leads to the upregulation of p21 and/or a decrease in survivin, eliciting growth arrest. The effects of HSF1 knockdown on growth inhibition and senescence are associated with decreased protein levels of HSP27. Therefore, HSF1 is required for HER2-induced cellular transformation and tumorigenesis, most likely because it maintains HSP27 levels, which, in turn, controls p21 and survivin, critical regulators of senescence. This mechanism also explains why HSF1 has a critical role in the proliferation of HER2-positive cells [16].

In non-cancer cells, overexpressed HSPs cooperate with HSF1 to inhibit the activity of HSF1, which helps maintain the balance of the synthesis of HSPs. However, in tumor cells, this feedback mechanism may be non-functional. Therefore, HSPs are efficient targets for cancer therapy.

HSF1 regulates cellular metabolism

Studies have also shown that HSF1 regulates cellular metabolism, especially glycolysis and lipid metabolism, and has an important role in cancer development [13, 28, 29]. The current knowledge regarding HSF1's regulation of cellular metabolism in cancer is summarized below.

The role of HSF1 in glycolysis

Cancer cells are fundamentally different from normal cells in their metabolic properties. For the production of ATP, normal cells mostly rely on the process of mitochondrial oxidative phosphorylation, which consumes oxygen and glucose to produce energy. In contrast, cancer cells mostly depend on glycolysis for energy production, even in the presence of oxygen. This shift in the metabolism of cancer cells is called the "Warburg effect." The Warburg effect is one of the most fundamentally important differences between normal and cancer cells [28–34]. Mouse mammary epithelial cells transformed by the proto-oncogene *HER2/neu* exhibit deregulated bioenergetic metabolism and increased glycolysis compared to normal cells [35]. Recent evidence indicates that increased glycolysis is not simply a consequence of oncogenic transformation that facilitates tumor growth and survival but rather that increased glycolysis plays a causal role in promoting both the cancer stem cell (CSC) and epithelial-mesenchymal transition (EMT) phenotypes [35–37].

ErbB2 (*Her2/neu*) is an oncogene [38] that when overexpressed increases the transformation and metastatic potential of breast cancer cells [39–41]. Lactate dehydrogenase A (LDHA) is an enzyme that is almost ubiquitously expressed and catalyzes the conversion of pyruvate to lactate, the last step in the glycolysis pathway. LDHA plays a critical role in glycolysis and in the maintenance of mouse tumors resulting from *neu*-transformed cells. Knockdown of LDHA in tumor cells results in a decreased ability to proliferate in hypoxic conditions as well as suppressed tumorigenicity [35]. Zhao et al. reported that in human breast cancer cells, HER2 promotes glycolysis at least partially through the HSF1-mediated upregulation of LDHA [42]. The mechanism by which this occurs is that HER2 overexpression upregulates HSF1 at the translational level, and HSF1 upregulates LDHA at the transcriptional level by binding to the LDHA promoter. This HER2-HSF1-LDHA pathway may have a major role in regulating the glucose metabolism of breast cancer cells. These results demonstrated that HSF1 is a key mediator in the upregulation of glycolysis in HER2-overexpressing cancer cells [42]. This is an important mechanism by which HSF1 regulates glycolysis and promotes breast cancer progression.

The role of HSF1 in lipid metabolism

The different metabolic profiles between cancer cells and normal cells are reflected not only in glycolysis but also in lipid metabolism. Altered metabolism provides cancer cells with enough energy for growth and helps them synthesize macromolecules, such as fatty acids, membrane lipids, and proteins that are essential for rapid proliferation [43]. Recent evidence shows that dysregulation of lipid metabolism has an important role in cancer development [44].

HCC is one of the most prevalent malignant cancers worldwide and is linked to metabolic syndromes including hepatic steatosis and insulin resistance. Jin et al. reported that HSF1 is a key determinant of HCC development through regulation of lipid metabolism. They found that loss of HSF1 inhibits chemical-induced HCC formation and hepatic steatosis and also decreases insulin resistance. Additionally, they found that loss of HSF1 decreases hepatic lipogenesis by activating AMP-activated protein kinase (AMPK), an important regulator of energy homeostasis and inhibitor of lipid synthesis. These data suggest that HSF1 activation promotes HCC progression by both increasing hepatic lipid biosynthesis and accumulation and increasing insulin resistance. Therefore, HSF1 may be a promising potential target for the treatment of HCC [45].

HSF1 regulates signaling pathways

Numerous important signaling pathways regulate cancer development and progression. These signaling pathways coordinate to drive tumorigenesis, cancer development, EMT, migration, invasion, metastasis, and apoptosis. HSF1 plays complex roles in several of the signaling pathways involved in these processes.

HSF1 and HuR-HIF-1 pathway

Oncogene-induced senescence (OIS) is a major blockade on the path toward neoplastic transformation. HSF1 depletion led to both an increase in p21 protein levels and a decrease in survivin protein levels. Therefore, HSF1 supports oncogene-induced cellular transformation by preventing OIS [16]. Meng et al. found that knockdown of HSF1 in human mammary epithelial MCF10A cells prevents HER2-induced neoplastic transformation and tumor development in nude mice, indicating that HSF1 is essential for the initial stages of tumorigenesis. Hypoxia-inducible factor 1 (HIF-1) is considered to be the major regulator of tumor angiogenesis [46]. Researchers found that HSF1 plays an important role in cancer initiation by promoting HIF-1-dependent angiogenesis [14]. They found that HSF1 knockout suppressed HER2-induced mammary hyperplasia and reduced tumor emergence. HSF1 controls HIF-1 via the mRNA binding protein HuR. HSF1 increases HuR expression at the transcriptional level and increased HuR protein then increases the translation of HIF-1, which is essential for tumor neovascularization. HIF-1 is a master regulator not only of genes that control tumor neovascularization but also of genes that control glycolysis, pH regulation, invasion, and metastasis, such as pyruvate kinase M2, carbonic anhydrase 9, endothelin 1, and CXC chemokine receptor 4 (CXCR4) [46, 47]. This HSF1-HuR-HIF-1 pathway demonstrates that HSF1 is essential not only for tumor initiation by preventing OIS but also for progression of established tumors (Table 2).

HSF1 and Slug

EMT is a cellular process whereby epithelial cells are reprogrammed to mesenchymal cells. EMT facilitates the migration of epithelial tumor cells from the primary tumor site to distant locations and is an essential step for tumor progression and metastasis [48]. Slug can promote EMT [49] and is a

Table 2 HSF1-regulated signaling pathways in cancer

Cancer types	Pathways	Functions	References
Breast cancer	HSF1-HuR-HIF-1	Essential for tumor initiation and progression	[14]
Breast cancer	AKT-p-HSF1(S326)-Slug	Plays a critical role in EMT	[51]
Breast cancer	Her2-PI3K/AKT-mTOR-p-HSF1(S326)-HSP90 clients	Promotes tumor growth	[20]
Breast cancer	mTORC1-p-HSF1(S326)-HuR-β-catenin	Important for carcinogenesis	[60]
Breast cancer	HSF1-MAPK-ERK1/2-EMT	Promotes tumorigenesis, EMT, and metastasis	[15]
Breast cancer	HSF1-MTA1-NuRD	Promotes malignant transformation, invasion, and metastasis	[71]
Breast cancer	MAPK/AKT-HSF1-FUT4	Promotes cell proliferation	[72]
HCC	HSF1-BAG3-NF-κB HSF1-MAPK	Anti-apoptosis Promotes cell proliferation	[5]
Colon cancer	HNE-HSF1-BAG3-Bcl-2 family proteins	Anti-apoptosis	[58]
Colon cancer	Oxidative stress-HSF1-Tra2β	Promotes cell proliferation and cancer progression	[73]
Cervical cancer	HSF1-JUN-AP1	Promotes cell proliferation	[74]
MPNST	NF1 loss→RAS→MEK→HSF1 ↑ ↓ KSR1←HSP90	Promotes carcinogenesis	[67]

AP1 the transcription factor activator protein-1; *BAG3* bcl-2-associated athanogene domain 3; *FUT4* fucosyltransferase IV; *HCC* hepatocellular carcinoma; *HNE* 4-hydroxynonenal; *KSR1* kinase suppressor of ras 1; *MPNST* malignant peripheral nerve sheath tumor; *MTA1* metastasis-associated protein 1; *NF1* neurofibromatosis type 1; *Tra2β* transformer 2β

marker of malignancy [50]. A recent study has shown that HSF1 plays a critical role in EMT by upregulating Slug [51]. Heregulin β1 treatment in HER2-positive breast cancer cells activates the HER2 signaling pathway and also results in EMT. Carpenter et al. further studied the mechanisms involved in this process and found that activated HER2 leads to activation of AKT, which directly interacts with and phosphorylates HSF1 at Ser326, the critical residue for HSF1's activation. Activated HSF1 then binds to and transactivates the Slug promoter independent of heat shock, resulting in increased Slug expression. Therefore, the AKT-HSF1-Slug signaling pathway is an important mechanism in HER2-mediated EMT and contributes to the progression of HER2-positive breast cancer [51] (Table 2).

HSF1 and PKC

Apoptosis is a process of programmed cell death in which a cell utilizes its own machinery to commit suicide under tightly controlled physiological conditions. Malfunctions in the apoptotic process may result in degenerative disorders, cancer, or autoimmune diseases [26]. Published data show that HSF1 and its downstream target gene tumor necrosis factor (TNF) protect cells against apoptotic cell death and reverse the senescence phenotype [52, 53]. Physiological stressors, by a series of downstream signaling cascades, induce HSF1 nuclear translocation and activation, leading to the overexpression of HSPs, which play a central role in cytoprotection by preventing cell death under stress [54]. HSF1 has also been shown to serve as a regulator of certain apoptosis-related genes, including *IL-1β* and TNF-α [55, 56], indicating its direct involvement in the apoptotic process.

Recent studies show that HSF1 can also protect cells from apoptosis through the PKC signaling pathway [26]. PKC is a family of serine/threonine kinases known to play an essential role in apoptosis. The activation of PKC has been shown to increase the expression of anti-apoptotic factors, such as Bcl2 and Bcl-xL, which prevent the execution of apoptotic events [26]. Under stressful conditions, PKC is activated and then phosphorylates serine/threonine residues on HSF1, thereby activating HSF1. Activated HSF1 forms a homotrimer and binds to HSE, thus promoting the translation of HSPs. Overexpression of HSPs is thought to trigger the phosphorylation of Bcl2 family proteins and promote their heterodimerization with Bcl-xL, leading to anti-apoptosis [26].

HSF1 and NF-κB

NF-κB transcription factors are critical regulators of genes involved in inflammation and the suppression of apoptosis. Activation of the NF-κB pathway is one of the most important anti-apoptotic signals. Under basal conditions, NF-κB binds to cytosolic inhibitory proteins, IκBs, keeping NF-κB in its deactivated state. Upon stimulation, IκBs are phosphorylated by IκB kinase (IKK), leading to their degradation and subsequent release of active NF-κB, which then translocates to the nucleus. Once active NF-κB has entered the nucleus, it induces the transcription of anti-apoptotic genes, including TNF-α [57]. It was reported that the expression of bcl2-associated athanogene domain 3 (BAG3) was reduced in HSF1-knockdown HCC cells compared with control cells [5, 17, 58]. Moreover, HSF1 positively regulated BAG3 expression in HCC cells, which stabilized the IKKγ protein, the regulatory subunit of IKK, leading to NF-κB activation. These results suggest that HSF1 accelerates HCC development by activating BAG3-NF-κB signaling [5] (Table 2).

In colon cancer cells, BAG3 is functionally downstream of HSF1, and HSF1-mediated BAG3 expression protects colon cancer cells from apoptosis induced by 4-hydroxynonenal (HNE) via stabilizing anti-apoptotic Bcl-2 family proteins, such as Bcl-xL [58] (Table 2). These reports suggest that the anti-apoptotic effect of HSF1 via BAG3 plays an important role in HCC and colon cancer development.

HSF1 and PI3K-AKT-mTOR pathway

The PI3K-AKT-mTOR pathway generally acts to regulate the growth, survival, and apoptosis of tumor cells and is therefore a major important signaling pathway in cancer. The PI3K-AKT-mTOR pathway is often dysregulated in human cancers, such as breast cancer [20] and endometrial carcinoma [59]. mTOR is a key kinase downstream of PI3K-AKT that regulates the proliferation, growth, survival, and angiogenesis of tumor cells. HSF1 status has significant effects on the mTOR pathway. One study found that inhibition of mTOR function by rapamycin impairs protein translation and reduces cell size. $Hsf1^{-/-}$ cells were significantly more sensitive than $Hsf1^{+/+}$ cells to rapamycin-induced growth inhibition [13].

In HER2-overexpressing breast cancer cells, the PI3K-AKT-mTOR pathway is the predominant signaling cascade that leads to phosphorylation of HSF1 at Ser326, which activates HSF1 and induces expression of HSP90. The activated HSP90 machinery stabilizes numerous HSP90 clients, such as macrophage migration inhibitory factor (MIF), AKT, and HSF1 itself, which promote tumor growth in HER2-positive breast cancer [20] (Table 2).

Both AKT and mTORC1, one of two mTOR complexes, are direct upstream activators of HSF1. It was reported that AKT directly interacts with HSF1 and activates HSF1 by phosphorylation at S326. This activated HSF1 promotes Slug overexpression and EMT in HER2-overexpressing breast cancer cells [51]. In addition to AKT, mTORC1 is able to directly phosphorylate HSF1 on Ser326. The activated HSF1 increases HuR expression, which, in turn, promotes the expression of β-catenin, a stem cell renewal factor. This

mTORC1-HSF1-HuR-β-catenin pathway is therefore important in mammary carcinogenesis [60] (Table 2).

HSF1 and MAPK signaling pathway

The MAPK pathway regulates numerous crucial cellular processes, such as survival, proliferation, EMT, cell migration, and invasion [61–64]. In primary hepatocytes and HCC cells, HSF1 deficiency significantly impaired EGF-mediated MAPK activation and inhibited the development of HCC, indicating that HSF1 promotes HCC proliferation by activating MAPK signaling [5] (Table 2). In HER2-positive breast cancer, HER2 heterodimerizes with HER3 or HER4, and following ligand binding, activates MAPK, which enhance cellular proliferation, increases motility, and reduces apoptosis [65]. However, even in the presence of HER2, when HSF1 is knocked out, mammary tumorigenesis, proliferation, invasive properties, and metastasis are decreased [65]. This means that HSF1 is a key regulator of HER2-induced oncogenic signaling.

Cell migration plays an important role in tumor development and progression, especially in tumor invasion and metastasis. Studies on the role of HSF1 in cell migration have shown that in *Hsf1*$^{-/-}$ MEF cell migration is strongly inhibited both in naïve cells and upon EGF stimulation. Further mechanistic exploration demonstrated that HSF1 deletion leads to independent defects in EGFR expression and Ras activation, which impair MEK/ERK and/or SEK2/JNK signaling cascades, resulting in suppression of migration. These results suggest that HSF1 is necessary for cell migration via MAPK signaling and is involved in the metastatic process [66]. In support of this evidence, it was also reported that HSF1 deficiency leads to reduced p-ERK1/2 activity, inefficient EMT, and reduced cellular migration in response to TGFβ in mammary epithelial cells, which suggests that HSF1 promotes mammary tumorigenesis, EMT, and metastasis via activating MAPK signaling [15] (Table 2).

Neurofibromatosis type 1 (NF1) is a common hereditary cancer syndrome resulting from loss-of-function mutations of *Nf1*, a tumor suppressor gene. Recent evidence has shown that NF1 loss activates HSF1 through the RAS-MEK pathway. In turn, active HSF1 increases HSP90 and kinase suppressor of ras 1 (KSR1) protein levels and increases levels of p-ERK. This feed-forward loop of MEK/HSF1 facilitates NF1-associated carcinogenesis such as malignant peripheral nerve sheath tumors (MPNSTs) [67] (Table 2).

Additional alterations in HSF1-mediated signaling pathways are summarized in Table 2.

HSF1 regulates miRNA and lncRNA

In addition to its participation in the signaling pathways discussed above, HSF1 also exerts coordinated effects with miRNAs and lncRNAs, both of which have significant roles in tumorigenesis and cancer progression.

miRNAs are endogenous RNAs consisting of approximately 22 nt that act as negative regulators of gene expression. Dysregulation of miRNAs has been shown to be involved in various diseases including cancer. Recent evidence has shown that HSF1 can regulate miRNA levels. For example, miR-214 is overexpressed in human epithelial ovarian tumors and promotes cell survival. Chen et al. found that in ovarian cancer cells, HSF1 overexpression upregulated miR-214 expression and HSF1 knockdown decreased miR-214 expression. This result suggests that HSF1 also possesses the ability to regulate miRNA biogenesis [68]. In human cervical cancer cell line, HSF1 regulates miR-432 expression in a heat shock-dependent manner via binding to the HSE present in upstream sequence of miR-432 [69].

LncRNAs have emerged as essential regulators in nearly all aspects of biology. LncRNAs target chromatin modification complexes or RNA-binding proteins to alter gene expression programs and play important roles in tumorigenesis [70]. Recent evidence has shown that HSF1 can regulate lncRNA levels. HSF1 knockdown in breast cancer cells leads to increased lincRNA-p21 expression. Further investigation of the mechanism involved revealed that HSF1 decreases lincRNA-p21 levels likely via miR-320 or let-7-mediated lincRNA-p21 degradation. LincRNA-p21 negatively regulates β-catenin translation, and therefore, HSF1 increases the protein levels of β-catenin, which plays a role in carcinogenesis [60]. Surely, further study of the interactions between HSF1 and specific miRNAs and lncRNAs will reveal additional unique mechanisms to explain HSF1's multifaceted roles in human cancer.

Conclusions

HSF1 is a double-edged sword. On one hand, it can protect cells and organisms from heat, ischemia, inflammation, oxidative stress, and other noxious conditions [2]. On the other hand, HSF1 is often overexpressed in human cancer cells and has detrimental effects on human health. HSF1 is an important regulator of numerous aspects of cancer such as initiation, development, EMT, migration, invasion, and metastasis.

In summary, HSF1 is a powerful multifaceted regulator of cancer. First, HSF1 promotes the expression of HSPs to protect proteins that are essential for tumorigenesis and survival from degradation, such as mutant p53 proteins. Second, HSF1 regulates cellular metabolism, including glycolysis and lipid metabolism. Third, HSF1 serves as a regulator of different signaling pathways, such as HuR-HIF-1, Slug, PKC, NF-κB, PI3K-AKT-mTOR, and MAPK pathways, which are essential for cell proliferation, anti-apoptosis, EMT,

migration, invasion, and metastasis. Finally, HSF1 regulates the expression of both miRNAs and lncRNAs (Fig. 1).

The emergence of HSF1 as an important regulator of cancer cells has garnered much interest not only from a scientific perspective but also from a clinical perspective. HSF1 and HSPs are not only promising biomarkers for the diagnosis of cancer but also hold potential for drug target identification and as direct targets for clinical intervention in the future. For example, 17-AAG, an inhibitor of HSP90, has entered clinical trials. Further investigation of HSF1-regulated molecular mechanisms will provide greater insight on the identification and development of selective HSF1 inhibitors for cancer patients.

Acknowledgments The authors thank Dr. Ming Tan (Mitchell Cancer Institute, University of South Alabama) for helping to revise our manuscript. The authors acknowledge financial support for the projects supported by National Natural Sciences Foundation of China (81272907, J1103604) and the project 2012-1707-7-7 sponsored by the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry.

References

1. Pirkkala L, Nykanen P, Sistonen L. Roles of the heat shock transcription factors in regulation of the heat shock response and beyond. FASEB J. 2001;15:1118–31.
2. Sorger PK. Heat shock factor and the heat shock response. Cell. 1991;65:363–6.
3. Westerheide SD, Morimoto RI. Heat shock response modulators as therapeutic tools for diseases of protein conformation. J Biol Chem. 2005;280:33097–100.
4. Whitesell L, Lindquist SL. HSP90 and the chaperoning of cancer. Nat Rev Cancer. 2005;5:761–72.
5. Chuma M, Sakamoto N, Nakai A, Hige S, Nakanishi M, Natsuizaka M, et al. Heat shock factor 1 accelerates hepatocellular carcinoma development by activating nuclear factor-kappaB/mitogen-activated protein kinase. Carcinogenesis. 2014;35:272–81.
6. Fang F, Chang R, Yang L. Heat shock factor 1 promotes invasion and metastasis of hepatocellular carcinoma in vitro and in vivo. Cancer. 2012;118:1782–94.
7. Santagata S, Hu R, Lin NU, Mendillo ML, Collins LC, Hankinson SE, et al. High levels of nuclear heat-shock factor 1 (HSF1) are associated with poor prognosis in breast cancer. Proc Natl Acad Sci U S A. 2011;108:18378–83.
8. Engerud H, Tangen IL, Berg A, Kusonmano K, Halle MK, Oyan AM, et al. High level of HSF1 associates with aggressive endometrial carcinoma and suggests potential for HSP90 inhibitors. Br J Cancer. 2014;111:78–84.
9. Ishiwata J, Kasamatsu A, Sakuma K, Iyoda M, Yamatoji M, Usukura K, et al. State of heat shock factor 1 expression as a putative diagnostic marker for oral squamous cell carcinoma. Int J Oncol. 2012;40:47–52.
10. Hoang AT, Huang J, Rudra-Ganguly N, Zheng J, Powell WC, Rabindran SK, et al. A novel association between the human heat shock transcription factor 1 (HSF1) and prostate adenocarcinoma. Am J Pathol. 2000;156:857–64.
11. Cen H, Zheng S, Fang YM, Tang XP, Dong Q. Induction of HSF1 expression is associated with sporadic colorectal cancer. World J Gastroenterol. 2004;10:3122–6.
12. Scherz-Shouval R, Santagata S, Mendillo ML, Sholl LM, Ben-Aharon I, Beck AH, et al. The reprogramming of tumor stroma by HSF1 is a potent enabler of malignancy. Cell. 2014;158:564–78.
13. Dai C, Whitesell L, Rogers AB, Lindquist S. Heat shock factor 1 is a powerful multifaceted modifier of carcinogenesis. Cell. 2007;130:1005–18.
14. Gabai VL, Meng L, Kim G, Mills TA, Benjamin IJ, Sherman MY. Heat shock transcription factor Hsf1 is involved in tumor progression via regulation of hypoxia-inducible factor 1 and RNA-binding protein HuR. Mol Cell Biol. 2012;32:929–40.
15. Xi C, Hu Y, Buckhaults P, Moskophidis D, Mivechi NF. Heat shock factor Hsf1 cooperates with ErbB2 (Her2/Neu) protein to promote mammary tumorigenesis and metastasis. J Biol Chem. 2012;287:35646–57.
16. Meng L, Gabai VL, Sherman MY. Heat-shock transcription factor HSF1 has a critical role in human epidermal growth factor receptor-2-induced cellular transformation and tumorigenesis. Oncogene. 2010;29:5204–13.
17. Mendillo ML, Santagata S, Koeva M, Bell GW, Hu R, Tamimi RM, et al. HSF1 drives a transcriptional program distinct from heat shock to support highly malignant human cancers. Cell. 2012;150:549–62.
18. Craig EA. The heat shock response. CRC Crit Rev Biochem. 1985;18:239–80.
19. Ciocca DR, Arrigo AP, Calderwood SK. Heat shock proteins and heat shock factor 1 in carcinogenesis and tumor development: an update. Arch Toxicol. 2013;87:19–48.
20. Schulz R, Streller F, Scheel AH, Ruschoff J, Reinert MC, Dobbelstein M, et al. HER2/ErbB2 activates HSF1 and thereby controls HSP90 clients including MIF in HER2-overexpressing breast cancer. Cell Death Dis. 2014;5, e980.
21. Bellmann K, Jaattela M, Wissing D, Burkart V, Kolb H. Heat shock protein hsp70 overexpression confers resistance against nitric oxide. FEBS Lett. 1996;391:185–8.
22. Simon MM, Reikerstorfer A, Schwarz A, Krone C, Luger TA, Jaattela M, et al. Heat shock protein 70 overexpression affects the response to ultraviolet light in murine fibroblasts. Evidence for increased cell viability and suppression of cytokine release. J Clin Invest. 1995;95:926–33.
23. Jaattela M. Escaping cell death: survival proteins in cancer. Exp Cell Res. 1999;248:30–43.
24. Zylicz M, King FW, Wawrzynow A. Hsp70 interactions with the p53 tumour suppressor protein. EMBO J. 2001;20:4634–8.
25. Fourie AM, Hupp TR, Lane DP, Sang BC, Barbosa MS, Sambrook JF, et al. HSP70 binding sites in the tumor suppressor protein p53. J Biol Chem. 1997;272:19471–9.
26. Kumar S, Tomar MS, Acharya A. HSF1-mediated regulation of tumor cell apoptosis: a novel target for cancer therapeutics. Future Oncol. 2013;9:1573–86.
27. Ciocca DR, Calderwood SK. Heat shock proteins in cancer: diagnostic, prognostic, predictive, and treatment implications. Cell Stress Chaperones. 2005;10:86–103.
28. Kim JW, Dang CV. Cancer's molecular sweet tooth and the Warburg effect. Cancer Res. 2006;66:8927–30.
29. Warburg O. On respiratory impairment in cancer cells. Science. 1956;124:269–70.
30. Chen Z, Lu W, Garcia-Prieto C, Huang P. The Warburg effect and its cancer therapeutic implications. J Bioenerg Biomembr. 2007;39:267–74.
31. DeBerardinis RJ, Lum JJ, Hatzivassiliou G, Thompson CB. The biology of cancer: metabolic reprogramming fuels cell growth and proliferation. Cell Metab. 2008;7:11–20.
32. Gatenby RA, Gillies RJ. Glycolysis in cancer: a potential target for therapy. Int J Biochem Cell Biol. 2007;39:1358–66.

33. Gillies RJ, Robey I, Gatenby RA. Causes and consequences of increased glucose metabolism of cancers. J Nucl Med. 2008;49 Suppl 2:24S–42.
34. Hsu PP, Sabatini DM. Cancer cell metabolism: Warburg and beyond. Cell. 2008;134:703–7.
35. Fantin VR, St-Pierre J, Leder P. Attenuation of LDH-A expression uncovers a link between glycolysis, mitochondrial physiology, and tumor maintenance. Cancer Cell. 2006;9:425–34.
36. Matoba S, Kang JG, Patino WD, Wragg A, Boehm M, Gavrilova O, et al. p53 regulates mitochondrial respiration. Science. 2006;312:1650–3.
37. Schieber MS, Chandel NS. ROS links glucose metabolism to breast cancer stem cell and EMT phenotype. Cancer Cell. 2013;23:265–7.
38. Slamon DJ, Godolphin W, Jones LA, Holt JA, Wong SG, Keith DE, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science. 1989;244:707–12.
39. Guy CT, Webster MA, Schaller M, Parsons TJ, Cardiff RD, Muller WJ. Expression of the neu protooncogene in the mammary epithelium of transgenic mice induces metastatic disease. Proc Natl Acad Sci U S A. 1992;89:10578–82.
40. Tan M, Lan KH, Yao J, Lu CH, Sun M, Neal CL, et al. Selective inhibition of ErbB2-overexpressing breast cancer in vivo by a novel TAT-based ErbB2-targeting signal transducers and activators of transcription 3-blocking peptide. Cancer Res. 2006;66:3764–72.
41. Tan M, Li P, Klos KS, Lu J, Lan KH, Nagata Y, et al. ErbB2 promotes Src synthesis and stability: novel mechanisms of Src activation that confer breast cancer metastasis. Cancer Res. 2005;65: 1858–67.
42. Zhao YH, Zhou M, Liu H, Ding Y, Khong HT, Yu D, et al. Upregulation of lactate dehydrogenase A by ErbB2 through heat shock factor 1 promotes breast cancer cell glycolysis and growth. Oncogene. 2009;28:3689–701.
43. Menendez JA, Lupu R. Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis. Nat Rev Cancer. 2007;7:763–77.
44. Siegel AB, Zhu AX. Metabolic syndrome and hepatocellular carcinoma: two growing epidemics with a potential link. Cancer. 2009;115:5651–61.
45. Jin X, Moskophidis D, Mivechi NF. Heat shock transcription factor 1 is a key determinant of HCC development by regulating hepatic steatosis and metabolic syndrome. Cell Metab. 2011;14:91–103.
46. Semenza GL. Defining the role of hypoxia-inducible factor 1 in cancer biology and therapeutics. Oncogene. 2010;29:625–34.
47. Gordan JD, Simon MC. Hypoxia-inducible factors: central regulators of the tumor phenotype. Curr Opin Genet Dev. 2007;17:71–7.
48. De Craene B, Berx G. Regulatory networks defining EMT during cancer initiation and progression. Nat Rev Cancer. 2013;13:97–110.
49. Hajra KM, Chen DY, Fearon ER. The SLUG zinc-finger protein represses E-cadherin in breast cancer. Cancer Res. 2002;62:1613–8.
50. Cobaleda C, Perez-Caro M, Vicente-Duenas C, Sanchez-Garcia I. Function of the zinc-finger transcription factor SNAI2 in cancer and development. Annu Rev Genet. 2007;41:41–61.
51. Carpenter RL, Paw I, Dewhirst MW, Lo HW. Akt phosphorylates and activates HSF-1 independent of heat shock, leading to Slug overexpression and epithelial-mesenchymal transition (EMT) of HER2-overexpressing breast cancer cells. Oncogene. 2014.
52. Csermely P. A nonconventional role of molecular chaperones: involvement in the cytoarchitecture. News Physiol Sci. 2001;16:123–6.
53. Locksley RM, Killeen N, Lenardo MJ. The TNF and TNF receptor superfamilies: integrating mammalian biology. Cell. 2001;104: 487–501.
54. Kroeger PE, Morimoto RI. Selection of new HSF1 and HSF2 DNA-binding sites reveals difference in trimer cooperativity. Mol Cell Biol. 1994;14:7592–603.
55. Ma ZN, Cao Y. [The relationship between the polymerization of HSF1 and the expression of IL-1beta, TNF-alpha mRNA of monocytes in fever rabbits]. Zhongguo Ying Yong Sheng Li Xue Za Zhi. 2006;22:445–9.
56. Singh IS, He JR, Calderwood S, Hasday JD. A high affinity HSF-1 binding site in the 5′-untranslated region of the murine tumor necrosis factor-alpha gene is a transcriptional repressor. J Biol Chem. 2002;277:4981–8.
57. Bouwmeester T, Bauch A, Ruffner H, Angrand PO, Bergamini G, Croughton K, et al. A physical and functional map of the human TNF-alpha/NF-kappa B signal transduction pathway. Nat Cell Biol. 2004;6:97–105.
58. Jacobs AT, Marnett LJ. HSF1-mediated BAG3 expression attenuates apoptosis in 4-hydroxynonenal-treated colon cancer cells via stabilization of anti-apoptotic Bcl-2 proteins. J Biol Chem. 2009;284:9176–83.
59. Oda K, Stokoe D, Taketani Y, McCormick F. High frequency of coexistent mutations of PIK3CA and PTEN genes in endometrial carcinoma. Cancer Res. 2005;65:10669–73.
60. Chou SD, Murshid A, Eguchi T, Gong J, Calderwood SK. HSF1 regulation of beta-catenin in mammary cancer cells through control of HuR/elavL1 expression. Oncogene. 2014.
61. Beeram M, Patnaik A, Rowinsky EK. Raf: a strategic target for therapeutic development against cancer. J Clin Oncol. 2005;23: 6771–90.
62. Klemke RL, Cai S, Giannini AL, Gallagher PJ, de Lanerolle P, Cheresh DA. Regulation of cell motility by mitogen-activated protein kinase. J Cell Biol. 1997;137:481–92.
63. Thiery JP. Epithelial-mesenchymal transitions in development and pathologies. Curr Opin Cell Biol. 2003;15:740–6.
64. Viala E, Pouyssegur J. Regulation of tumor cell motility by ERK mitogen-activated protein kinases. Ann N Y Acad Sci. 2004;1030: 208–18.
65. Ciocca DR, Gago FE, Fanelli MA, Calderwood SK. Co-expression of steroid receptors (estrogen receptor alpha and/or progesterone receptors) and Her-2/neu: clinical implications. J Steroid Biochem Mol Biol. 2006;102:32–40.
66. O'Callaghan-Sunol C, Sherman MY. Heat shock transcription factor (HSF1) plays a critical role in cell migration via maintaining MAP kinase signaling. Cell Cycle. 2006;5:1431–7.
67. Dai C, Santagata S, Tang Z, Shi J, Cao J, Kwon H, et al. Loss of tumor suppressor NF1 activates HSF1 to promote carcinogenesis. J Clin Invest. 2012;122:3742–54.
68. Chen YF, Dong Z, Xia Y, Tang J, Peng L, Wang S, et al. Nucleoside analog inhibits microRNA-214 through targeting heat-shock factor 1 in human epithelial ovarian cancer. Cancer Sci. 2013;104:1683–9.
69. Das S, Bhattacharyya NP. Heat shock factor 1 regulates hsa-miR-432 expression in human cervical cancer cell line. Biochem Biophys Res Commun. 2014.
70. Tsai MC, Spitale RC, Chang HY. Long intergenic noncoding RNAs: new links in cancer progression. Cancer Res. 2011;71:3–7.
71. Khaleque MA, Bharti A, Gong J, Gray PJ, Sachdev V, Ciocca DR, et al. Heat shock factor 1 represses estrogen-dependent transcription through association with MTA1. Oncogene. 2008;27:1886–93.
72. Yang X, Wang J, Liu S, Yan Q. HSF1 and Sp1 regulate FUT4 gene expression and cell proliferation in breast cancer cells. J Cell Biochem. 2014;115:168–78.
73. Kajita K, Kuwano Y, Kitamura N, Satake Y, Nishida K, Kurokawa K, et al. Ets1 and heat shock factor 1 regulate transcription of the transformer 2beta gene in human colon cancer cells. J Gastroenterol. 2013;48:1222–33.
74. Sawai M, Ishikawa Y, Ota A, Sakurai H. The proto-oncogene JUN is a target of the heat shock transcription factor HSF1. FEBS J. 2013;280:6672–80.