Targeting heat shock transcription factor 1 for novel hyperthermia therapy (Review)

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Abstract. Hyperthermia (HT) has shown promising antitumor effects against various types of malignant tumors, and its pleiotropic effects support its combined use with radiotherapy and/or chemotherapy. However, HT is rendered less effective by the acquisition of thermoresistance in tumors, which arises through the elevation of heat shock proteins (HSPs) or other tumor responses. In mammals, the induction of HSPs is principally regulated at the transcriptional level by the activation of heat shock transcription factor 1 (HSF1). This transactivator has been shown to be abundantly expressed in a wide variety of tumors in humans. In addition, HSF1 participates in the initiation, proliferation and maintenance of tumors. Of note, HSF1 silencing has been shown to prevent the progression of tumors and to enhance their sensitivity to HT. Here, we review the physiological and pathological roles of HSF1 in cancer cells, and discuss its potential as a therapeutic target for HT therapy.

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Abbreviations: BMP, bone marrow progenitor; DN, dominant-negative; ER, estrogen receptor; HER2, epidermal growth factor receptor-2; HSE, heat shock element; HSP, heat shock protein; HSF, heat shock transcription factor; HSF1, heat shock transcription factor 1; HT, hyperthermia; KO, knockout; MTA1, metastasis-associated 1; MEF, mouse embryonic fibroblast; OSCC, oral squamous cell carcinoma; p-TEFb, positive transcription elongation factor b; shRNA, short hairpin RNA; siRNA, small interfering RNA

Key words: hyperthermia, heat shock transcription factor 1, cancer

1. Introduction

Hyperthermia (HT) is considered to have potential as a cancer treatment modality (1). HT in combination with radiotherapy and/or chemotherapy has been used for various types of cancer, and the anticancer effects of such combinations have been verified in many clinical trials (1-7). One of the problems with HT therapy is the acquisition of thermoresistance against heat stress (8-12). In general, cells have protective functions for various stressors that occur from outside of the cell. Heat shock proteins (HSPs), molecular chaperones with strong cytoprotective and antiapoptotic properties, are induced by a wide variety of stresses, particularly heat stress (13-16); they are also induced by treatment with HT, and, thus, it has been considered that HSPs play a role in the acquisition of thermoresistance in cells (10-12). In mammals, the expression of HSPs is mainly regulated by heat shock transcription factor 1 (HSF1) (17,18). Elevation of HSF1 has been observed in several types of human tumor tissues (19-26), and it has been shown to participate in the initiation, proliferation and maintenance of tumors (12,25-29). Notably, both inhibition of the expression of HSF1 and the functional loss of HSF1 have been suggested to enhance the sensitivity to HT under basic experimental conditions (29-38). In the present review, the physiological and pathological roles of HSF1 in cancer cells are summarized, and the potential of HSF1 as a therapeutic target for HT therapy is discussed.

2. Function of HSF1

The heat-shock response, which is a universal cellular response to heat, is a critical cellular event for cell adaptation. Heat stress elicits a wide spectrum of stress responses, including an induction of HSPs, protein aggregation, an imbalance of protein homeostasis, DNA and RNA damage, reactive oxygen species production, cell growth arrest and cell death in mammalian cells. HSPs are characterized as molecular chaperones and they exert strong cytoprotective effects against stress-induced proteotoxic damage (13-16). Their functions and amino acid sequences are well conserved in a wide range of species from yeast to humans. The expression of HSPs is primarily regulated by heat shock transcription factors (HSFs). In humans, three HSFs (HSF1, HSF2 and HSF4) have been identified and, among them, HSF1 plays the most important

role against stress responses (17,18). Under nonstress conditions, HSF1 is localized in the cytoplasm as an inactive monomer. Upon exposure to stresses, especially heat stress, a series of events is triggered: the HSF1 inactive monomer is converted to a DNA-binding homotrimer that translocates from the cytoplasm to the nucleus, binds to the heat shock elements (HSEs) that are located in the regions of inducible HSP genes including Hsp27, Hsp70 and Hsp90, undergoes a hyperphosphorylation reaction and activates transcription (17,18,39) (Fig. 1). In mammalian cells, heat activates the transcription of heat responsive genes, including HSPs, coincident with a bulk decrease in mRNA and protein syntheses, and this overall reprogramming of gene expression permits the selective synthesis of HSPs (40-42). In our previous studies using global-scale microarrays, we also detected a number of genes that were downregulated and participated in biological functions, including post-transcriptional modification and gene expression (43-45). This bulk decrease has been considered to represent a form of transcriptional suppression due to the binding of activated HSF1 to the promoter region of the gene (40). Mariner *et al* (41) recently reported that non-corded RNA is very closely related to the mechanism by which heat induces a decrease in gene expression.

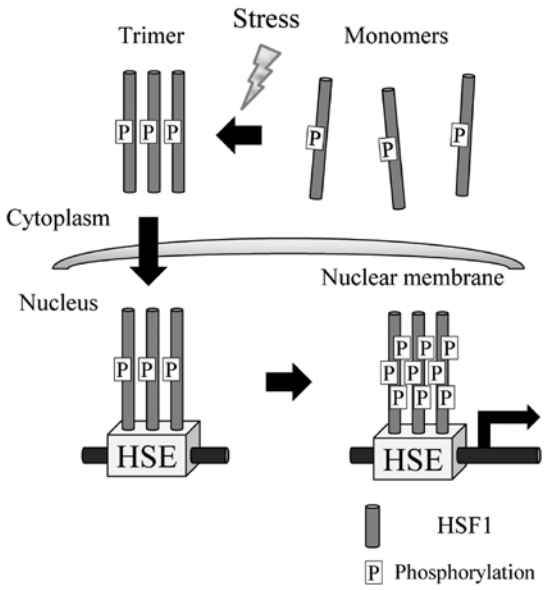

Figure 1. Schematic illustration of the activation of HSF1. HSF1 exists as an inactive monomer in the cytoplasm under nonstress conditions. Upon the introduction of stresses, especially heat stress, the HSF1 monomer is converted to a DNA-binding homotrimer that translocates from the cytoplasm to the nucleus. Then, the homotrimer binds to the HSE in the promoter of the gene, undergoes a hyperphosphorylation reaction and activates transcription.

Numerous studies targeting HSFs in gene-modified animals have enhanced our understanding of the pleiotropic roles of HSFs in mammals (46). A previous study with HSF1-knockout (KO) mice demonstrated that the HSF1 protein was dispensable for the maintenance of the mice, since the KO mice remained alive under normal environmental conditions (30). On the other hand, HSF1 is reported to be required for extra-embryonic development, postnatal growth and fertility of the female in the HSF1-KO mice (47). Homma *et al* (48) observed hallmarks of central nervous system disease, such as demyelination, astrogliosis and accumulation of ubiquitinated proteins in HSF1-deficient mice. Furthermore, previous studies with HSF1 KO animals have shown that HSF1 is involved in the development and maintenance of several organs, such as the heart (49), trachea (50), nose (50) and placenta (47). It has also been demonstrated that both HSF2 (51) and HSF4 (52) play critical roles in the neural functions or lens development by using HSF2- and HSF4-KO mice. Thus, accumulating evidence suggests that HSFs are closely associated with longevity (53), neurodegenerative diseases (54) and cancer (12,25-29). Indeed, HSFs play a versatile role in the organism, from homeostatic maintenance to disease.

3. HSF1 and cancer

In humans, tumorigenesis is a multistep development including genome instabilities (mutation and chromosomal deletion) and epigenetic changes (abnormal histone acetylation and DNA methylation). During the multistep tumorigenesis, mutated nonnative proteins are synthesized and deregulated and abnormal signal transduction pathways exist in cancer cells. Moreover, the conditions within the tumor microenvironment where cancer cells are present include hypoxia, acidity, and low glucose levels, and these differ from the conditions in normal tissue. Therefore, cancer cells are generally exposed to more stresses compared with normal cells (55). Several types of tumors contain high expression levels of one or more HSPs (Hsp27, Hsp40, Hsp60, Hsp70, Hsp90 and/or Hsp110) compared with adjacent normal tissues (12,56,57). A significant elevation of HSF1 has been reported in a wide variety of cancer cells or tumor tissues in nonclinical studies (19-26) (Table I). In human prostate carcinoma cell lines, the expression levels of HSPs and HSF1 are elevated in cells with more highly malignant features (19,20). An abundant expression of HSF1 protein has been observed in the tumor tissues of human prostate (19) and pancreas (22) or oral squamous cell carcinoma (OSCC) cells (24) compared to their normal counterparts. In addition, Khaleque *et al* (21) have shown that the protein level of HSF1 is upregulated in breast carcinoma sections and that HSF1 co-localizes and binds to the corepressor metastasis-associated 1 (MTA1) protein in this cancer.

In 2007, Dai *et al* (27) found that HSF1, a non-oncogene, plays a major role in enabling the initiation and maintenance of cancer in several mouse tumor models. Knockdown of HSF1 using short hairpin RNA (shRNA) technology effectively inhibited cell viability in several cancer cell lines, whereas it had no effect on normal human fibroblasts. They concluded that HSF1 function helps to maintain the growth and survival of human cancer cells (27). Similar results were reported when other *in vitro* experiments were performed using melanoma cells (29,36), OSCC cells (37), pancreatic cancer cells (22) and human epidermal growth factor receptor 2 (HER2)-positive cancer cells (58) (Table II). Although the molecular mechanisms by which HSF1 regulates cellular proliferation and survival in cancer cells are less understood, genome-wide transcriptome studies have indicated that HSF1 regulates numerous other targets in addition to HSPs (25,59-62).

Basic experiments using HSF1 KO mice clearly demonstrate that this protein participates in the development of skin tumors (27) and hepatocellular carcinomas (28) induced by 7,12-dimethylbenzanthracene (DMBA) and diethylnitrosamine

Table I. Examples of nonclinical and clinical studies elevating HSF1.

Cancer type	Observations	Author/(Ref.)
Nonclinical studies		
Prostate cancer specimens	Protein level is upregulated in the malignant prostate epithelial cells	Hoang *et al* (19)
Prostate carcinoma cells	Protein level is elevated in the more highly malignant carcinoma cells	Hoang *et al* (19) Tang *et al* (20)
Breast carcinoma sections	Protein level is upregulated and it co-localizes with MTA1 protein	Khaleque *et al* (21)
Pancreatic cancer tissues	Protein level is upregulated in cancer tissues	Dudeja *et al* (22)
OSCC cells	Protein and mRNA levels are elevated in carcinoma cells	Ishiwata *et al* (24)
Clinical studies		
Breast cancer	Nuclear level is associated with poor prognosis	Santagata *et al* (23)
OSCC	Nuclear level is related to tumor size	Ishiwata *et al* (24)
Breast, colon or lung cancer	Active HSF1 transcriptional program is strongly associated with metastasis and mortality	Mendillo *et al* (25)
Breast cancer	mRNA level is correlated with grade, metastasis and poor prognosis	Gabai *et al* (26)

HSF1, heat shock transcription factor 1; OSCC, oral squamous cell carcinoma; MTA1, metastasis-associated 1.

Table II. Examples of experimental anticancer effects targeting HSF1.

Cancer type	Treatment	Effect	Author/(Ref.)
HSF1 silencing			
Pancreatic cancer cells	Quercetin	Quercetin increases the apoptosis of cells	Aghdassi *et al* (64)
Pancreatic cancer xenografts	Quercetin	Quercetin reduces the growth of tumors	Aghdassi *et al* (64)
Colon cancer xenografts	KRIBB11	KRIBB11 inhibits the growth of tumors	Yoon *et al* (65)
Pancreatic cancer xenografts	Ly101-4B	Ly101-4B inhibits the growth of tumors	Xia *et al* (66)
Mammary epithelial cell xenografts	shRNA	shRNA inhibits HER2-induced cellular transformation and tumorigenesis	Meng *et al* (59)
Melanoma cell xenografts	shRNA	shRNA inhibits the growth of melanomas	Fujimoto *et al* (29)
Cancer cells	shRNA	shRNA inhibits the growth of cancer cells	Dai *et al* (27)
HER2-positive cancer cells	shRNA	shRNA decreases proliferation of cancer cells	Meng *et al* (59)
Melanoma cells	shRNA	shRNA inhibits the growth of melanoma cells	Nakamura *et al* (36) Fujimoto *et al* (29)
Pancreatic cancer cells	siRNA	siRNA decreases the viability of cancer cells	Dudeja *et al* (22)
OSCC cells	siRNA	siRNA inhibits the growth of OSCC cells	Tabuchi *et al* (37)
Genetically modified mice			
Chemical-induced skin carcinomas	HSF1 KO mouse	KO inhibits carcinogen-induced tumorigenesis	Dai *et al* (27)
p53-deficient spontaneous tumors	HSF1 KO mouse x $p53^{R172H}$ mouse[a]	KO increases survival and alters the distribution of tumor types	Dai *et al* (27)
p53-deficient spontaneous tumors	HSF1 KO mouse x p53 KO mouse[b]	KO selectively decreases lymphomas	Min *et al* (63)
Chemical-induced hepatocellular carcinomas	HSF1 KO mouse	KO inhibits carcinogen-induced tumorigenesis	Jin *et al* (28)
NeuT-induced breast tumors	HSF1 KO mouse x Her2/NeuT mouse[c]	KO suppresses tumor progression	Gabai *et al* (26)

[a]HSF1 KO mice were crossed with knockin mice caring the $p53^{R172H}$ hot spot mutation. [b]HSF1 KO mice were crossed with p53 KO mice. [c]HSF1 KO mice were crossed with transgenic mice expressing HER2/NeuT (a rodent homolog of HER2 caring an activating mutation). HSF1, heat shock transcription factor 1; OSCC, oral squamous cell carcinoma; shRNA, short hairpin RNA; HER2, human epidermal growth factor receptor 2; KO, knockout.

Table III. Examples of the enhancement of HT sensitivity targeting HSF1.

Cell type targeting	Heat treatment	Effect	Author/(Ref.)
HT and HSF1 silencing			
MEF cells KO mouse	43˚C for 30 min followed by 45˚C for 40 min	KO prevents resistance to HT	McMillan *et al* (30)
MEF cells KO mouse	43˚C for 30 min followed by 45˚C for 60 min	KO prevents resistance to HT	Luft *et al* (31)
MEF and BMP cells KO mouse	43˚C for 20 min followed by 44˚C for 10-40 min	KO prevents resistance to HT	Zhang *et al* (32)
Breast cancer cells DN mutant	42˚C for 30 min followed by 43˚C for 20-100 min	Blocking prevents resistance to HT	Wang *et al* (33)
Cervical cancer cells triptolide	42˚C for 60 min followed by 45˚C for 40 min	Inhibition enhances HT sensitivity	Westerheide *et al* (35)
Cervical cancer cells DN mutant	48˚C for 10 min	DN mutant increases HT sensitivity	Xia *et al* (34)
Melanoma cells shRNA	42˚C or 43˚C for 60 min or 45˚C for 60-180 min	Silencing enhances HT sensitivity	Nakamura *et al* (36) Fujimoto *et al* (29)
OSCC cells siRNA	42˚C or 44˚C for 90 min	Silencing enhances HT sensitivity	Tabuchi *et al* (37)
Breast cancer cell xenografts DN mutant	43˚C for 30 min every day for a week	Blocking inhibits growth of cancer cells	Wang *et al* (33)
HT, compound and HSF1 silencing			
Cervical cancer cells siRNA and cisplatin	43˚C for 60 min	Silencing sensitizes hyperthermochemotherapy	Rossi *et al* (38)
Melanoma cells shRNA and dacarbazine	42˚C for 60 min	Silencing sensitizes hyperthermochemotherapy	Nakamura *et al* (36)

HSF1, heat shock transcription factor 1; OSCC, oral squamous cell carcinoma; HT, hyperthermia; shRNA, short hairpin RNA; KO, knockout; BMP, bone marrow progenitor; MEF, mouse embryonic fibroblast.

(DEN), respectively. In line with these results, different animal experiments with genetically modified mice showed an essential role of HSF1 in tumor development (26,27,63) (Table II).

Interest in the role of HSF1 in cancer has grown gradually over the last decade, and notable papers in clinical research have recently been published (23-26) (Table I). Santagata *et al* (23) indicated that nuclear localization and increased levels of HSF1 are well associated with poor prognosis in estrogen receptor (ER)-positive breast carcinomas. Ishiwata *et al* (24) reported that higher nuclear HSF1 expression was closely related to tumor size and histopathologic types in OSCCs. Moreover, high expression of HSF1 mRNA in human breast cancer was correlated with grade, metastasis, and poor prognosis, suggesting that HSF1 is involved in tumor progression (26). Mendillo *et al* (25) identified an HSF1-regulated transcriptional program specific to highly malignant cells and distinct from heat shock by using chromatin immunoprecipitation coupled with massively parallel DNA sequencing. They established an 'HSF1-cancer signature' of 456 genes that were bound by HSF1 near their transcription start sites, and found that this HSF1 cancer program is active in several types of tumors and is strongly associated with metastasis and mortality (25) (Table I).

To date, several types of HSF1 inhibitors have been developed, and their inhibitory effects to cancer have been reported (35,64-68) (Table II). Quercetin, a plant-derived flavonoid, is shown to increase apoptosis and to reduce the growth of pancreatic cancer cells (64). Meanwhile, this flavonoid inhibits multiple target proteins, such as HSF1, Hsp70 and NF-κB (67-69). In a colon cancer xenograft mouse model, a newly synthesized KRIBB11 [N^2-(1*H*-indazole-5-yl)-N^6-methyl-3-nitropyridine-2,6-diamine] significantly inhibited the growth of colon cancer, and its mechanism is considered to inhibit Hsp70 synthesis through suppression of HSF1 function by impairing the recruitment of positive transcription elongation factor b (p-TEFb) to the Hsp70 promoter (65). Ly101-4B, a novel triazole nucleoside analog, targets the heat shock response pathway by downregulation of HSF1 and consequential inhibition of HSPs, Hsp27, Hsp70 and Hsp90 (66). This compound caused the shutdown of several oncogenic pathways and caspase-dependent apoptosis, resulting in a potent anticancer effect in pancreatic cancer cell xenografts (66,68). Similar results were obtained when shRNA for HSF1 was used (29,59). These findings have helped to elucidate the specific role of HSF1 in the pathogenesis of cancer.

4. HSF1 and hyperthermia

HT has been considered a possible mode of cancer treatment (1). HT in combination with radiotherapy and/or chemotherapy has been used for various types of cancer, and the anticancer effects of such combinations have been verified in many clinical trials (1-7). One of the problems with HT therapy is the acquisition of thermoresistance against heat stress (8-12). As the expression of HSPs is primarily mediated at the transcription level by HSF1 (17,18), it is predicted that downregulation of HSPs by the targeting of HSF1 will render tumors more sensitive to HT. Examples of the enhancement of HT sensitivity targeting HSF1 are summarized in Table III. It is well established that preconditioning of the cells with mild-HT results in an increase in HSP levels and

leads to the acquisition of thermoresistance to HT. However, McMillan *et al* (30) were the first show that targeted disruption of HSF1 abolished thermoresistance against lethal HT at 45˚C for 40 min in preheated (43˚C, 30 min) mouse embryonic fibroblast (MEF) cells from HSF1-KO mice. In the MEF cells, silencing HSF1 prevented induction of the expression of two inducible HSPs, Hsp27 and Hsp70, whereas the expression of the constitutive HSPs, Hsp60 and Hsc70, remained constant, suggesting that inducible HSPs are involved in acquired cellular resistance to HT (30). Consistent with this result, functional silencing by using KO mice (31,32) or a dominant-negative (DN) mutant (33) prevented the thermoresistance to HT in MEF and bone marrow progenitor (BMP) cells or breast cancer cells, respectively (Table III).

Of note, targeting of HSF1 has been suggested to enhance the sensitivity to HT under basic experimental conditions (29-38). We recently showed that silencing HSF1 using small interfering RNA (siRNA) enhances the mild HT (42˚C, 90 min) and HT (44˚C, 90 min) sensitivity in human OSCC cells (37). Significant enhancement of the HT sensitivity has also been observed in HSF1-silenced cervical cancer (35) and melanoma cells (29,36) treated with triptolide, an inhibitor of the human heat shock response, and shRNA for HSF1, respectively. In addition, although HT had only a slight effect on tumor growth in breast cancer cell xenografts, functional defect of HSF1 by its DN mutant in combination with HT had a lower tumorigenic capacity than the control tumors (33).

The effects of inhibition of HSH1 on the hyperthermochemotherapy have been reported (36,38). When HSF1 of cervical cancer cells was silenced by siRNA technology, the silencing in combination with hyperthermochemotherapy (treatment at 43˚C for 60 min plus cisplatin) markedly increased the level of apoptosis compared to hyperthermochemotherapy alone (38). In human melanoma cells, although HSF1 silencing did not sensitize to chemotherapy with dacarbazine, it significantly enhanced the sensitivity to this chemotherapy in combination with HT (42˚C, 60 min) (36). These results strongly suggest that silencing HSF1 can enhance the sensitivity to either HT or hyperthermochemotherapy. It is also noteworthy that combined treatment with HT and cisplatin effectively suppresses the activation of HSF1 in human glioblastoma cells (70).

5. Discussion

Although HT is considered to be a promising approach in cancer therapy, the thermoresistance due to the increase in HSPs in cancer cells remains a disadvantage, reducing the effects of HT in clinical treatment. The expression of HSPs is mainly regulated by HSF1 (17,18). HSPs (12,56,57) as well as HSF1 (19-26) are abundantly expressed in human cancer cells of various origins, and HSPs (12,56,57) and HSF1 (12,25-29) play critical roles in the initiation, proliferation and maintenance of cancer. Thus, the combination of HT and HSF1-targeting may be an attractive option and worthy of further investigation. As expected, the inhibition of functions of HSF1 by using gene targeting or HSF1 inhibitors was shown to reduce the acquisition of thermoresistance (30-33) and to sensitize tumors to HT-induced cell death (29-38). In the near future, targeting HSF1 (67,68) in combination with HT may come to be a promising approach for the treatment of cancer.

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