Small Heat Shock Proteins in Cancer Therapy

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Small heat shock proteins (sHSPs) are ubiquitous ATP-independent chaperones that play essential roles in response to cellular stresses and protein homeostasis. sHSPs are ubiquitously expressed in numerous types of tumors, and their expression is closely associated with cancer progression. sHSPs have been suggested to control a diverse range of cancer functions, including tumorigenesis, cell growth, apoptosis, metastasis, and chemoresistance, as well as regulation of cancer stem cell properties.

Keywords: sHSPs ; cancer ; cancer stem cells ; cancer therapy

1. Anticancer Drugs Targeting sHSPs

As a majority of clinical and preclinical findings indicate sHSPs as a promising therapeutic target in cancer, a number of drugs or inhibitors have been reported and utilized to interrogate sHSPs' roles in cancer. The reports are mainly focused on HspB1 as a molecular target for cancer therapy. Hence, in the present subsection, the drugs targeting HspB1 are analyzed in more detail. Although several drugs or compounds for other sHSPs in cancer therapy have been described, other sHSPs are omitted here because no selective inhibitors targeting these sHSPs have been reported.

The drugs aimed at reducing HspB1 expression or inhibiting its actions in cancer therapy (**Table 1**). Small molecule inhibitors (RP101, quercetin, J2, ovatodiolide, and methyl antcinate) bind to the HspB1 protein and inhibit its function. Another strategy utilizes peptide aptamers (PA11, PA50) that bind directly to the protein and inhibit its oligomerization or dimerization. Moreover, the third approach is antisense oligonucleotide (OGX-427), which targets HspB1 mRNA and prevents translation of the protein.

Table 1. Summary of reported cancer drugs targeting HspB1.

Types	Names	Mechanism	Binding Sites	Reference
Small Molecules	RP101	Binds to HspB1 protein and inhibits HspB1 function	Phe29 and Phe33	[1][2][3][4][5]
	quercetin		No data available	[6][7][8][9][10][11][12][13][14][15]
	J2		Cysteine thiol group	[16]
	ovatodiolide		No data available	[17]
	methyl antcinate		No data available	[18]
Peptide Aptamers	PA11	Binds to HspB1 protein and inhibits its oligomerization or dimerization	No data available	[19][20][21]
	PA50		No data available	
Antisence Oligonucleotide	OGX-427	Binds to HspB1 mRNA and prevents translation of the protein	No data available	[22][23][24][25][26]

Several small molecule inhibitors targeting HspB1 are currently under development: RP101, quercetin, J2, ovatodiolide, and methyl antcinate. RP101 (also known as bromovinyldeoxyuridine, BVDU, or brivudine) is a nucleoside that inhibits HspB1 function via binding with Phe29 and Phe33 of HspB1. RP101 functions as a chemo-sensitizing agent that inhibits the resistance and potentiates the effects of many chemotherapeutic drugs including mitomycin [1][2], gemcitabine [2][3],

cisplatin [2][3], and cyclophosphamide [2]. In clinical studies, RP101 [2][3] or RP101 with gemcitabine [3][4] increased the overall survival rate of pancreatic cancer patients. However, overdosing of RP101 caused increased toxic side effects of gemcitabine in some patients [2], and new second-generation candidates of RP101 have been identified and are being developed for further evaluation [5]. Quercetin is a plant-derived bioflavonoid with anticancer properties [8]. It suppresses the HSF1-dependent induction of the Hsps and shows antitumor effects in gastric, oral, lymphomas, prostate, colorectal, breast, pancreatic, liver, and lung cancer cell lines and various cancer stem cells [9][10][11][12]. Quercetin can act as a chemo-sensitizer, and it enhances the antitumor effects of first-line chemotherapeutic drugs such as doxorubicin, gemcitabine, 5-fluorouracil, and cisplatin [13][14]. Interestingly, besides its inhibitory effect on HspB1 expression, quercetin can suppress HspB1 activity by impairing its phosphorylation in CSCs [7]. Despite studies showing that quercetin can be a suitable agent for cancer treatment, there are no ongoing anticancer trials for quercetin. J2, a synthetic chromone compound, can induce the crosslinking of HspB1 protein and form HspB1 abnormal dimerization, thereby inhibiting its functions [15]. Recently, ovatodiolide [6] and methyl antcinate [16], two plant-derived compounds, have been reported to decrease HspB1 protein expression in breast CSCs and inhibit CSCs. It has to be elucidated whether these compounds are clinically applicable against breast cancer.

The second approach to targeting HspB1 is the use of specific peptides, which are called peptide aptamers, to bind the protein and inhibit the functions of HspB1. Peptide aptamers are short peptides that are designed to bind to specific protein domains and disrupt the protein function. Recent research showed that two peptide aptamers, PA11 and PA50, can specifically bind to HspB1, inhibiting HspB1 dimerization or oligomerization, thereby negatively modulating the functions of HspB1 [17]. These peptide aptamers are reported to show antitumor effects in vitro [17] and in vivo [18]. Similar to the small molecule inhibitors of HspB1, a peptide aptamer is always more effective when used with other anticancer drugs than when used alone. More efforts are needed to promote the preclinical and clinical application of peptide aptamers and provide a potential application to cancer therapy.

The third approach utilizes antisense oligonucleotide (ASO) targeting HspB1 mRNA, and OGX-427, which prevents the expression of HspB1 protein. OGX-427 reduced xenograft tumor growth when used in combination with chloroquine [19] or gemcitabine, respectively [20], compared to treatment with the drug alone. The Phase I study of dose-escalation OGX-427 in prostate, bladder, breast, and lung cancers showed that OGX-427 was well tolerated at a high dose (1000 mg), and it can decrease tumor marker expression and the number of circulating tumor cells (CTCs) in patients with prostate and ovarian cancers [21]. In a Phase II trial for castrate-resistant prostate cancer (CRPC), 71% of patients treated with OGX-427 and prednisone were progression-free at 12 weeks, compared to 40% of patients treated with prednisone alone [22]. However, in another Phase II trial for metastatic non-small-cell lung cancer (NSCLC), the addition of OGX-427 to the carboplatin–pemetrexed regimen did not improve outcomes and the efficacy of first-line chemotherapy for patients [23]. More clinical studies are needed to evaluate the efficacy and side effects of OGX-427 as a combinational clinical therapy in the treatment of different cancer patients.

2. sHSPs-Based Cancer Therapy

Other than a molecular target for cancer therapy, sHsps have been reported to be used as a multifunctional scaffold for the targeted therapeutic and imaging systems in cancers. The naturally occurring small heat shock protein 16.5, which originates from *Methanocaldococcus jannaschii*, is reported to form a cage-like structure to act as multifunctional biomaterials. The genetically and chemically modified Hsp16.5 cages, Cy5.5-HspDEVD-BHQ3, were developed for imaging caspase activity in vitro and in vivo [24]. Thus, these sHsp cages may provide efficient imaging agent carriers to monitor the therapeutic evaluation by imaging caspase activity within tumors. Similarly, Hsp16.5-based nanocages, conjugated with gadolinium (III)-chelated agents and iRGD peptides, were developed for the diagnosis of pancreatic cancers by magnetic resonance imaging (MRI) [25]. It showed that sHsps have great potential in the diagnosis of cancers as a carrier to construct a specific and sensitive MRI contrast agent. Moreover, Hsp16.5-based cages carrying doxorubicin (an anticancer agent) were tested in various cancer cell lines [26] and could provide a useful drug delivery system in cancer therapy. As sHsps cages have good biocompatibility, biodegradability, and easy fabrication, they may be promising as biomedical materials for drug or imaging agent delivery in cancer therapy and other biomedical applications.

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