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Review Article

HSF1: a potential target for therapeutic intervention in cancer

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Abstract: Heat-Shock Transcription Factor 1 (HSF1) is an evolutionarily highly conserved transcription factor, which plays a key role in the heat-shock response of stressed cells and increases their survival by protecting them against environmental stressors. The last decade of research has revealed that HSF1 is chronically activated or overexpressed in a wide range of cancers, in which it facilitates cancer cell survival, malignant transformation, and cancer proliferation in model systems. HSF1 has a role in cellular homeostasis to transactive genes that encode heat-shock proteins. Apart from its role in reprogramming transcriptions, HSF1 acts as a remarkably potent modifier of signal modulation, stimulating kinase activity and regulating energy metabolism. In addition, HSF1 plays a pivotal role in the development of cancer tumor-free survival in whole animals. The high incidence of HSF1 overexpression in human tumors suggests that the protein is important in the carcinogenic process and therefore a potential candidate for therapeutic intervention. In the present review, we will summarize the current knowledge and highlights in the HSF1 field, discuss disrupting the influence of HSF1 physiological condition, received stimuli and the organismal control over HSF1 in cancer.

Keywords: HSF1, carcinogen, cancer

Introduction

The last century has witnessed a remarkable evolution of insights in the cellular activity and physiology. Among numerous changes most remarkable activity in stressed cells is the production of heat shock of stress proteins, which are a highly conserved set of proteins. The heat shock response is mediated by the heat shock element (HSE), characterized by increased expression of heat shock proteins (HSPs), which is an important homeostatic mechanism that maintains protein homeostasis in all organisms from bacteria to humans [1-4]. This protein has been proven to be essential for survival of all these organisms under stressful conditions. The heat shock factor (HSF) is an activator protein, and can be specifically bind to the HSE and regulate the HSP expression on stress stimulation [5]. In vertebrates and plants, HSF are grouped into four major families according to their biological characteristics as follows: HSF1, HSF2, HSF3 and HSF4. In addition, HSF1 and HSF2 are currently known to be existed in all vertebrates, and it was found that HSF3 is specific for avian species and HSF4 for mammals [6]. Among the HSF family, HSF1 has been considered a master regulator of the heat shock response in eukaryotes [7]. Work over the last three decades has further revealed the importance of HSF1 as a transcriptional activator of chaperones, ubiquitin and cochaperones as well as translational regulator and also as a coordinator of the expression of many transcriptional, mitotic determinants and signaling molecules [8-11]. This review summarizes the current knowledge regarding the potential of influence of HSF1 in cancer and evaluates the usefulness of using HSF1 as a biomarker in clinical practice.

The structure and activation of HSF1

A number of studies have shown that HSF1 is highly conserved in eukaryotic species. The

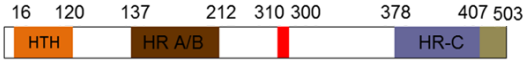

Figure 1. Graphic of the HSF1 protein structure. HTH, helix-turn-helix; HR, hydrophobic heptad repeats.

functional properties of HSF1 are linked to a highly conserved structural domains in these proteins (**Figure 1**): they contain an N-terminal DNA-binding helix-turn-helix (HTH) domain and an adjacent oligomerization domain that consists of an adjacent bipartite oligomerization domain (HR-A/B) [12-16]. It has been reported that spontaneous trimerization of HSF1 is allosterically inhibited by a C-terminal heptad repeat (HR-C), which folds back and forms intramolecular contacts with the oligomerization domain HR-A/B [15]. The transactivation domain of HSF1 is targeted by several proteins to link directly to the HSF1 activation and to direct HSF1 to specific target genes [17]. The activity of HSF1 is known to be complex mechanisms protein-protein interactions and post-translational modifications [18]. Currently, our understanding of the phosphorylated, trimerized, and translocation to the nucleus, induces chaperone gene, expression by binding to DNA sequence motifs known as HSEs [19]. Several reports have shown that phosphorylation of S326 and S230 have significantly increased the transcriptional capacity of HSF1 [20, 21]. Studies suggested the importance of HSF1 in transcriptional activation of chaperones, ubiquitin, cochaperones, translational regulators. It also coordinates the expression of many transcriptional, mitotic determinants and signaling molecules [8-11].

The remarkable property of HSF1 activation by stress, such as: heavy metals, exposure to oxidants, elevated temperatures, and bacterial or viral infections, and is found on the promoters of target genes within a few seconds of heat shock [22]. After the stresses, HSPs are expressed abundantly [23], and to deter unfolding of client proteins in the stress and to mediate refolding [24]. The proteome is constantly vulnerable to protein stress due to replicative, mitotic, proteotoxic, metabolic, oxidative stress and the expression of proteins with dominant aggregation prone conformations [25]. Tumors, is a consequence of the multitude of stressful conditions involves the opposite scenario-elevated HSP levels that closely related to malignancy [26]. Furthermore, cancer cells are mutation prone that correlate with metabolism, cell-cycle regulation, signaling, adhesion and translation. It is well known that HSF1 is an essential factor in the heat-shock response, in which it causes facilitates malignant transformation, proliferation, and cancer cell survival in model systems, however, many are remain elusive in malignancy.

Calderwood et al. and Ciocca et al. revealed that HSF1 can bind to 5'-promoter regions of all HSP genes and trigger rapid and abundant transcription of these stress protein genes [27, 28]. Importantly, HSP genes involve stress-induced formation of a HSF1 homotrimer. Furthermore, the posttranslational modifications (PTM) that convert the factor into an active form that lead to a nuclear localization and binds the promoter of HSP genes in a fruitful manner [29]. There are five main HSP families that is organized by molecular size and functional class, include the Hsp90 (HSPC), Hsp70 (HSPA), Hsp60 (HSPD), small HSP family (HSPB), and large HSP (HSPH) families [30], many of the families are thought to play key roles in cancer [27, 28]. HSF1 has been shown to involved in etiology of cancer by its multiple effects in: (i) Increased transcription and translation of HSPs; (ii) Regulation of translation [28]. However, the pathways of the induction of HSF1 in cancer are still under intense investigation.

The role of HSF1 in cell cycle

It has been shown that the transcriptional responses are involved in all phases of the cell cycle [31], and that the HSF1 is involved in the regulation of mitosis [32]. Additionally, the depletion of HSF1 in established human cancer lines strongly impaired the cell proliferation and survival [33-37]. Huang et al. [38] shown that HSF1 promotes polyploidy in p53 deficient cells, and expressions of dominant negative HSF1 delays the decay in cyclin B1. In addition, studies have suggested that silencing HSF1 by short hairpin RNA decreases cell proliferation in human melanoma cell lines [39]. Interestingly, there are several lines of evidence to suggest that Cdc20 binds directly to HSF1 and this interaction may thus be involved in the cell cycling. In a recent review, it has been suggested that HSF1 impacts a large array of healthy and malignant cells [9, 11, 40]. It has been shown that HSF1 can bind to a number of pro-

tein kinases to modulate a range of signal transduction pathways [38, 41, 42], leading to phosphorylation of HSF1 and potentially other substrates in cancer cells.

HSF1 relationship with cancer and therapeutic potential

A few recent studies have shown that elevated expression of the HSF1 can be associated with advanced stages in hepatocellular carcinoma, oral squamous cell carcinoma and breast cancer, suggesting HSF1 activity as a mechanistic link between stages in tumor progression and cancer cell invasion and metastasis [43-46]. Others have reported that HSF1 overexpression may contribute to mammary carcinoma with an Epithelial-mesenchymal transition (EMT) phenotype and ability to grow under anchorage independent conditions [47]. In a recent pilot study, increasing expressions of HSF1 in tumors was associated with the tumorigenesis in multiple animal models [33, 45, 48]. This may provide further mechanistic information on HSF1 activity and explain why expressions a higher level of HSF1 in tumors is a predictor of advanced stage events. This section summarizes the important roles of HSF1 in all reported types of cancer to date.

Breast cancer: Several recent studies have suggested that over-expression of HSF1 led to massive cell death of human breast cancer Bcap37 cells by promoting apoptosis induced by heat shock [49]. In addition, over-expression of HSF1 enhances the Adel55 killing Bcap37 cell line potential through increasing the viral replication both in vitro and in vivo [50]. Wang et al. [51] showed that HSF1 over-expression augment Breast cancer stem cells (CSC) phenotype in breast cancer cell lines, suggested that HSF1 may be one route to target CSCs in breast cancer. Interestingly, HSF1 depletion decreases the MICB expression leads to a reduction in the natural killer (NK) cell-mediated cytotoxicity, promotes tumor development, metastasis and therapy resistance [52]. Schilling et al. [53] demonstrated that indicated the Hsp90 inhibitor NVPAUY922 induced Hsp70 expression by inhibition of HSF1 activity and suppressed invasion and migration in human breast tumor cells. In in vitro tests, withaferin A induces apoptosis breast cancer cell lines down-regulation of protein expression [54]. There is increasing evidence that elevation of HSF1 expression elevated the risk of breast cancer among patients with Triple-Negative Breast Cancer (TNBC) and poor prognosis of HER2-/ER+ subtypes [55].

Schulz et al. [56] reported that over-expressed HER2 constitutively activates HSF1 promoted tumor proliferation via the PI3K-AKT-mTOR signaling pathway. Xi et al. [57] have shown that deletion of HSF1 in mice over-expressing ErbB2/Neu significantly reduces mammary metastasis and tumorigenesis via RAS/RAF/MEK/ERK1/2 signaling pathway with suppressed levels of HSP90 in complex with threonine-protein kinase (RAF1). In addition, HSF1 has been shown to be essential for HER2-induced tumorigenesis, might be a target of rs4919510:C.G in mature miR-608 and may influence HER2+breast cancer risk and tumor proliferation [58]. Zhao et al. [37] found that trastuzumab inhibits glycolysis induced tumor growth via down-regulation of HSF1in ErbB2+ breast cancer cells. Chou et al. [59] experiments suggested that activated HSF1 is a key factor in inducer of gene expression at the post transcriptional level in mammary cancer with influence translation of a range of proteins through its effects on RNA-binding protein HuR, microRNAs, and lincRNA-p21.

Studies demonstrated that HSF1 plays an important role in the pathogenesis of ErbB2-overexpressing cells by increased the expression of glycolysis-regulating molecules lactate dehydrogenase A (LDH-A), and inhibited human breast cancer MCF7 cells growth [48]. Kim et al. [60] found that it could be a more effective therapeutic approach for use in combination with Hsp90 inhibitor and silent information regulator two homologue one (SIRT1) inhibitor, and the approach would be aimed at the treatment of Hsp90 inhibitor-resistant multi-drug resistance (MDR) human breast cancer cell lines via down-regulation of HSF1. Yang et al. [61] reported that HSF1 plays an important role in breast cancer epithelial cells cycle progression via ERK1/2 MAPK and PI3K/Akt signaling pathways. Interestingly, another recently published study report that the natural isothiocyanate significantly inhibited the expression of HSF1, accompanied by cell-cycle arrest at G2/M phase and apoptosis in breast cancer cell lines [62]. Studies have reported that during HSF1-

overexpression, the autophagy-related 7 (ATG7) regulates the cytoprotective autophagy in breast cancer cells [63, 64]. In addition, breast cancer cell lines was transfected with HSF1d-202-316 exhibiting a highly resistant phenotype undergo apoptosis [65]. Wang et al. [66] suggested that mHSF1 sensitizes breast cancer cell line Bcap37 to hyperthermia by promoting the apoptotic process via enhancing JNK and caspase-3 pathways.

Studies evaluating the HSF1-MTA1 complex formation were induced to assemble on the chromatin of breast carcinoma cell MCF7, participate in repression of estrogen-dependent transcription [47, 67]. It was reported that HSF1 protein levels are up-regulated in response to expressions of JWA protein expression and enhance intracellular defenses against H_2O_2-induced oxidative damage in MCF7 cell lines [68]. Hansen et al. [69] showed that quercetin slightly affected HSF1 expression Hansen n in MDA-MB-231 breast cancer cells through regulation of HSF transcriptional activity. Thus, when taken together, these findings reinforce the carcinogenic and therapeutic potential of HSF1 in breast cancer, which could have important clinical implications for HSF1 use as a therapeutic target in breast cancer.

Colorectal cancers: HSF1 is highly expressed in colorectal cancer tissues, and its expression level correlates with the carcinogenesis of colorectal cancer [70]. Moreover, pHSF1 (Ser230) protein is strongly expressed in human colorectal carcinoma tissues and overexpression of HSF1 promotes an increase in DAPK mRNA level and induced apoptosis colorectal cancer cells [71]. Additionally, overexpression of HSF1 in Colo205 cells enhanced sensitivity to NK cell killing following mild thermal stress via up-regulation of molecularly imprinted colloidal array (MICA) expression [72]. Wales et al. [73] study showed that silencing HSF1 results in a significant enhancement of drug potency, which dependent on activation of ERK-1/2 mitogen-activated protein kinase pathway. Additionally, in vitro assays revealed that HCT-116 colorectal cancer cells were treated with the natural compound cantharidin, significantly suppressed the expression of HSF1 downstream target proteins: HSP70 and BCL2-associated athanogene 3 (BAG3) by blocking HSF1 binding to promoters [74]. It was observed that glutamine protects the ethanol induced intestinal barrier function in human epithelial colorectal carcinoma cells (Caco-2), by modulating HSF1-mediated Hsp70 protein expression [75].

It was reported that intra-dermal murine models of colorectal carcinoma (CT26) were treated with Adel55-cHSF1 showed sustained resistance upon re-challenge with autologous tumor cells, suggesting that cHSF1 is a better gene beneficial to prevent tumor recurrence for neoadjuvant immunotherapy [76]. Moreover, fisetin abolished HSF1 target proteins including: HSP70, HSP27 and BAG3 activity with an IC_{50} of 14 μM, led to HCT-116 cancer cells proliferation and apoptosis [77]. Additionally, mixed-lineage leukemia 1 (MLL1) depletion is combined with HSP90 inhibition through block a HSF1-mediated feedback mechanism inhibits HCT-116 cell proliferation [78]. Observations by Jacobs et al. [79] indicated that HSF1-mediated BAG3 expression impairs apoptosis treatment with 4-hydroxynonenal through stabilization of Bcl-2 proteins in colon cancer cells. These findings imply that target HSF1 gene attracted considerable interest for further preclinical studies to challenge the current paradigm available for treatment of colon cancer which is characterized by elevated levels of HSF1 protein.

Skin tumor: HSF1 has been shown to be essential for the proliferation and survival of the immortalized Hsf1+/+ MEF cells [33]. Kourtis et al. [80] have shown that the ubiquitin ligase FBXW7 α interacts with HSF1 correlates with increased metastatic potential and disease progression in human melanoma. Additionally, MLL1 regulates HSF1-target genes upon HSP90 inhibition inhibits A375 and A2058 melanoma cell line proliferation [78]. The results indicate that HSF1 have shown its mechanism of action as a carcinogenic in skin tumor.

Glioblastoma: HSF1 has also been investigated in correlated with forkhead box transcription factor (FoxM1) overexpression in human glioblastoma specimens. Additionally, study showed that HSF1 bound to FoxM1 promoter induced FoxM1 promoter activity enhanced cell survival under lethal heat shock stress condition in mouse embryo fibroblast cells. It was reported that Ectopic expression of BAG3 leads to the activation of an HSF1-driven stress response, results in a remarkable increase in colony for-

mation capacity in glioblastoma cells [81]. Recently Oh et al. [82] demonstrated that HSF1 plays an important role in induces HSP72 expression thus activating the Rac1-NADPH oxidase-independent ROS production pathway in C6 glioma cell. Liu et al. [83] assumed that glioma cells were treated with PS-341-induced cell damage by upregulated HSF1 expression. Grogan et al. [84] discovered that withaferin A prevented glioblastoma multiforme cell proliferation by dose-dependent G2/M cell cycle arrest and cell death through the Akt/mTOR apoptotic pathway, through decreased the expression of HSF1. Additionally the nature of H-7 (1-(5-isoquinolinesulfonyl)-2-methylpiperazine dihydrochloride) was significantly suppressed HSF1 gene expression, which dependent on cyclic AMP-dependent PK, calcium-dependent PK, and cyclic GMP-dependent PK, in in a human glioblastoma cell line (A-172) [85]. The results demonstrated that HSF1 as a potential of carcinogenic in glioblastoma, suggested that HSF1 can act as therapeutic targets for glioblastoma.

Head and neck cancers: It was reported that p-HSF1 is highly expressed in oral squamous cell cancer (OSCC) tissues, and its expression level correlates with advanced clinical stage, metastasis and recurrence of the patients [86]. This suggests that HSF1 mediates the metastatic potential of OSCC cells and also points to HSF1 as a potential therapeutic target for the clinical management of head and neck cancer.

Hepatic cancers: A more recent study showed a high prevalence of total and phosphorylated HSF1 protein, mRNA expression, induces DNA-PKcs upregulation via the activation of the MAPK/JNK/AP-1 axis, which is significantly correlated with aggressive features and unfavorable prognosis in hepatocellular carcinoma (HCC). Additionally, HSF1 high expression in peritumoral tissue and significantly correlate with poorer overall survival and early recurrence [87]. Recently, in vitro tests reported that HSF1 is overexpressed in HCC at both mRNA and protein level, and HSF1 knockdown could inhibit the proliferation of Hep3B [88]. It was report that HSF1 is over-expressed in HCC with adverse pathologic and clinical features, and was capable of promoting HepG2, MHCC97-L and HCCLM3 cell lines migration, invasion in vitro and in vivo by facilitating the expression of p-Hsp 27 [43]. In addition, overexpression of HSF1 led to induction of insulin sensitivity and activation of AMP-activated protein kinase, suppressed cancer progression, mitigating adverse effects of carcinogens on hepatic metabolism [45]. Interestingly, down-regulated of heat-induced p53/HSF1 led to the inhibition of Hsp70 protein expression, induced carboplatin-triggered HepG2 cells death by restoring the sensitivity of heat-stressed [89].

Chuma et al. [90] have shown that knockdown HSF1 reduced tumorigenesis and appeared attributable to increased apoptosis and decreased proliferation in KYN2 HCC cells. In vitro tests, the collaboration of HSF1 and APOBEC3B cytidine deaminase promoted the growth of neoplastic human HepG2 liver cells [91]. It was demonstrated that, HSF1 activated miR-135b expression via kazal motifs and ecotropic viral integration site 5 pathway, promoted HCC cell motility and invasiveness [92]. Lee et al. [93] results indicate that mitochondrial respiratory defects induced Cln-1-mediated SNU hepatoma cells invasiveness through reactive oxygen species (ROS)-mediated HSF1 activation. Additionally, the phosphorylation of HSF1/S326 can be activated by glucose-mTOR pathway via upregulate the expression of HSF1-s downstream alpha B-crystallin and Hsp70, promoted plc/prf5 cell proliferation [94]. Above in vitro and in vivo trials have demonstrated that HSF1 acts as an oncoprotein can be expected to be expanded as research progresses, and target HSF1 therapy may be an important modality to treat HCC.

Leukemia: Previous description has shown that knockdown of HSF1 abrogated the colony formation capacity of the acute myeloid leukemia (AML) cancer stem cells (CSCs), through HSP90-mediated AKT activation [95]. Additionally, inhibition of HSF1 resulted in reduced the expression level of FOP2-FGFR1 could lead to block the oncoprotein induced proliferation of KG-1a leukemic cells [96]. Interestingly, resveratrol down-regulation of Hsp70 correlated with a diminished presence of HSF1 induced apoptosis in K562 cells [97]. Takaki et al. [98] reported that leukemia inhibitory factor (LIF) expression are lacking in HSF1-null mice. It was demonstrated that overexpression of HSF1 in CLL sensitive to triptolide treatment induces apoptosis in cultured through reduced associa-

tion of HSP90 with co-chaperone cell division cycle [99]. There is also some evidence suggesting that silent information regulator two homologue one (SIRT1) depletion caused significant down-regulation of HSF1 led to the sensitization of human chronic myeloid leukemia K562 cells to Hsp90 inhibitor by SIRT1 inhibitor [100]. It has been shown that geldanamycin induced the phosphorylation of HSF1 stimulates HSP70 protein expression in the human erythroleukemic cell line K562 [101, 102]. Sarkar et al. [67] showed that overexpression of HSF1, HSP27, HSP70, HSP90, and histone deacetylase 6 (HDAC6) were down-regulated by curcumin, which resulted in cell cycle arrest at the G2/M stage, leading to apoptosis in two different leukemia cell lines (K-562 and HL-60) [103]. It can be suggested that HSF1 is involved in leukemia metastasis, and HSF1 treatment may be used as an alternative treatment against leukemia.

Lung cancers: It has been shown that HSF1 is highly expressed in non-small cell lung cancer tissues, and its expression level correlates with node metastasis of the patients [104]. Both in vitro and in vivo tests, Coxsackievirus B3 (CVB3) replication and leads to phosphorylation of HSF1 enhanced Hsp70-1 transcription [105]. Chang et al. [106] shown that human non-small cell lung cancer H460 cells were treated with geldanamycin induces HSF1 activation and HSP70 protein expression. Kim et al. [107] reported that Coniferyl aldehyde protected normal lung tissues from the therapeutic irradiation by increased expression of the HSF1 protein, but not in A549 lung orthotopic lung tumor model. Ma et al. [108] demonstrated that HSF1 as a regulator of energy metabolism through activation of the PGC1α-dependent metabolic program, represents a potential strategy for treating obesity and metabolic syndrome. In addition, it has been shown that 2,4-Bis(4-hydroxybenzyl)phenol inhibited HSF1 activity with decreased levels of hsp27 and hsp70, which induced growth arrest and apoptosis of NCI-H460 human lung cancer cells [109]. These results indicate that HSF1 is a potential anti-metastatic and anti-invasive agent, and may be useful in gene therapy strategies for the treatment lung cancer.

Prostate cancers: It was also shown that prostate cancer shows a high prevalence of HSF1 expression, which is significantly correlated with aggressive cell growth, differentiation, or apoptosis [110]. In addition, HSF1 plays an important role in the human prostate cancer PC-3 cells influences cell cycle behavior and progression via mitosis and promotes the development of the aneuploid state, by regulation of cyclin B1 degradation [111]. Other authors [112], demonstrating that in in vivo experiments, severe hypothermia and rewarming increased expression of HSF1 mRNA level in rat ventral prostate were quantified hypothermia and in rewarming, which promote proliferation of cells in healthy rat prostate tissue through ErbB signaling pathway. This suggests that targeting the destruction of HSF1 expression maybe provides a novel specific lead into prostate cancer therapy.

Lymphoma: Recent studies have reported that AG490 (JAK/STAT inhibitor) induced a complete autophagy by reduction of HSP70 and HSF1 protein expression in primary effusion lymphoma (PEL) cells [113]. Moreover, chelerythrine reductions the expression of HSF1 and hsp70 in Dalton's lymphoma (DL) cells by PKC phosphorylation [114]. This finding also provides a significant cue to lymphoma treatment, by targeting the destruction of HSF1 expression.

Pancreatic cancer: Recently, it has been demonstrated that downregulation of HSF1 expression induces apoptosis via caspase-3 activation in pancreatic cancer (MIA PaCa-2 and S2-013) and cholangiocarcinoma (KMBC and KMCH) cell lines [115]. In addition, triptolide induced apoptotic cell death through decreased levels of hsp70 and HSF1 in pancreatic cancer cell lines [116, 117]. Furthermore, studies shown that active hexose-correlated compound down-regulated hsp27 via reduction of the HSF1 in human pancreatic cancer cells [118]. There is also some evidence suggesting that HSF1 reinforce the carcinogenic in pancreatic cancer, and target HSF1 may be a potent and novel therapy for treatment of patients with pancreatic cancer.

Cervical cancer: It was shown that HSF1 was essential for the transcriptional regulator of dystrophin Dp71 expression in human cervical carcinoma HeLa cells, suggesting that target HSF1 could be effective in future therapeutic strategies in cervical cancer [119].

Perspectives

In summary, HSF1 is involved in a multitude of physiological processes and associated with the development of a multitude of cancer types. Undoubtedly, these effects include: HSF1 controls the cell cycle, the signaling and the mediation of tumor progression; therefore, the role of pleiotropic and essential properties in carcinogenesis and tumor progression of HSF1 as a predictor of beneficial target in therapy should be thoroughly evaluated for different cancer types and treatment regimens.

Finally, although our understanding of the importance of HSF1 activity has driven a transcriptional program to support highly malignant human cancers, however, a number of essential aspects of HSF1 remain to be elucidated, and investigations regarding HSF1 cannot yet be applied in the clinic. In addition, there is still a long road ahead before HSF1 determination can leave the laboratory bench and can be deployed in cancer therapy. At the moment, HSF1 as a carcinogen that may prove to be clinically relevant in the future, however a large number of well-designed studies to test for suitable in vivo properties are needed before this can become a reality.

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Disclosure of conflict of interest

None.

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