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Targeting heat shock response pathways to treat pancreatic cancer

Yi Xia[1], Palma Rocchi[2], Juan L. Iovanna[2] and Ling Peng[1]

[1] Centre Interdisciplinaire de Nanoscience de Marseille, Département de Chimie, CNRS UPR 3118, 163, avenue de Luminy, 13288 Marseille, France
[2] INSERM U624, «Stress Cellulaire», 163, avenue de Luminy, 13288 Marseille, France

Pancreatic cancer belongs to the group of extremely aggressive human cancers; conventional cancer treatments have little impact. Increasing understanding of the pathways associated with pancreatic cancer progression has enabled the development of targeted therapy on this cancer. Heat shock proteins (HSPs) and related heat shock response (HSR) pathways control multiple important oncogenic pathways for pancreatic cancer development. Consequently, they represent promising novel targets for pancreatic cancer therapy. Various strategies have been proposed and elaborated to target HSPs/HSR in pancreatic cancer with the corresponding modulators, the details of which are highlighted in this review.

Introduction

Pancreatic cancer belongs to the most lethal and devastating human cancers owing to its poor diagnosis, lack of effective therapies and rapid development of drug resistance [1]. Although pancreatic cancer accounts for only 3% of all cancers, it is the leading cause of cancer death in Western countries. Conventional treatments have little impact on this disease. Surgical resection followed by adjuvant treatment with both chemotherapy and radiation offers the best possibility of curing pancreatic cancer for a small percentage of patients at early-stage disease, whereas chemotherapy based on gemcitabine remains the standard of care for the majority of patients with advanced pancreatic cancer that precludes surgery [1].

Gemcitabine is a nucleoside drug, which exerts its anticancer activity mainly by inhibiting DNA synthesis alongside other possible modes of action [2]. However, gemcitabine is only moderately effective for pancreatic cancer, yielding a mere 12% response rate, a median survival period of five months and a five-year survival rate as low as 3%. Attempts to increase the efficacy of gemcitabine by modulating pharmacokinetic parameters or using combined treatments with a second cytotoxic agent, such as cisplatin, oxaliplatin, 5-fluorouracil (5-FU) or capecitabine, have been largely unsuccessful [3]. Consequently, there is an urgent need to explore new drug candidates with novel modes of action to combat pancreatic cancer.

Over the past few decades, considerable research has focused on understanding the mechanisms behind pancreatic cancer pathogenesis and the related molecular cascades [4,5]. Targeted therapies aimed at the regulation of molecules in pancreatic carcinogenesis, the activation of tumor suppressor genes and the inactivation of oncogenes have been exploited for pancreatic cancer treatment and have brought about several therapeutic advances [4,6]. Several drugs have been elaborated to target these pathways, some of which have been advanced to clinical trials. However, the clinical results have been rather disappointing. Although gemcitabine combined with erlotinib resulted in a small but significant improvement, the outcome in patients was not related to the expected targeted pathway and requires further detailed clarification [7]. Therefore, the discovery of novel molecular targets and the development of multitarget strategies constitutes an emerging and challenging issue for pancreatic cancer treatment.

It is well known that the intrinsic resistance to cytotoxic and therapeutic agents contributes to the extremely aggressive nature of pancreatic cancer [1,4,8]. Therefore, therapies targeting cellular pathways essential for drug resistance are considered to hold great promise for pancreatic cancer treatment. Research on different cancer forms over the past decade has revealed that heat shock proteins (HSPs), molecular chaperones with strong cytoprotective

Corresponding author:. Peng, L. (ling.peng@univmed.fr)

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and antiapoptotic properties, have crucial roles in tumor progression and drug resistance [9–12]. However, the direct targeting of HSPs for pancreatic cancer treatment is still at the exploratory stage. Meanwhile, an ever increasing amount of evidence shows the enormous potential of targeting HSPs in pancreatic cancer treatment, the details of which will be highlighted below.

Heat shock proteins and heat shock response pathways

HSPs, also called stress proteins, are a family of highly homologous proteins present in all species. As molecular chaperones, HSPs function to regulate protein folding, transport, translocation and assembly. Cells usually overexpress HSPs in response to a multitude of insults, such as heat, heavy metals, oxidative stress or cytotoxic agents among others, to prevent cell death and enable cells to survive under otherwise stressful and lethal conditions (Fig. 1) [9]. The rapid induction of HSPs in response to stress results from a variety of genetic and biochemical events is collectively referred to as the heat shock response (HSR) [13]. Dysregulation of the HSR has proven to be associated with pathological development. Considering its prosurvival nature, the HSR has an important role in carcinogenesis. The HSR is mediated at the transcriptional level by heat shock factors (HSFs), the upstream transcriptional regulators of HSPs [14]. Among the HSF family, HSF1 is crucial for the HSR. It not only regulates the expression of HSPs but also orchestrates the survival of cells [15,16]. Collectively, HSPs and HSFs that form the HSR network are upregulated in cancer to promote the continuous protein translation, cellular proliferation and invasion required for cancer cell survival and development (Fig. 1).

Although normal cells also express HSPs under stressful conditions, it appears that their uncontrolled expression in cancer cells has a key role in tumor progression and in drug resistance [17]. Because the microenvironment of tumors is usually hostile, characterized by hypoxia and acidity, the ability of HSPs to maintain protein homoeostasis can enable the malignant cells to survive and grow even in growth factor-deprived conditions. The expression of several HSPs has been shown to differ in pancreatic cancer compared with normal pancreas or chronic pancreatitis [18]. This finding suggests the specific role of HSPs in the pathogenesis of pancreatic cancer, and highlights the interest in targeting HSPs as a promising therapeutic approach.

The mammalian HSPs are classified into six groups according to their molecular size: HSP100, HSP90, HSP70, HSP60, HSP40 and small HSPs (15–30 kDa) including HSP27. Among them, HSP90,

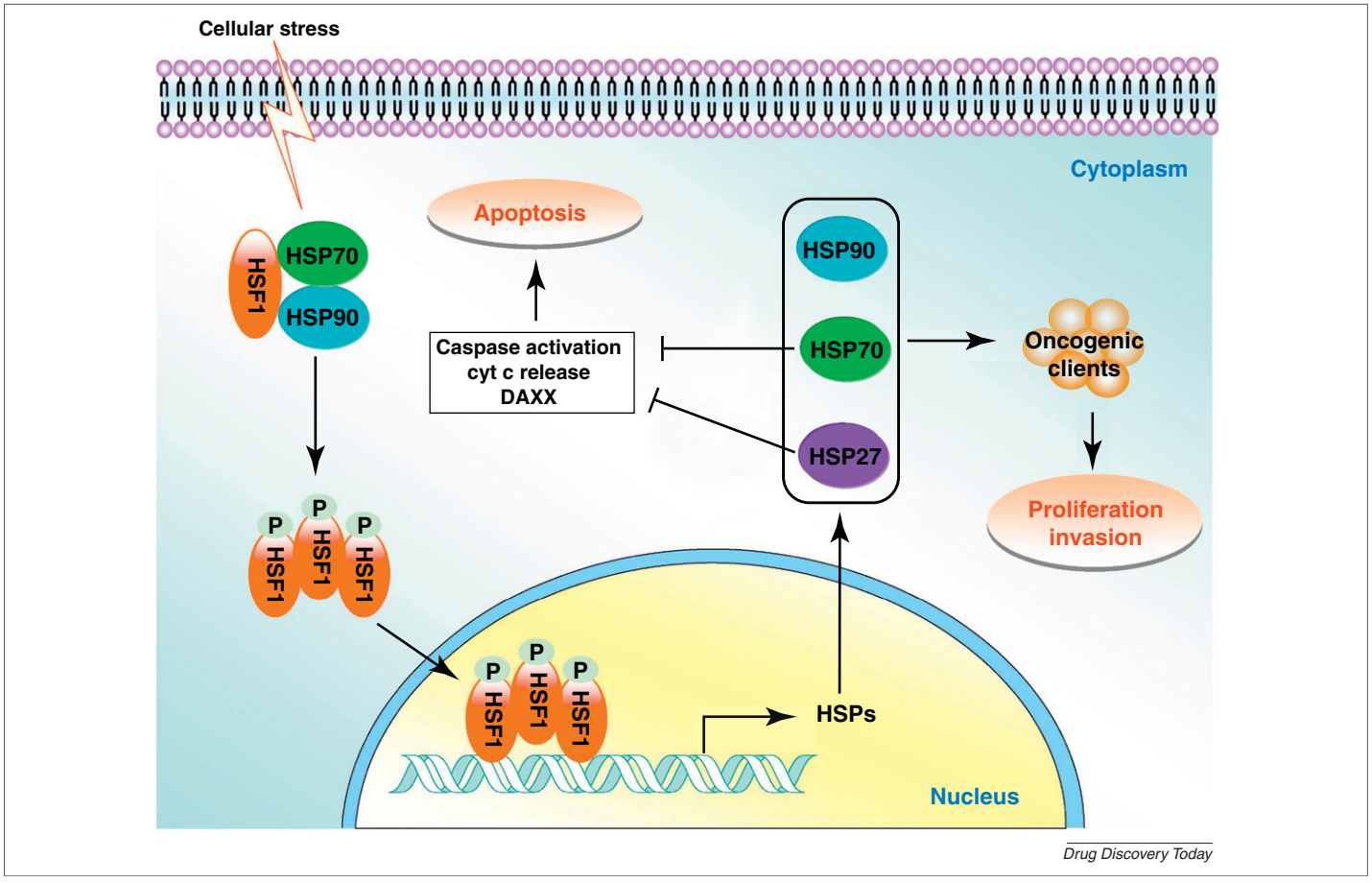

FIGURE 1

Heat shock factor 1 and heat shock proteins in the regulation of apoptosis and proliferation. The exterior cellular stress leads to the dissociation of HSP90 and HSP70 from HSF1 and the activation of HSF1. Then the monomeric HSF1 trimerizes, phosphorylates and translocates to the nucleus. In the nucleus, HSF1 can activate the HSP genes (e.g. HSP27, HSP70 and HSP90). HSP27 and HSP70 inhibit the apoptosis by repressing caspase activation, cytochrome (cyt) c release and DAXX. All the HSPs chaperon the normal function of their client proteins. Some of these client proteins possess of oncogenic properties, which promote the proliferation and invasion of tumor. DAXX: death-domain-associated protein 6; HSF: heat shock factor; HSP: heat shock protein.

HSP70 and HSP27 chaperones are particularly attractive as anticancer targets, because they are master regulators of multiple oncoproteins (particularly their client proteins) and have been demonstrated to have tumorigenic properties [19] (Fig. 1). Moreover, the expression of these three HSPs is mainly regulated by HSFs among which HSF1 predominates [15] (Fig. 1). Consequently, the targeting of HSF1 can be considered as a potentially efficient strategy to combat pancreatic cancer.

Targeting HSPs and HSR pathways in pancreatic cancer

The link between the HSR and cancer development was revealed more than 20 years ago. Today, the targeting of HSPs and the HSR pathways is emerging as the leading cancer therapy thanks to the increasing understanding of the structural and biological functions of HSPs. Different inhibitors of the HSR have been developed in the past decade [20]. In this article, we focus specifically on the recent progress in small molecules which target HSP27, HSP70,

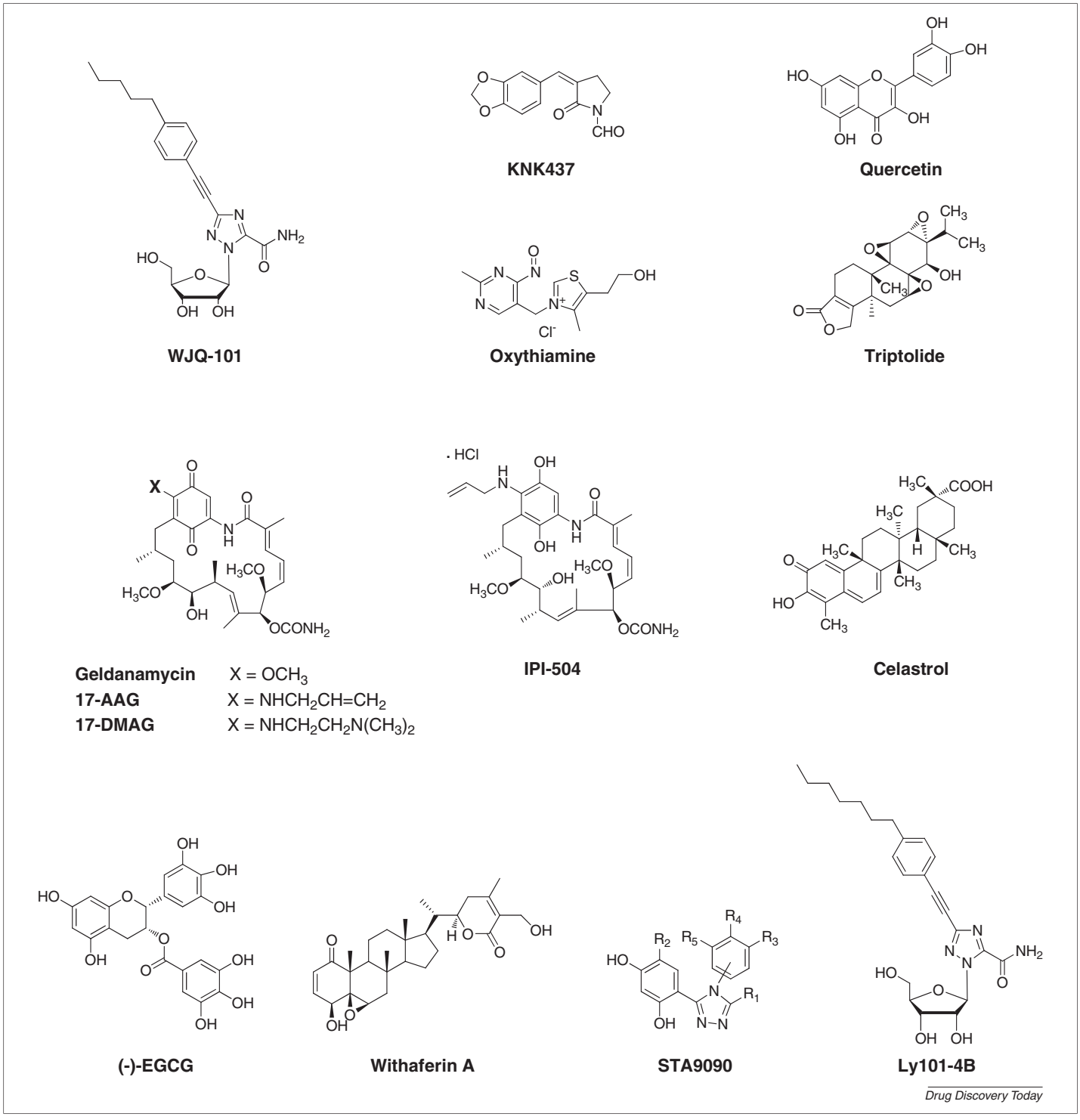

FIGURE 2

Reported small molecules targeting heat shock proteins and heat shock factor 1 in pancreatic cancer.

TABLE 1

Small molecules targeting HSR in pancreatic cancer at preclinical and clinical stage

Drug	Targets	Development status	Route of administration	Refs
WJQ-101	HSP27	Preclinical	i.p.	[32,33]
Quercetin	HSP70	Preclinical	i.p.	[41]
Tripolide	HSP70	Preclinical	i.p.	[43,45]
17-AAG	HSP90	Phase II[a]	i.v.	[51]
IPI-504	HSP90	Preclinical	i.p.	[56]
STA 9090	HSP90	Phase II	i.v.	http://www.clinicaltrials.gov
Celastrol	HSP90	Preclinical	i.p.	[58]
Withaferin A	HSP90	Preclinical	i.p.	[59]
Ly101-4B	HSF1	Preclinical	i.p.	[32]

i.p.: intraperitoneal; i.v.: intravenous.
[a] 17-AAG in combination with gemcitabine was used in clinical trials to treat pancreatic cancer.

HSP90 and HSF1 to treat pancreatic cancer (Fig. 2 and Table 1), together with the HSPs as vaccine adjuvants for immunotherapy.

HSP27

HSP27 is an ATP-independent small chaperone, it functions to protect against protein aggregation and can form oligomers in response to stress, which is modulated by its phosphorylation state (Fig. 3) [11]. It displays enhanced synthesis in response to stress and has antiapoptotic properties [21]. The basal expression of this HSP in cancer cells is abnormally high, suggesting the importance of this protein in cancer diagnosis [22]. This aberrant expression has also been associated with increased tumorigenicity and treatment resistance, and hence poor prognosis. Inhibiting this HSP can increase cell sensitivity to drugs and can thus overcome drug resistance. Antisense oligonucleotides and small interfering (si)RNA developed to downregulate HSP27 have been demonstrated to produce effective anticancer activity [23–26], and the antisense oligonucleotides have already entered into clinical trials for several human cancers, including lung, breast, prostate, bladder and ovarian cancers [27,28].

The knockdown of HSP27 by siRNA has been reported to restore the sensitivity to gemcitabine in drug-resistant pancreatic cancer cells [29]. In addition, increased HSP27 expression in tumor specimens suggested the important role of HSP27 in the resistance shown by patients with pancreatic cancer to gemcitabine [29]. Thus, HSP27 has also been considered as a possible biomarker for predicting the resistant response of pancreatic cancer to chemotherapy. Moreover, the analysis of serum from patients and healthy controls has further validated HSP27 as a potential serum marker thereby advancing the clinical status of HSP27 for pancreatic cancer [30]. Besides siRNA, interferon-γ was also found to downregulate HSP27 and produce effective antiproliferation activity in drug-resistant pancreatic cancer cells [31]. These findings collectively demonstrate the general utility and importance of downregulating HSP27 in treating drug-resistant pancreatic cancer.

In 2009, our group developed a triazole nucleoside analog called WJQ-101 (Fig. 2), which could effectively downregulate HSP27, resulting in apoptosis-induced anticancer activity against drug-resistant pancreatic cancer both *in vitro* and in a xenografted mice model [32,33]. This compound represents the first small-molecular anticancer lead with such a mode of action to treat pancreatic cancer. KNK437, a benzylidene lactam [34] (Fig. 2) was recently used to downregulate HSP27 with the aim to enhance the antitumor cytotoxic effect of gemcitabine in chemoresistant pancreatic cancer cell lines [35]. However, KNK437 treatment alone did not elicit significant anticancer activity. This might limit its further application on pancreatic cancer. In addition, both WJQ-101 and KNK437 displayed their inhibitory activity on HSP27 at high concentrations (more than 50 μM), which might increase the possibility of off-target effects. Consequently, the specificity and detailed mechanism of action for both WJQ-101 and KNK437 need further detailed investigation (Fig. 3).

Recent research has shown that not only the total protein level of HSP27 but also that of phosphorylated HSP27, might contribute to the antiproliferative and antiapoptotic properties of drug-resistant pancreatic cancer cells [36]. Thus, inhibiting the phosphorylated form of HSP27 can be another alternative. It has been reported that oxythiamine (Fig. 2), an inhibitor on pancreatic cancer cell proliferation, markedly suppressed the expression of phosphorylated HSP27, whereas the total level of HSP27 remained unchanged in drug-resistant pancreatic cancer MiaPaCa-2 cells (Fig. 3) [37]. Although the exact role is not yet completely understood, development of specific and efficient drugs that modulate HSP27 phosphorylation might offer insightful understanding [38].

Collectively, the regulation of HSP27 by different therapeutic strategies, especially those using small-molecular inhibitors, is an attractive approach to treating pancreatic cancer. However, the complicated molecular composition and the lack of knowledge on its structure restrict both the high throughput screening and rational design of specific agents targeting HSP27. Thus, the quest for more specific and efficacious drug candidates able to target HSP27 in the treatment of pancreatic cancer remains extremely challenging.

HSP70

Like HSP27, HSP70 is another highly stress-inducible HSP with strong cytoprotective properties [11]. It contains an ATPase domain, which is connected to a peptide-binding domain (PBD) through a hydrophobic linker (Fig. 3), and both domains

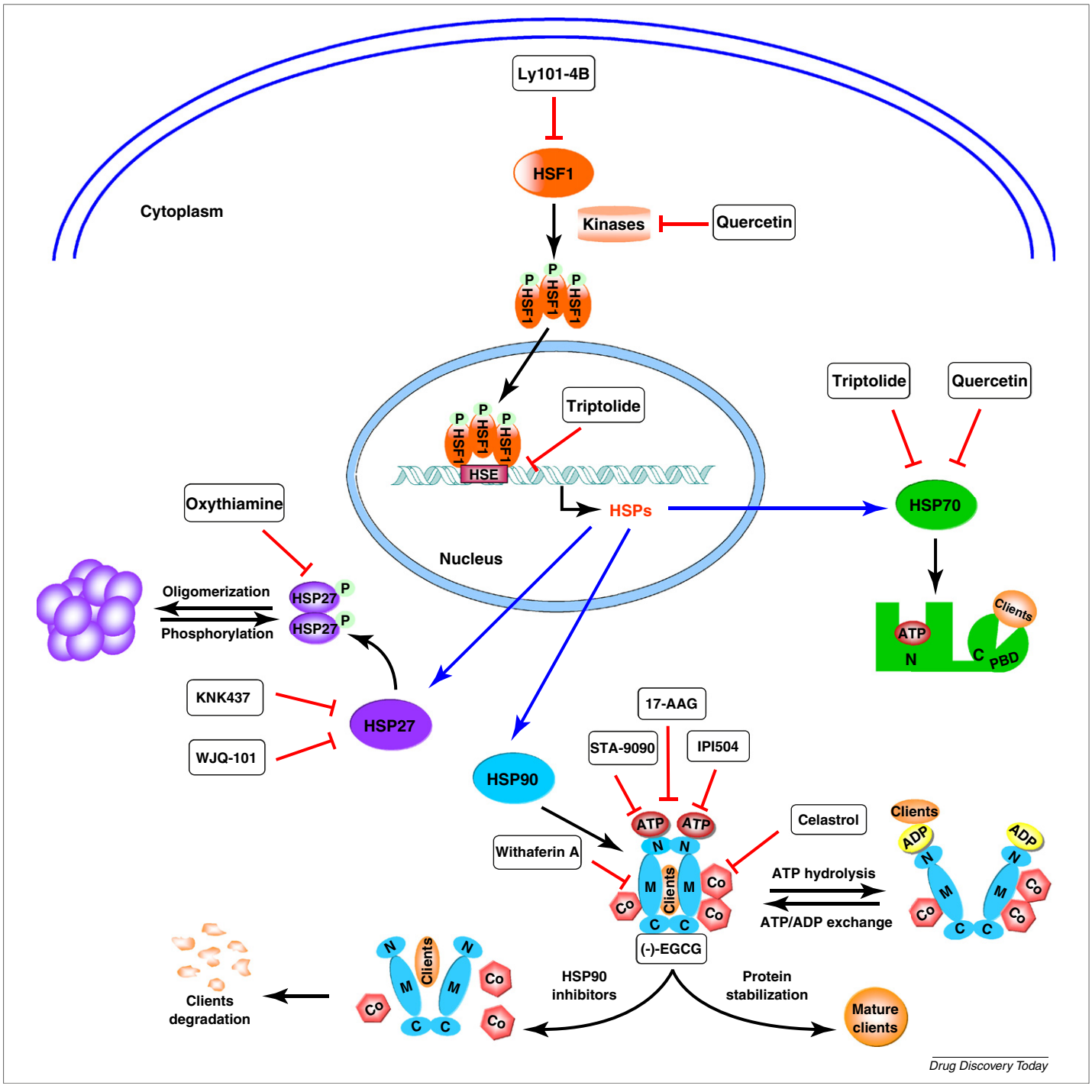

FIGURE 3

Proposed mechanisms for different modulators targeting heat shock response pathways on pancreatic cancers. *Abbreviations*: ADP: adenosine diphosphate; ATP: adenosine-5′-triphosphate; Client: client protein; Co: co-chaperon; C: C-terminal region; HSE: heat shock element; M: middle region; N: N-terminal region; PBD: peptide binding domain.

are important for the substrate binding and stabilization [39]. This ATP-dependent molecular chaperone exists in multiple isoforms, including the constitutive and stress-inducible isoforms, and assists in the folding, assembly and transport of proteins [40]. Similar to HSP27, HSP70 is also abundantly expressed in many tumor forms and is accompanied by increased cell proliferation, metastases and poor response to chemotherapy. Several studies on the role of HSP70 in the apoptotic pathway have revealed HSP70 as a decisive negative regulator of apoptosis (Fig. 1) with the ability to block cell death at different mitochondrial stages [10,17]. As such, the development of small-molecular inhibitors to pharmacologically manipulate HSP70 has recently emerged as a potential therapeutic approach. To date, various HSP70 inhibitors have been reported, including small-molecular chemical entities, antisenses, siRNAs, peptides and aptamers, although no candidate has yet been advanced to clinical trials.

The development of HSP70 inhibitors has been extensively reviewed recently [39].

The original idea to target HSP70 with the aim of fighting pancreatic cancer came from its high expression levels in different pancreatic cancer cell lines compared with normal pancreatic ductal cells [41]. Quercetin (Fig. 2), a natural bioflavonoid, was reported to downregulate HSP70 expression (Fig. 3) in drug-resistant pancreatic cancer cells, both *in vitro* and *in vivo*, leading to caspase-dependent apoptosis, whereas similar treatment of normal pancreatic ductal cells had no antiproliferation effect [42]. It is reported that the mode of action of quercetin might involve inhibition of the kinases, which activate HSP70 expression by phosphorylation of HSF1 (Fig. 3) [42] or reduce the HSP70 mRNA accumulation [43]. Unfortunately, quercetin was found to be insufficiently potent for clinical use owing to its required high concentration and pleiotropic activity on protein kinase activity [44]. Later, triptolide (Fig. 2) was identified as a potent suppressor of HSP70 (Fig. 3) in pancreatic cancer [43,45]. It could inhibit HSP70 at nanomolar concentrations and cause, at low doses, cell death of different drug-resistant pancreatic cancer cell lines both *in vitro* and *in vivo* by the induction of apoptosis. Furthermore, triptolide efficiently reduced the local–regional spread of pancreatic cancer in an orthotopic model [46]. The inhibitory mechanism of triptolide on HSP70 transcription might be owing to the inhibition of the interaction of HSF1 with heat shock elements (Fig. 3) or the activation of HSF1 [47]. A recent study showed that triptolide might be also involved in other pathways to suppress cell proliferation [48], in line with its toxicity at elevated dose.

So far, the use of HSP70 inhibitors to treat pancreatic cancer has achieved some encouraging results at preclinical stages and is impelling their advancement to clinical trial. Target specificity will be a primary concern in future developments of HSP70 inhibitors, taking into account the multiple isoforms of HSP70 and the current therapeutic efficiency.

HSP90

HSP90 belongs to another important class of the HSP family and accounts for 1–2% of total cellular proteins [19]. It is an ATP-dependent chaperone with various isoforms among which HSP90α (inducible form) and HSP90β (constitutive form) represent the major ones associated with tumor development [49]. The structure of HSP90 consists of an N-terminal region, a middle region and a C-terminal region, which are essential for its dimerization, ATP binding and the chaperone–client protein cycle (Fig. 3). The main cancer-relevant function of HSP90 is in aiding the folding and stabilizing the conformation of its client proteins, most of which are protein kinases and transcription factors known to be notorious oncoproteins (Fig. 1) [50]. Among the reported HSP90 clients, several have been clinically validated as cancer targets, such as human epidermal growth factor receptor 2 (HER-2)/neu, AKT, STAT3, Raf-1, Bcr-Abl, estrogen and androgen receptor, vascular endothelial growth factor (VEGF), among others [51]. Because these oncogenic proteins substantially rely on the function of HSP90 for their maturation and/or stabilization, inhibition of HSP90 therefore provides the unique advantage of causing depletion of multiple oncoproteins, while simultaneously attacking several pathways necessary for cancer development, and hence leads to potent anticancer effect. Unlike HSP27 and HSP70, HSP90 is not only upregulated in tumor cells but is also abundant in normal tissue. Several studies have, however, shown that the activity of HSP90 is higher in tumor cells than in normal cells and the oncogenes depend more on HSP90 than on housekeeping proteins. This offers the opportunity to develop HSP90 inhibitors. Several inhibitors of HSP90, mainly derived from the natural product geldanamycin (Fig. 2) have achieved encouraging clinical results on multiple myelomas and gastrointestinal stromal tumors. Some other HSP90 inhibitors are also under clinical evaluation; however, their structures have not yet been disclosed [52]. Owing to the increasing interest in HSP90 inhibitors for cancer treatment, several excellent reviews have been written on this topic [52–54].

Targeting HSP90 as a therapeutic approach in treating pancreatic cancer began with 17-AAG (Fig. 2), an analog of geldanamycin. Geldanamycin is the first discovered HSP90 inhibitor, which exhibits antiproliferative activity by binding to the ATP-binding site of HSP90 and thereby preventing its function. However, it has limited therapeutic potential owing to its hepatotoxicity. Its analog, 17-AAG, has a retained ability by inhibition of ATP binding of HSP90 (Fig. 3) but a reduced toxicity *in vivo* and is therefore the first HSP90 inhibitor to reach clinical trial stage. 17-AAG can inhibit insulin-like growth factor-I receptor (IGF-IR) signaling and STAT3 pathways, both of which are implicated in the progression of pancreatic cancer, leading to significant growth-inhibitory effects [55]. Presently, 17-AAG combined with gemcitabine for use in the treatment of patients with stage IV pancreatic cancer is under clinical trial (Table 1) [51]. However, the poor solubility and the lack of oral bioavailability remain the major problems of 17-AAG for clinical application. Its analog, 17-DMAG (Fig. 2) has come out with improved water solubility and tolerable toxicity therefore to enter clinical trial soon for various cancer therapies [52].

Inspired by clinical data on 17-AAG and its analogs in cancer treatment, a considerable number of other new HSP90 inhibitors have been proposed. IPI-504 (Fig. 2) could pharmacologically inhibit HSP90 and displayed potent antitumor activity in pancreatic cancer both *in vitro* and *in vivo* [56]. The pharmacological effects of IPI-504 have been well proved *in vitro* by the upregulation of HSP70 and downregulation of various HSP90 client proteins. However, no consistent effects were documented in the xenografted tumors, suggesting that IPI-504 might inhibit the pancreatic tumor through a rather elusive mechanism, although it is generally considered to target HSP90 ATP-binding site like geldanamycin and 17-AAG (Fig. 3). STA-9090 (Fig. 2) is a potent inhibitor of HSP90 developed by Synta Pharmaceuticals (http://www.syntapharma.com/) with a novel chemical structure unrelated to the geldanamycin family. With a strong affinity to the ATP-binding domain of HSP90 N-terminus (Fig. 3) [57], STA-9090 has displayed excellent activities on hematological and solid malignancies [57]. At present, STA-9090 is in clinical trials as the second-line therapy to treat patients with metastatic pancreatic cancer [ClinicalTrials.gov: http://www.clinicaltrials.gov] (Table 1). Celastrol (Fig. 2) is another novel HSP90 inhibitor identified to disrupt protein–protein interactions of HSP90/Cdc37 superchaperone complex (Fig. 3), resulting in downregulation of many oncogenes involved in pancreatic cancer [58]. The mechanism of action of celastrol is different from classic HSP90 inhibitors which interfere with the ATP-binding domain. Similar to celastrol,

Withaferin A (WA) (Fig. 2) was also shown to exhibit potent antiproliferative activity and induce apoptosis in different pancreatic cancer cell lines by affecting the superchaperone complex of HSP90 without blocking the ATP-binding domain (Fig. 3), further confirming the ATP-independent mechanism for HSP90 inhibition [59]. (−)-Epigallocatechin-3-gallate [(−)-EGCG] (Fig. 2), the most abundant polyphenolic catechin in green tea with potent anticancer activity, was reported to inhibit the transcriptional activity of aryl hydrocarbon receptors (AhR) through the direct binding of the C-terminal region of HSP90 (Fig. 3). In line with this, a recent study suggested that the binding of (−)-EGCG to HSP90 impaired the association of HSP90 superchaperone complexes and thus inhibited the HSP90 chaperone function, leading to the degradation of cancer-related HSP90 client proteins and antiproliferative effects in pancreatic cancer cells [60]. The activities of all the above-mentioned HSP90 inhibitors have already been validated on drug-resistant pancreatic cancer models, thus implying the promising clinical future of these molecules. In summary, HSP90 inhibitors are currently the most extensively studied and the best developed candidates to target HSP in the view to treating pancreatic cancer. Similar to the HSP70 inhibitors, improving the specificity on the different HSP90 isoforms associated with tumor development will be crucial for future advance in the status of HSP90 inhibitors in cancer therapy.

HSPs as vaccine adjuvants for immunotherapy

Besides their chaperone functions, immunomodulatory activities represent another important function of HSPs. Apart from the HSPs located inside the cells, HSPs can also be found on the plasma membrane or in the extracellular environment [61]. The extracellular HSPs are usually released from the cells through a necrotic mechanism [61,62]. These HSPs can activate natural killer cells, or activate dendritic cells through the interaction with different receptors involved in immune response, such as toll-like receptors (TLR)-2 and TLR-4. HSPs are therefore also considered as inducers of the innate and adaptive immunity. Several HSPs–peptide complexes, such as HSP70, HSP90 and glycoprotein (gp)96 (glucose regulated protein (GRP)94, a HSP90 paralog) have been developed as effective vaccines to produce antitumor immune responses [61,62]. Among the different HSP vaccines, the vaccination with autologous HSP70 has been proved to be feasible and safe in clinical trial to treat chronic myeloid leukemia (CML) in chronic phase [63]. The HSP peptide complex vaccine based on tumor-derived gp96 has also been used as an immunological strategy to treat pancreatic cancer patients [61,64].

HSF1

Of the existing multiple HSFs, HSF1 is considered as the master transcription factor of the stress-inducible HSPs and is activated by diverse forms of stress [14,65]. It is well known that HSP90 can bind to HSF1 in unstressed state to abrogate the transcription function of HSF1 (Fig. 1) [47]. The inhibition of HSP90 expression therefore should activate HSF1 with the increased expression of its downstream genes, such as HSP27 and HSP70 [47]. Because both HSP27 and HSP70 are antiapoptotic proteins with tumorigenic properties, the overall anticancer effect of the HSP90 inhibitors might be impaired. Considering this fact, targeting HSF1 should enable the simultaneous downregulation of several HSPs. Moreover, increasing evidence shows that HSF1 orchestrates the initiation and maintenance of cancer. Tumor cells are more dependent on HSF1 than normal cells for proliferation and survival, as confirmed by both cell-based and clinically relevant examples [15]. Targeting HSF1 has therefore been regarded as an appealing anticancer approach [15,66].

RNAi technology has been used to validate HSF1 as a drug target in cancer therapy [67]. Several chemical modulators have since been found to alter HSF1 expression, such as the previously mentioned HSP inhibitors, KNK437, quercetin, triptolide, celastrol and quinacrine (Fig. 2) [66]. However, none of these compounds have been found to target HSF1 directly, hence raising concerns about low potency and poor specificity. Importantly, HSF1 is abundantly expressed in human pancreatic cancer cells [68]. We therefore wished to develop more potent and specific small-molecular candidates to treat pancreatic cancer by targeting the common HSR pathways controlled by HSF1. As such, we recently identified a triazole nucleoside analog Ly101-4B (Fig. 2) based on our previous lead WJQ-101 (Fig. 2) [69]. Ly101-4B induces caspase-dependent apoptosis and exhibits significantly superior anticancer activity on drug-resistant pancreatic cancer models *in vitro* and *in vivo*. Most interestingly, this new lead compound targets HSR pathways by the HSF1-mediated downregulation of multiple HSPs, such as HSP27, HSP70 and HSP90, all of which are crucial players in cancer development and survival and contribute importantly to drug resistance. Ly101-4B is also the first triazole nucleoside analog disclosed with such a mode of action. Further investigation of Ly101-4B on the HSF1-mediated pathway will focus on the realization of its specificity and detailed HSF1-related functions.

Concluding remarks

Owing to the complicated pathogenesis, poor prognosis and resistance to treatments, pancreatic cancer remains a notoriously unsolved medical issue and desperately requires efficacious drug candidates. Targeted therapies on different pathways related to pancreatic cancer progression were hoped to bring new breakthroughs, however, translation to clinical trial has been far from satisfying. The quest for novel targets/pathways for intervention in pancreatic cancer is of utmost importance given the urgent need to promote current therapy. HSPs have crucial roles in controlling many signaling pathways involved in the proliferation and survival of cancer cells. By commanding over the folding and stabilization of relevant oncoproteins, HSPs stand at the crossroads of multiple important oncogenic pathways. Inhibition of HSPs hereby offers the unique advantage of depleting multiple oncoproteins while simultaneously attacking several pathways necessary for tumor progression. Additionally, it has the added advantage of reducing the likelihood of the tumor acquiring resistance to any single therapeutic strategy. Recent studies have demonstrated that targeting HSPs constitutes a promising strategy for treating pancreatic cancer.

Targeting individual HSPs has been affirmed to produce an effective anticancer effect in several pancreatic cancer models. Specificity remains an important issue for the therapeutic outcome of all tested HSP inhibitors. So far HSP90 inhibitors represent the best developed candidates whereas those of HSP27 and HSP70 are still at the preclinical stage to treat pancreatic cancer. Ample evidence suggests that HSP90 inhibitors often induce a significant

upregulation of HSP27 and HSP70, which would impart cancer cells with strong cytoprotective activity and thus compromise the anticancer effect. Consequently, developing drug candidates able to target multiple HSPs or their upstream modulator HSF1 or the combination of inhibitors of different HSPs could be particularly appealing. In addition, because several drug candidates for target therapy in pancreatic cancer are currently under development, targeting HSPs in combination with these new validated targets might provide promising therapeutic benefits. Although many issues remain unsolved, scientists in the field continually strive toward a better understanding of the mechanisms of HSPs/HSR and other essential oncogenic pathways in the hope that this will eventually lead to successful drug targeting and a significantly improved clinical therapeutic index for pancreatic cancer.

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