# Targeting HSP47 for cancer treatment

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**Heat shock protein 47 (HSP47) serves as an endoplasmic reticulum residing collagen-specific chaperone and plays an important role in collagen biosynthesis and structural assembly. HSP47 is encoded by the *SERPINH1* gene, which is located on chromosome 11q13.5, one of the most frequently amplified regions in human cancers. The expression of HSP47 is regulated by multiple cellular factors, including cytokines, transcription factors, microRNAs, and circular RNAs. HSP47 is frequently upregulated in a variety of cancers and plays an important role in tumor progression. HSP47 promotes tumor stemness, angiogenesis, growth, epithelial-mesenchymal transition, and metastatic capacity. HSP47 also regulates the efficacy of tumor therapies, such as chemotherapy, radiotherapy, and immunotherapy. Inhibition of HSP47 expression has antitumor effects, suggesting that targeting HSP47 is a feasible strategy for cancer treatment. In this review, we highlight the function and expression of regulatory mechanisms of HSP47 in cancer progression and point out the potential development of therapeutic strategies in targeting HSP47 in the future.**
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## Introduction

Protein misfolding and aggregation are implicated in tumor development, providing for new therapeutic opportunities targeting protein homeostasis in cancer therapy [1]. The maintenance of protein homeostasis is mediated by numerous participants, including the heat shock response [1,2]. Heat shock response controls protein quality and is an evolutionarily conserved defense system consisting of heat shock proteins (HSPs) [1,2].

As chaperones, HSPs are abundant and highly conserved in all organisms [3]. HSPs can be induced by different stresses, including heat shock, and play important roles in protein homeostasis [3]. HSPs also have been shown to inhibit cell death and to participate in cell proliferation and differentiation processes, and tumor cells require these stress-inducible chaperones for their survival [4–6]. Mounting evidence have shown that the expression of HSPs is frequently upregulated in a variety of cancers, such as breast, lung, liver, colorectal, ovarian, gastric, and prostate cancer [7–16]. HSPs are involved in the regulation of immune responses, apoptosis, angiogenesis, metastasis, and resistance, suggesting HSP as a promising therapeutic target in cancer [17]. Detection of the expression level of HSPs can play an important role in cancer diagnosis [4,17].

As a member of HSPs, heat shock protein 47 (HSP47) is encoded by the *SERPINH1* gene, which is located on chromosome 11q13.5, one of the most frequently amplified regions in human cancer [18,19]. On the one hand, HSP47 serves as an endoplasmic reticulum (ER)-residing collagen-specific chaperone essential for the correct folding of procollagen [18,20], and HSP47 is closely related to collagen-related diseases, including osteogenesis imperfecta, keloid, and fibrosis [18,20]. On the other hand, HSP47 can regulate ER stress via maintaining cellular protein homeostasis [21]. HSP47 is frequently overexpressed in a variety of tumors and contributes to cancer progression, including breast, pancreatic, lung, glioblastoma, prostate, and gastric cancer [19]. HSP47 can regulate tumor stemness, angiogenesis, growth, epithelial-mesenchymal transition (EMT), and metastatic capacity. HSP47 also regulates the efficacy of tumor therapies, such as chemotherapy, radiotherapy, and immunotherapy. The expression of HSP47 is regulated by multiple cellular factors, including cytokines, transcription factors, microRNAs (miRNAs), and circular RNAs (circRNAs). Inhibition of HSP47 expression has been reported to have antitumor effects, suggesting that targeting HSP47 is a feasible strategy for cancer treatment. In this review, we emphasize the function and expression regulation mechanisms of HSP47 in cancer progression and point out the future treatment strategies for HSP47.

## The function of HSP47 in collagen synthesis and endoplasmic reticulum stress

As a collagen-specific chaperone, HSP47 not only participates in collagen synthesis and secretion but also regulates ER stress (Fig. 1). In the following section, we will

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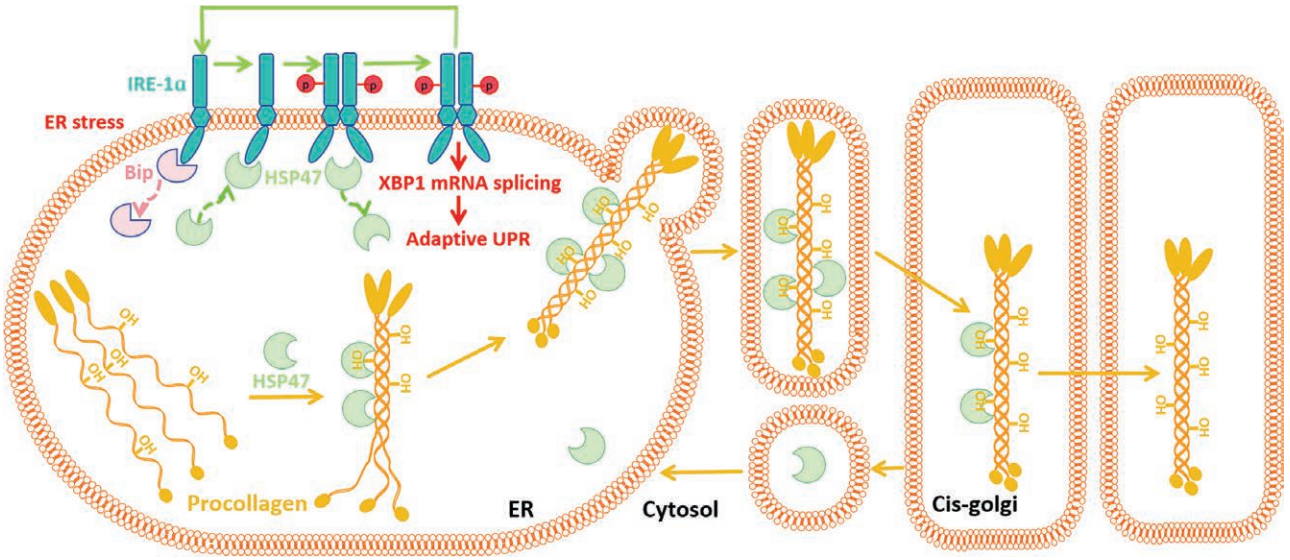
**Fig. 1**




HSP47 participates in regulating collagen synthesis and ER stress. HSP47 directly binds to the ER luminal domain of IRE1α, displacing the negative regulator BiP from the complex to facilitate IRE1α oligomerization and modulate IRE1α signaling. As a collagen-specific chaperone, HSP47 also binds to Gly–Xaa–Arg repeats within triple-helical procollagen in the ER and accelerates triple-helix formation of procollagen. Then, triple-helical procollagen is transported and secreted via the ER–Golgi pathway. HSP47 returns to the ER due to its RDEL ER-retention signal sequence. ER, endoplasmic reticulum; HSP47, Heat shock protein 47; IRE1α, inositol-requiring enzyme 1 alpha; RDEL, Arg-Asp-Glu-Leu.

introduce the function of HSP47 in collagen synthesis and ER stress.

## HSP47 in collagen synthesis

Collagen is the most abundant mammalian protein, constituting approximately 30% of protein in the human body [22]. Almost 28 different types of collagen have been identified in mammalian cells [22], all of which share a common structural feature: a triple-helix domain composed of the Gly–Xaa–Yaa three amino acid repeat sequences, where Xaa and Yaa are typically proline and hydroxyproline, respectively [23]. HSP47 binds to Gly–Xaa–Arg repeat sequence within triple-helix procollagen in ER, which can prevent its unfolding or aggregate formation, resulting in accelerating the triple-helix formation of procollagen. HSP47 dissociates from procollagen in the cis–Golgi or ER–Golgi intermediate compartment via a pH-dependently way and is then transported back to the ER via its "Arg-Asp-Glu-Leu" retention sequence [18,20](Fig. 1). Disruption of the HSP47 gene in mice leads to impairments in the basement membrane and collagen fiber formation, resulting in embryonic death [24]. Depletion of HSP47 leads to delayed secretion of type I and type IV collagen, resulting in the accumulation of immature procollagens in the ER [25–28]. Thus, the expression of HSP47 is closely related to the expression of collagens in multiple types of cells and tissues.

As part of the tumor extracellular matrix (ECM), collagens are relevant features of solid tumors and are deeply involved in cancer progression [29]. Collagens are deposited in the tumor microenvironment (TME) to form a collagen wall along which tumor cells can infiltrate and prevent drug action on the tumor cells [30]. During cancer progression, collagen contributes to tumor-cell infiltration, expansion, and distant metastasis [30,31]. Therefore, collagen in TME is regarded as a better target for cancer therapy [30]. HSP47 is primarily expressed in collagen-producing cells, such as fibroblasts, myofibroblasts, and cancer-associated fibroblasts (CAFs), and possesses the ability to facilitate the secretion of various types of collagens [18,20,32,33]. Within the TME, CAFs have been shown to play multiple roles in tumor development. They promote cancer cell proliferation, therapy resistance, and immune exclusion via secreting collagens [34]. Taken together, HSP47 overexpression in CAFs can promote cancer progression via facilitating collagen synthesis.

## HSP47 in endoplasmic reticulum stress

The ER plays a role as a quality control organelle for protein homeostasis [35]. When protein homeostasis is broken with an accumulation of misfolded and unfolded proteins in the ER, ER stress is activated [36]. As a response, cells trigger an adaptive mechanism to restore ER protein homeostasis, known as the unfolded protein response (UPR). The three main UPR signaling branches are initiated by inositol-requiring enzyme 1 alpha (IRE1α), protein kinase RNA-activated-like ERKinase (PERK), and activating transcription factor 6 (ATF6), which are also crucial for tumor growth, aggressiveness, and therapeutic resistance [37].

Among the three main UPR signaling branches, IRE1α is a major UPR transducer that determines cell fate under

ER stress [38,39]. The binding of the ER chaperone BiP to the luminal domain of IRE1α can maintain its monomeric inactive state [40]. Under ER stress, BiP preferentially associates with misfolded proteins, allowing IRE1α dimerization and auto-transphosphorylation to activate IRE1α [40], and then produces an active transcription factor, spliced X-box binding protein 1, which can control the transcription of gene encoding proteins for ER-associated degradation, eliminating excessive misfolded and unfolded proteins [41]. HSP47 can instigate IRE1α signaling through a physical interaction [21]. HSP47 can directly bind to the ER luminal domain of IRE1α, displacing the BiP from the complex to facilitate IRE1α dimerization, auto-transphosphorylation, and activation (Fig. 1). HSP47 deficiency makes cells and animals sensitive to ER stress [21]. The ER stress is closely related to cancer progression [42]. ER stress initiates UPR to reestablish ER homeostasis as an adaptive pathway for tumor development, and blocking the adaptive pathway of ER stress could be an anticancer strategy [43]. Here, although almost all tumor cells express HSP47, the expression level of collagen in tumor cells is very low [44,45]. However, silencing HSP47 expression in cancer cells can inhibit tumor growth [46]. Thus, HSP47 promotes tumor growth, survival, and metastasis to some extent by regulating ER stress in a collagen-independent way. For instance, collagen expression is scarcely detectable in high-invasive breast cancer cells, and the impaired proliferation of high-invasive breast cancer cells silenced by HSP47 cannot be restored by adding type I collagen, type IV collagen, or fibronectin, which indicates that HSP47 regulates high-invasive breast cancer via a collagen-independent way [47].

## HSP47 in cancer

HSP47 is highly expressed in a variety of cancers, and upregulation of HSP47 promotes the aggressiveness of many types of cancers. However, the potential mechanisms by which HSP47 is upregulated are not completely understood. Elucidating the mechanisms of HSP47 regulating cancer progression is essential for developing a better strategy for cancer treatment.

Analysis of the The University of ALabama at Birmingham CANcer datasets (http://ualcan.path.uab.edu/) shows that HSP47 mRNAs are significantly upregulated in a variety of human tumor tissues, such as bladder urothelial carcinoma, breast invasive carcinoma, colon adenocarcinoma, glioblastoma multiforme, head and neck squamous cell carcinoma, kidney renal clear cell carcinoma, liver hepatocellular carcinoma, lung adenocarcinomas, lung squamous cell carcinoma and stomach adenocarcinoma, compared to their respective normal tissues (Fig. 2a). Furthermore, Kaplan–Meier survival analysis (http://kmplot.com/analysis/index.php?p=service&cancer=pancancer_rnaseq) shows that higher HSP47 mRNA levels in patients with bladder urothelial carcinoma, kidney renal clear cell carcinoma, liver hepatocellular carcinoma, lung adenocarcinomas, and stomach adenocarcinoma are significantly correlated with poorer overall survival (OS) (Fig. 2b). To date, only one study has reported that overexpression of HSP47 inhibits tumor progression [48], while other studies have demonstrated that overexpression of HSP47 promotes tumor progression.

### Breast cancer

Breast cancer is an aggressive cancer that is the leading cause of cancer-related death among women worldwide. ECM is increasingly recognized as an important regulator in breast cancer [49]. MicroRNA-29 (miR-29) consists of three mature members, miR-29a, miR-29b, and miR-29c, and is significantly downregulated in several types of cancers, indicating that miR-29 may be an antitumor miRNA in human cancers [50–52]. A potential binding site for miR-29 has been identified in the 3′-untranslated region (3′UTR) of the HSP47 gene. HSP47 is regulated by miR-29 during breast cancer development and progression, and increased HSP47 expression promotes cancer progression by enhancing the deposition of ECM proteins [53]. HSP47 also promotes breast cancer metastasis by enhancing collagen-dependent cancer cell-platelet interaction [54]. In addition, HSP47 interacts with nonmuscle myosin IIA (NMIIA) via IRE1α, resulting in the enhancement of the metastatic potential of breast cancer cells by augmenting the contractile force of actin filaments [47]. Above studies indicate that targeting HSP47 may be a promising strategy for blocking breast cancer metastasis.

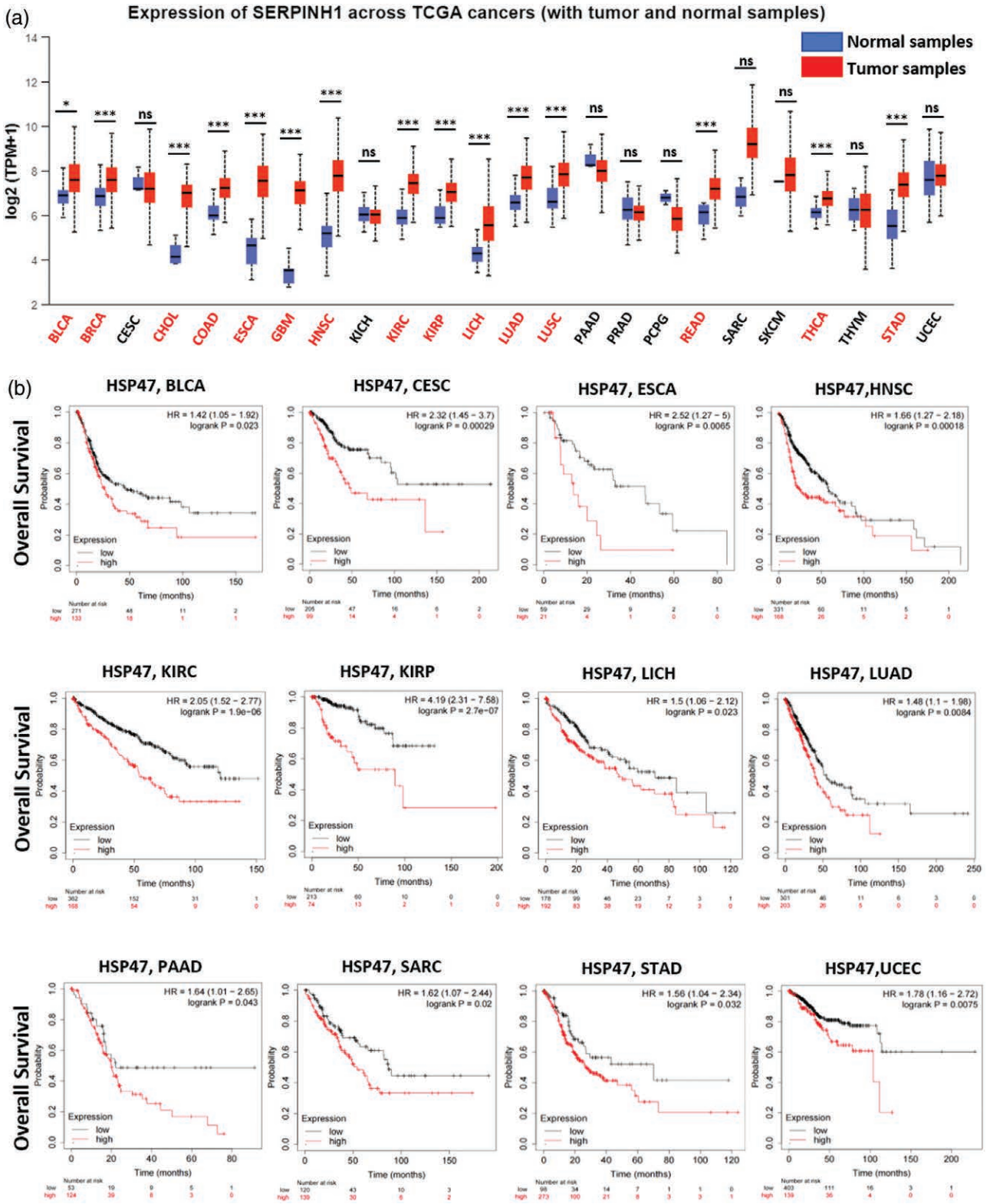
### Pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal diseases, with an average 5-year survival rate of less than 10% [55]. Immunohistochemistry is used to detect differential protein expression in 57 cases of primary invasive PDAC, and the expression of HSP47 can be detected in all neoplastic samples, with HSP47 being the most intense in the tumor-associated stroma [56]. More importantly, the higher expression level of HSP47 in patients with PDAC is significantly correlated with poorer OS [56,57]. In addition, PDAC is one of the most chemoresistant cancers, and gemcitabine has been widely used as a first-line drug for PDAC [58–61]. HSP47 can induce gemcitabine resistance in PDAC cells, and disruption of HSP47 improves the efficacy of chemotherapy for patients with PDAC [62].

### Gynecological cancers

Gynecologic cancer is a group of cancers that affect the tissue and organs of the female reproductive system, including cervical, ovarian, uterine, vaginal, and vulvar cancers [19]. In cervical squamous cell carcinoma (CESC), miR-29a is normally found to be downregulated, and the expression of HSP47 is upregulated in cancer tissues and

**Fig. 2**




HSP47 is frequently upregulated in a variety of human cancers and elevated HSP47 is associated with poorer prognosis for cancer patients in many cases. (a) HSP47 is significantly upregulated (red) in a variety of human cancers. Boxplot showed the relative expression of HSP47 in tumor tissues compared to normal tissues from the TCGA database. (ns: no significance; *:.01 < $P$ < 0.05; **:.001 < $P$ < 0.01; ***: $P$ < 0.001); (b) The enhanced level of HSP47 is associated with a poorer prognosis for patients with some types of cancers. mRNA expression of HSP47 in tumor tissue is stratified into a high or low expression using the median expression value as the cutoff point. Kaplan–Meier survival curves for OS analysis with HSP47 in different cancers. HSP47, heat shock protein 47; OS, overall survival; TCGA, The Cancer Genome Atlas.

cervical intraepithelial neoplasia [63,64]. HSP47 is a target of miR-29a in the CESC cell line, and silencing the HSP47 gene significantly inhibits CESC cell migration and invasion [64].

### Lung cancer

Lung cancer is a major public health problem and a huge social burden in China, because of its increasing incidence and high mortality [65]. Non-small cell lung cancer (NSCLC) is the most common pathological type of lung cancer. HSP47 is upregulated in NSCLC [66–68], and inhibition of HSP47 expression represses NSCLC cell migration and invasion and also exhibits strong therapeutic effects on NSCLC *in vivo* [66]. More importantly, the high expression level of HSP47 in patients with NSCLC is significantly correlated with poor OS [68]. The analysis of the TME and immune infiltration reveals that the high and low expression of HSP47 is associated with different immune infiltration characteristics. The analysis of the immune checkpoints and antitumor drugs indicates that immunotherapy and antitumor therapy are more effective in the high HSP47 expression group [68].

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease that is refractory to treatment and has a high mortality rate [69]. IPF is frequently associated with lung cancer and plays a crucial role in the development of lung cancer [70]. During the progression of pulmonary fibrosis, HSP47 expression is upregulated in fibroblasts and is regarded as a therapeutic target in pulmonary fibrosis [71]. Lung cancer patients with more HSP47-positive CAFs in the cancer stroma had shorter disease-free survival than those with fewer HSP47-positive CAFs [72]. miR-29a, a suppressive mRNA, is also downregulated in IPF and lung cancer, and the downregulation of miR-29a causes overexpression of HSP47 in lung cancer and IPF, suggesting that HSP47 is involved in the pathogenesis of these two diseases [73].

### Gastric cancer

Gastric cancer is the third leading cause of cancer-related deaths worldwide and the most common gastrointestinal malignancy in China [74]. The 5-year survival rate of gastric cancer patients is poor because of cancer recurrence due to metastasis [75]. HSP47 is upregulated in gastric cancer samples compared to healthy gastric tissue [76–78]. HSP47 can regulate EMT via the Wnt/β-catenin pathway [77]. Besides, HSP47 promotes the proliferation and cell cycle of gastric cancer cells [79]. HSP47 is also a target of miR-148a-5p; miR-148a-5p inhibits gastric cancer cell aggressiveness by directly targeting HSP47 [78].

### Colorectal cancer

Colorectal cancer (CRC) is one of the three most commonly diagnosed cancers worldwide [80]. The expression level of HSP47 is significantly higher in CRC tissues compared with normal tissue [81,82]. High HSP47 expression is also significantly associated with tumor progression, including lymph node metastasis and venous invasion. Besides, HSP47 confers 5-fluorouracil resistance on CRC cells and disruption of HSP47 may improve the efficacy of chemotherapy for patients with CRC [81]. Thus, high HSP47 expression may serve as a novel predictive biomarker for determining patients with CRC [82]

### Glioblastoma

Glioblastoma is the most common and aggressive primary brain tumor in adults. The defined histopathologic features are necrosis and endothelial cell proliferation, leading to grade IV, which is the highest grade in the WHO classification of brain tumors [83]. HSP47 overexpression has been described in analyses of tissues and glioma cell lines, and this overexpression is associated with the grade of the disease [84–86]. HSP47 could promote primary invasion, angiogenesis, and stem-like properties of primary glioma cells [84–87]. HSP47 is also regulated by miR-29a to enhance glioma tumor growth and invasion [86]. In addition, HSP47 has been found to be expressed in glioma vessels and could promote glioma angiogenesis [85,88,89]. Immunotherapy has become a promising strategy for the treatment of glioma, with the ability to penetrate the blood-brain barrier [90]. HSP47 exhibits a positive association with the augmentation of neutrophils and macrophages, as well as the expression of immune checkpoint molecules within glioma, which may promote the progression of immunotherapy intervention in glioma [91].

### Osteosarcoma

Osteosarcoma is the most common primary malignant bone tumor, with a high propensity for local invasion and metastasis [92]. HSP47 is upregulated and associated with poor survival in patients with osteosarcoma. HSP47 not only promotes the proliferation, migration, and invasion of osteosarcoma cells but also facilitates the growth of osteosarcoma *in vivo* by activating the phosphatidylinositol 3-kinase (PI3K)/v-Akt murine thymoma viral oncogene homolog(AKT) signaling pathway. HSP47, as a tumor promoter involved in the biological process of osteosarcoma, may be an emerging biomarker in osteosarcoma [93].

### Head and neck squamous cell carcinoma

Local invasion and metastasis are the main characteristics of head and neck squamous cell carcinoma (HNSCC). Oral squamous cell carcinoma (OSCC) occurs in the oral mucosa and is a common type of HNSCC [94]. A study shows that overexpression of HSP47 in OSCC has a significant impact on prognosis, and inhibition of HSP47 can impair the proliferation, migration, and invasion of OSCC cells. Therefore, HSP47 may represent potential therapeutic targets for OSCC [95]. Laryngeal squamous cell carcinoma

(LSCC) is the second most common malignant cancer type of HNSCC [96], HSP47 expression in the LSCC tissues is markedly decreased compared to adjacent noncancerous tissues, and low expression of HSP47 is correlated with poor prognosis in patients with LSCC. Upregulation of HSP47 inhibits the proliferation, reduces the invasive ability, and increases the sensitivity to cisplatin chemotherapy of LSCC cells [48]. This conclusion is opposite to the conclusions of most articles.

### Bladder cancer

Bladder cancer is the tenth most common malignant tumor in the world and is the sixth most common cancer for men [97]. HSP47 is abnormally overexpressed in bladder cancer and is associated with poor prognosis. Downregulation of HSP47 suppresses the angiogenesis of bladder cancer cells. The activation of the extracellular signal-regulated kinase (ERK) pathway and the induction of C-C motif chemokine ligand 2 (CCL2) are responsible for HSP47-induced angiogenesis. In conclusion, HSP47 contributes to bladder cancer angiogenesis by inducing CCL2 and provides a potential antiangiogenesis target for bladder cancer therapy [98].

### Esophageal squamous cell carcinoma

Esophageal cancer (EC) is the ninth most common cancer and the sixth leading cause of cancer deaths worldwide. Esophageal squamous cell carcinoma (ESCC) is the most common EC subtype, accounting for 80% of EC cases [99]. Compared with normal esophageal tissues, HSP47 is highly expressed in ESCC tissue samples. The immunohistochemical staining level of HSP47 and pathologic stage are significantly correlated with OS and recurrence-free survival. Silencing of the HSP47 gene in the ESCC cell line inhibits cell proliferation and colony formation [100]. miR-29c-3p is remarkably lowly expressed in ESCC and targets HSP47 to inhibit ESCC angiogenesis through the Wnt signaling pathway [101].

### Prostate cancer

Prostate cancer is one of the malignant tumors that affects men and significantly contributes to increased mortality rates in men worldwide. Patients with prostate cancer present with either a localized or advanced disease [102]. HSP47 expression correlates bilaterality in prostate cancer. HSP47 expression may play a role in the pathogenesis of prostate cancer because its expression is significantly higher in prostate cancer than its normal counterpart [103].

In general, HSP47 expression is increased in a variety of cancers, and upregulation of HSP47 promotes the aggressiveness of many types of cancers by various mechanisms, depending on the tumor type (Table 1).

## Mechanisms of HSP47 regulating tumor progression

The underlying mechanisms by which HSP47 promotes tumor progression vary greatly. In the following sections, we describe how HSP47 regulates tumor progression.

### HSP47 stimulates the proliferation and survival of tumor cells

Mounting evidence have shown that overexpression of HSP47 promotes tumor growth [19,81,85,86]. HSP47 can form a complex with both IRE1α and ER chaperone BiP in cancer cells. HSP47 silencing triggers dissociation of BiP from IRE1α and IRE1α activation, followed by an increase in the intracellular level of reactive oxygen species (ROS). Increased ROS activates two UPR transducers, PERK and ATF6, resulting in impaired cancer cell growth [46]. As an important component of ECM, collagen stimulates the proliferation of tumor cells [31],

**Table 1 The diagnostic and prognostic significance of heat shock protein 47 expression in different human cancers**

| Cancer types | HSP47 expression | Sample size | Detection methods | Signification/reference |
|---|---|---|---|---|
| Breast cancer | Upregulation | Tumor tissue ($n = 217$) | IHC | Higher tumor cell metastasis[54] |
| PDAC | Upregulation | Tumor tissue ($n = 57$) | IHC | Poorer OS[56] |
| Gastric cancer | Upregulation | Tumor tissue ($n = 102$) | IHC | Higher tumor cells survival, migration, and invasion[77] |
| CESC | Upregulation | Tumor tissue ($n = 60$) | IHC | Higher tumor cells migration and invasion[64] |
| Glioblastoma | Upregulation | Tumor tissue ($n = 40$) | qPCR | Higher glioma tumor growth and invasion[86] |
| | | Tumor tissue ($n = 74$) | IHC | Glioma angiogenesis[85] |
| OSCC | Upregulation | Tumor tissue ($n = 339$) | IHC | Higher tumor cells proliferation, migration, and invasion[95] |
| CRC | Upregulation | Tumor tissue ($n = 139$) | qPCR | Poorer prognosis[82] |
| Osteosarcoma | Upregulation | Tumor tissue ($n = 12$) | WB | Higher tumor cells proliferation and poorer prognosis[93] |
| Bladder cancer | Upregulation | Tumor tissue ($n = 40$) | IHC | Higher angiogenesis and poorer prognosis[98] |
| ESCC | Upregulation | Tumor tissue ($n = 157$) | IHC | Higher tumor cells proliferation and poorer prognosis[100] |
| NSCLC | Upregulation | Tumor tissue ($n = 30$) | qPCR | Higher tumor cell migration, invasion[66] |
| Prostate cancer | Upregulation | Tumor tissue ($n = 49$) | IHC | Higher pathogenesis of prostate cancer[103] |
| LSCC | Downregulation | Tumor tissue ($n = 62$) | WB and IHC | Poorer prognosis[48] |

CRC, colorectal cancer; CESC, cervical squamous cell carcinoma; ESCC, esophageal squamous cell carcinoma; IHC, immunohistochemistry; LSCC, laryngeal squamous cell carcinoma; NSCLC, non-small cell lung cancer; OS, overall survival; OSCC, oral squamous cell carcinoma; PDAC, pancreatic ductal adenocarcinoma; qPCR, quantitative real-time PCR, WB, western blotting.

HSP47 overexpression also promotes tumor growth and survival via facilitating collagen expression.

### HSP47 promotes tumor epithelial-mesenchymal transition and metastatic potential

EMT is the process by which epithelial cells acquire mesenchymal features. During the EMT, cell-cell and cell-ECM interactions are remodeled, leading to the detachment of epithelial cells from each other and the underlying basement membrane [104]. In cancer, EMT is associated with tumor initiation, invasion, metastasis, and treatment resistance [105]. The wnt/β-catenin signaling pathway has been reported to participate in tumor EMT progression [106,107]. β-catenin is a key protein in the Wnt signaling pathway, because the accumulation of β-catenin in the cytoplasm leads to its translocation and activation in the nucleus, thereby further initiating the transcription of EMT-related genes [106]. HSP47 can promote EMT in gastric cancer cells, and inhibiting the expression of HSP47 increases E-cadherin and decreases N-cadherin protein. HSP47 also can increase the expression of other proteins in the Wnt/β-catenin signaling pathway, including β-catenin, Snail, Slug, and TWIST. HSP47 thus regulates EMT via the Wnt/β-catenin pathway, making HSP47 a potential prognostic biomarker and therapeutic target in gastric cancer patients [77]. However, the mechanism of HSP47 regulating the expression of protein in the Wnt/β-catenin signaling pathway is unclear. Discoidin Domain Receptor 2 (DDR2) is a collagen-activated receptor tyrosine kinase that can promote EMT and enhance cell migration and invasion [108,109]. HSP47 can bind to the DDR2 and increase its stability [110], and its expression also significantly maintains the membrane localization of the DDR2 protein [110]. Targeting the interaction between HSP47 and DDR2 might be a potential strategy for inhibiting DDR2-dependent cancer metastasis [110]. Transforming growth factor-β (TGF-β) promotes tumor invasion and metastasis by inducing EMT [111]. TGF-β induces EMT is a major feature of EMT invasiveness and metastasis for tumor progression [111–113]. Overexpression of HSP47 can promote TGF-β production and activation of TGF-β signaling [87]. HSP47 thus promotes EMT through increasing TGF-β production.

Metastasis involves the spread of cancer cells from the primary tumor to surrounding tissues and to distant organs, which is the primary cause of cancer morbidity and mortality [114]. Breast cancer has been categorized as high-invasive breast cancer and low-invasive breast cancer [115,116]. High-invasive breast cancer is an aggressive cancer with a highly metastatic potential to secondary organs such as the lung, brain, and bone [47]. HSP47 interacts with NMIIA via IRE1α, resulting in the enhancement of the metastatic potential of highly invasive breast cancer cells by augmenting the contractile force of actin filaments. NMIIA ablation abrogates the metastatic potential of HSP47-positive highly invasive breast cancer cells [47]. Platelets play an important role in cancer metastasis, and the interaction between platelets and circulating tumor cells (CTCs) promotes cancer metastasis. CTCs induce platelet activation and aggregation, activated platelets gather, and protect CTCs from shear stress and natural killer cells. Finally, platelets stimulate CTC anoikis resistance, EMT, angiogenesis, and extravasation, and ultimately stimulate metastasis [117]. CTCs exhibit increased expression of HSP47 and its target collagen. Increased expression of HSP47 and HSP47-dependent collagen deposition is crucial for cancer cell-platelet interaction and platelet-dependent cancer cell colonization. Targeting the HSP47/collagen axis is a promising strategy for blocking cancer cell-platelet interaction and cancer colonization in the secondary organs.

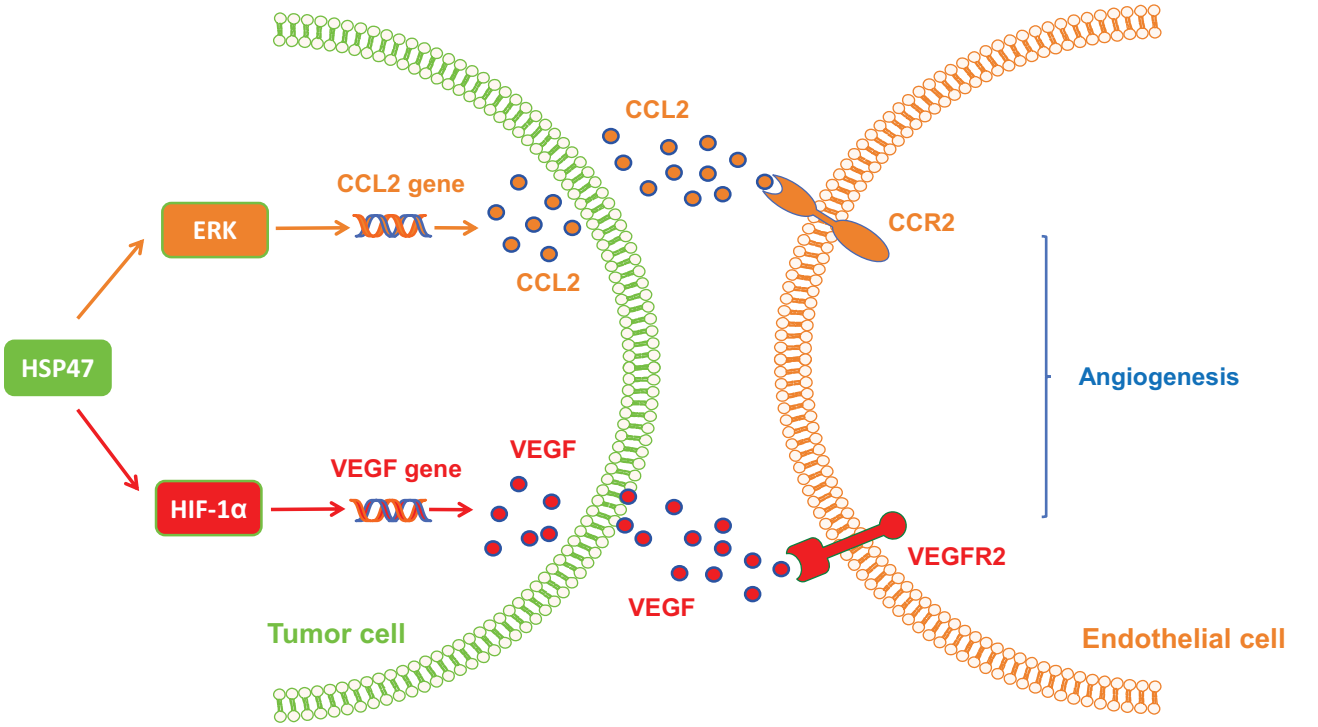
### HSP47 contributes to angiogenesis

Angiogenesis is a biological process in which novel capillary blood vessels grow from preexisting vasculature, providing oxygen and nutrients to tissues, which is required for the development and growth of solid tumors [118]. HSP47 can activate the ERK pathway to enhance the production of CCL2, which then binds to its receptor CCR2. CCL2-CCR2 signaling axis is implicated in many inflammatory and neurodegenerative diseases, such as atherosclerosis, multiple sclerosis, asthma, neuropathic pain, diabetic nephropathy, and cancer [119–121], so HSP47 is explored as a potential target for the treatment of these diseases. Here, the CCL2-CCR2 signaling axis promotes bladder cancer angiogenesis through p38 and Smad3 pathways [98] (Fig. 3). However, how HSP47 activates ERK and which transcription factor is involved in ERK regulating CCL2 expression are unclear. In addition, HSP47 has been found to express in glioma vessels [88]. HSP47 knockdown significantly inhibits tube formation, invasion, and proliferation of human umbilical vein endothelial cells (a commonly used cell line for studying angiogenesis). Vascular endothelial growth factor (VEGF) is a key angiogenic factor mainly released from tumor cells and targets vascular endothelial growth factor receptor 2 (VEGFR2) [122]. HSP47 promotes the expression of hypoxia-inducible factor-1α (HIF-1α) and VEGF in glioma cells, and VEGF is regulated by HIF-1α [123–125]. Here, silencing the HSP47 gene suppresses the expression of VEGFR2 in glioma cells. VEGF binding to VEGFR2 promotes glioma angiogenesis [85] (Fig. 3).

### HSP47 facilitates cancer stemness

Cancer stemness is defined as the self-renewal and tumor-initiation potential of cancer stem cells (CSCs) [126]. CSCs are involved in drug resistance, invasion, metastasis, and recurrence of tumors. CD44, CD133, and leucine-rich repeat-containing G protein-coupled receptor 5 (LGR5) are functional CSC markers [31,126]. ECM

**Fig. 3**




HSP47 contributes to angiogenesis. HSP47 can activate the ERK pathway to enhance the production of CCL2 in cancer cells, secreted CCL2 binding to its receptor CCR2 promotes bladder cancer angiogenesis. HSP47 also promotes the expression of VEGF in cancer cells via enhancing HIF-1α expression, secreted VEGF binding to VEGFR2 promotes glioma angiogenesis. CCL2, C-C motif chemokine ligand 2; ERK, extracellular signal-regulated kinase; HSP47, heat shock protein 47; VEGF, vascular endothelial growth factor; VEGFR, Vascular endothelial growth factor receptor.

and the surrounding stroma have been shown to play an essential role in cancer progression and stemness. ECM could provide structural and biochemical support to regulate the proliferation, self-renewal, and differentiation of CSCs [127]. Collagen, as an important component of ECM, can facilitate cancer stemness through different mechanisms [31]. Transcription of the HSP47 gene and many collagen genes is induced in tumorspheres, which are rich in CSCs [128]. Silencing HSP47 significantly reduces tumorsphere formation efficiency in breast cancer cells via a collagen-dependent manner [54,128]. In addition, HSP47 promotes glioblastoma stem-like cell survival by modulating TME through the TGF-β1 pathway. HSP47 can promote TGF-β1 production and activation of TGF-β1 signaling. TGF-β1 signaling has been shown to play an essential role in the maintenance of tumorigenicity of GSC [31], and blocking the TGF-β1 pathway overcomes HSP47-induced tumorigenesis and stemness [87]. The EMT is a cellular event that enhances cancer cell stemness [129], and HSP47 also promotes tumor EMT to facilitate cancer cell stemness.

### Role of HSP47 in tumor chemotherapy, radiotherapy, and immunotherapy

Chemotherapy is a type of cancer treatment that uses drugs to kill cancer cells, but resistance to chemotherapy is common in cancer treatment. Gemcitabine, a nucleoside analog, is widely used as a first-line drug for PDAC [58–61]. Gemcitabine has also been reported to trigger oxidative stress by the generation of ROS by the activity of nicotinamide adenine dinucleotide phosphate oxidase (NOX), resulting in the induction of apoptosis [130,131]. HSP47 can interact with calreticulin (CALR) and IRE1α in PDAC cells. Ablation of HSP47 promotes both the interaction of CALR with sarcoplasmic/endoplasmic reticulum $Ca^{2+}$-ATPase 2 (SERCA2) and the interaction of IRE1α with inositol 1,4,5-triphosphate receptor ($IP_3R$), which increases intracellular $Ca^{2+}$ level prone to be induced by oxidative stimuli. Disruption of HSP47 enhances NOX-induced generation of intracellular ROS and a subsequent increase in intracellular $Ca^{2+}$ level in PDAC cells after treatment with gemcitabine, resulting in the death of PDAC cells by activation of the $Ca^{2+}$/caspases axis. HSP47 thus confers gemcitabine resistance on PDAC cells [62]. PI3K is considered a significant cause of chemoresistance in cancer therapy, and AKT is a significant downstream effecter of PI3K signaling linked to drug resistance [132,133]. Knockdown of HSP47 sensitizes cells to 5-fluorouracil. Mechanistically, HSP47 promotes survival by enhancing AKT phosphorylation, and decreasing expression of the AKT-specific phosphatase PH domain leucine-rich repeat-containing

protein phosphatase 1 (PHLPP1) when cells are exposed to 5-fluorouracil. PHLPP1 can remove activating phosphorylations in AKT, thereby antagonizing the activity of AKT [134]. HSP47 can decrease PHLPP1 stability via interacting with PHLPP1, leading to more persistent AKT activity. HSP47 thus enhances 5-fluorouracil resistance via enhancing AKT phosphorylation [81]. Besides, collagen could be involved in chemoresistance. In the simplest scenario, cell surface-associated collagen imposes a physical barrier, preventing drug penetration to reduce the efficacy of chemotherapeutics. Collagen can also induce chemoresistant gene expression or activate signaling cascades, which possess detoxification capability [31]. HSP47 could promote collagen synthesis and secretion to reduce the efficacy of chemotherapeutics.

Another common cancer treatment is radiotherapy. Since collagen is in constant contact with tumor cells and can act as a physical barrier, an enhanced level of collagen may mitigate the effect of γ radiation [31]. Therefore, HSP47 overexpression can increase collagen synthesis and secretion, which mitigates the effect of γ radiation. Boron neutron capture therapy (BNCT) has a unique property of tumor-cell-selective heavy-particle irradiation. BNCT can form large dose gradients between cancer cells and normal cells, even if the two types of cells are mingled at the tumor margin [135]. BNCT could alter the ECM by decreasing collagen synthesis and inducing apoptosis. However, there is no alteration in HSP47 expression after BNCT treatment [136].

Immunotherapy has opened a new era in cancer treatment. The clinical goal of cancer immunotherapy is to prime the host immune system to provide passive or active immunity against malignant tumors [137]. Tumor-infiltrating immune cells are considered to be a marker of host antitumor immune response and prognostic features [138]. HSP47 can change the composition of immune cells by inducing the collagen synthesis [139]. HSP47 is significantly correlated with six immune infiltrating cells including B cell, $CD4^+$ T cell, $CD8^+$ T cell, dendritic cell, macrophage cell, and neutrophil cell in multiple cancers [140]. Here, HSP47 is negatively correlated with $CD8^+$ T cells but positively associated with M2 macrophages [141]. $CD8^+$ T cells are one of the primary tumor-infiltrating immune cells that deliver antitumor responses [142]. $CD8^+$ T cell tumor infiltration is a favorable prognostic factor for a wide range of human cancers. $CD8^+$ T cells traffic to the TME and execute tumor clearance by recognizing specific tumor-associated antigens on cancer cells and mediating tumor cytotoxic activity [143]. However, M2 macrophages can secrete inhibitory cytokines, such as interleukin (IL)-10 or TGF-β, to downregulate immune response and promote the development of tumors. Therefore, HSP47 may influence the infiltration of $CD8^+$ T cells and M2 macrophages by affecting the TME-related immune pathways to promote tumor development [140]. In addition, HSP47 is positively correlated with several immune modulators, including immunostimulator CD276 and CD70 expressions, immunoinhibitor TGF-β1 expression, and CCL21 expression [140]. Above results suggest that HSP47 interacts with immune regulation and may become a potential biomarker, which has an important impact on the development of cancers and the prognosis of patients [140].

## The regulation of HSP47 expression

As indicated above, the expression of HSP47 is frequently upregulated in a variety of cancers and is associated with a poor prognosis. It is thus important to understand the regulatory mechanisms of HSP47 expression to develop strategies for cancer therapies. A number of transcriptional factors, cytokines, and miRNAs have been shown to regulate the expression of HSP47.

HSP47 is the only heat-inducible chaperone in the ER of mammalian cells. Although many ER-resident chaperones, including BiP and Grp94, are induced by the accumulation of misfolded proteins in the ER, HSP47 is not induced by ER stress response pathways [144]. Upon heat shock, heat shock factor 1 (HSF1) monomer is activated by conversion to a trimer that is capable of binding to the heat shock element (HSE) located −180 bp from the transcription initiation site of HSP47 and activates the transcription of HSP47 mRNA [145,146]. HSP47 also exhibits constitutive expression, which is invariably correlated with the expression of various types of collagen in multiple tissues, cell types, and collagen-related pathological conditions [20]. The basic expression of HSP47 requires a binding site for the Sp1 transcriptional factor, whereas tissue-specific expression is regulated by two domains in the first and second introns [20]. Sp1 binding site at −210 bp in the promoter region and the first and second introns are required for the tissue-specific expression of HSP47 in transgenic mice [20].

miRNAs, the 19–25 nucleotide short RNA molecules, play important roles in posttranscriptional regulation. In animal cells, miRNAs regulate their targets by translational inhibition or mRNA destabilization [147]. The expression of HSP47 can be regulated by miR-29a [73], miR-148a-5p [78], and miR-29c-3p [101], which can regulate the progress of fibrosis and cancer progression via targeting HSP47 mRNA levels.

circRNAs are RNAs with a unique circular structure that is generated from back-splicing processes [148]. Insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2) is an important RNA-binding protein that can bind with the target mRNA and affect its stability. circ-transportin-3 (TNPO3) is downregulated in clear cell renal cell carcinomas (ccRCC). circ-TNPO3 can suppress ccRCC metastasis by directly binding to IGF2BP2 protein and destabilizing HSP47 mRNA

[149]. circ-CAMSAP1 is highly expressed in nasopharyngeal carcinoma tissues. circ-CAMSAP1 promoted HSP47 expression through improved HSP47 mRNA stability by binding to the 3′UTR of HSP47. Therefore, circ-CAMSAP1 promotes nasopharyngeal carcinoma proliferation and metastasis by promoting HSP47 expression [150].

As a primary factor that drives fibrosis and tumorigenesis, TGF-β1 can upregulate HSP47 expression via Smad2/3 signaling pathway in nasal fibroblasts [151,152]. The cytokine IL-1β is a key mediator of the inflammatory response and could regulate fibrosis and tumor progression [153]. IL-1β is able to upregulate HSP47 at both protein and mRNA levels, by itself or in combination with TGF-β1. TGF-β1 and IL-1β are able to favor nuclear localization of HSF1 and enhance HSF1 trimerization leading to an increase in HSF1 binding to HSE of HSP47 promoter [154]. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), a member of the Tumor necrosis factor family, is an important regulator of HSP47 expression through reduction of HSF1 trimerization and nuclear localization, therefore exhibiting antifibrotic potential in hepatic fibrosis [155]. α-defensins are the most abundant neutrophilic proteins involved in innate and acquired immunity. α-defensins can increase both the mRNA and the protein expression levels of HSP47 in normal human fibroblasts [156]. Nitric oxide (NO) is a ubiquitous gas and is involved in numerous physiological functions, including inflammatory and immune responses. NO has been shown to have both anticancer and carcinogenic effects [157]. Exogenous NO activates HSP47 expression in keloid or lung fibroblasts via the TGF-β1/Smad2 signal pathway [158], which would promote organ fibrosis.

## Cancer treatment with inhibitors of HSP47

Mounting evidence implicates that HSP47 may be a potential therapeutic target for cancer patients. Inhibiting the expression of HSP47 has been proposed to suppress cancer progression. HSP47 also promotes fibrosis progression via enhancing collagen synthesis and is regarded as a potential target in fibrotic diseases [71,159,160]. Fibrosis and cancer are known to be inextricably linked, and their shared features and mechanisms indicate common targeted therapeutic approaches [161,162]. To date, several pharmacological inhibitors targeting HSP47 have antifibrosis effects, and some of these compounds may be candidate inhibitors [71,159,160]. Thus, these pharmacological inhibitors targeting HSP47 with antifibrosis effects should have antitumor effects. For instance, in NSCLC, pirfenidone, a pyridine compound with therapeutic potential for IPF, significantly inhibits fibrosis and decreases tumor growth [163].

### AK-778

AK-778 is an HSP47 inhibitor that competitively mitigates the interaction between HSP47 and collagen [164]. When cancer cells are treated with AK-778, type I collagen is destabilized. AK-778 can be degraded into two fragments named Col002 and Col003, and the inhibitory effect on HSP47 is due to Col003. Col003 inhibits collagen secretion by binding with HSP47 in its collagen-binding region [165]. HSP47 is also found to be exposed on the surface of platelets and to strengthen the interaction between platelets and collagen in the formation of thrombi and hemostasis [166]. Col003, through competitively binding to the collagen-binding site on HSP47, inhibits the interaction between them [165]. Col003 inhibits collagen-induced platelet aggregation, adhesion and exerted antiplatelet effect and protective effect against brain damage induced by ischemic stroke [167].

### Benzbromarone

Benzbromarone (BBR) has been identified as an HSP47 inhibitor, which can inhibit collagen production and secretion in fibroblasts from patients with keloid by binding to HSP47 and inhibiting the interaction between HSP47 and collagen [168]. Interestingly, BBR not only inhibits HSP47 but also acts as a molecular gel degrader to promote its proteasome-dependent degradation. Through these molecular mechanisms, BBR effectively reduces hypertrophic scarring or excisional skin damage [168].

### Caveolin-1 scaffolding domain peptide

Decreased levels of caveolin-1 have been linked to fibrosis in several diseases. Caveolin-1 scaffolding domain peptide has been demonstrated to serve as a surrogate for caveolin-1 and thereby to reverse fibrosis *in vivo* in the lung [169,170]. Caveolin-1 scaffolding domain peptide can inhibit the expression of HSP47 and exerts antifibrotic effects [171].

### Pirfenidone

Pirfenidone is an antifibrotic drug that can inhibit the progression of fibrosis in animal models and in patients with IPF [172]. Pirfenidone exerts its antifibrotic effect by suppressing HSP47 expression through downregulation of the TGF-β1 signaling pathway [173]. A recent study by Polydorou *et al*. demonstrates that pirfenidone improves blood vessel perfusion and enhances the antitumor efficacy of doxorubicin, increasing the drug efficacy in chemotherapy [174].

### Terutroban

Terutroban is a specific antagonist of the thromboxane receptor that has been demonstrated to have antifibrotic efficacy [175]. Terutroban suppresses the expression of HSP47 in the aortic tissues of rats [176], indicating that terutroban may be a possible treatment for diseases that have altered HSP47 expression, such as cancer.

### PSK

PSK, a protein-bound polysaccharide obtained from cultured mycelia of Coriolus versicolor in basidiomycetes, is a biological response modifier that has an antitumor action [177]. PSK is observed to suppress the expression of HSP47 and HSP60 in human tumor cell lines. The pharmacological potential of PSK is suggested in the diseases derived from the aberrant expression of HSPs [178].

### ND-L02-s0201

ND-L02-s0201 is a lipid nanoparticle encapsulating an siRNA that inhibits the expression of HSP47. ND-L02-s0201 treatment leads to the substantial reduction of HSP47 and improvement of histological parameters in fibrotic models [179]. A phase II study evaluating the safety, biological activity, and pharmacokinetics of ND-L02-s0201 in patients with IPF is in progress (study details|JUNIPER: A phase 2 study to evaluate the safety, biological Activity, and PK of ND-L02-s0201 in Subjects With IPF|ClinicalTrials.gov).

### BMS-986263

BMS-986263 is a retinoid-conjugated lipid nanoparticle delivering small interfering RNA designed to inhibit the synthesis of HSP47 protein [180–182]. Thus, BMS-986263-mediated HSP47 mRNA inhibition may reduce or reverse liver fibrosis by disrupting collagen formation and promoting hepatic stellate cell apoptosis, respectively [183]. BMS-986263 administration results in biopsy-assessed histopathological improvements in patients with advanced fibrosis [181], and further evaluation of BMS-986263 in patients with active fibrogenesis is warranted.

### Other inhibitors of HSP47

Okuno *et al.* [184] prepare human HSP47 as a soluble fusion protein expressed in *Escherichia coli* and establish an assay system for HSP47 inhibitor screening. A total of 1023 natural and synthetic compounds are screened, and 13 compounds exhibit inhibitory activity against human HSP47, of which three compounds (Punicalagin, chestanin, and epigallocatechin-3-O-gallate) inhibit HSP47 function in a dose-dependent manner [184]. Besides, other four additional compounds (methyl 6-chloro-2-oxo-2, 3-dihydro-1, 2lambda4 and 3-benzodithiazole-4-carboxylate) inhibit the function of HSP47 without affecting HSP47 synthesis have been identified and verified having antifibrotic effects by suppressing collagen expression [164,185].

### Problems and challenges with pharmacological inhibitors targeting HSP47

Although no treatment for cancer targeting HSP47 is yet available to the public, it is hoped that the above advantages and disadvantages will be considered in drug development [71]. In most cases, small-molecule inhibitors offer advantages in terms of drug-like properties, oral administration, and bioavailability, but they may exhibit potential side effects. HSP47 inhibitors are expected to cause side effects due to their inhibitory effect on collagen production. Collagens are the most abundant proteins in mammals and play structural roles and contribute to the mechanical properties, organization, and shape of tissues [22], and inhibition of HSP47 may lead to structural changes in connective tissue[18]. Targeting HSP47 might affect normal bone development. Besides, HSP47 interacts with IRE1α, a regulator of the UPR, during ER stress [21]. Targeting HSP47 may cause potential ER stress and accumulation of misfolded proteins. Given the side effects of small-molecule inhibitors, a therapy that suppresses HSP47 only at sites of particularly high HSP47 expression in tumors may be preferable. Therefore, targeted drug delivery is necessary. Nanodrug delivery systems have shown excellent performance in tumor-targeted therapy, given their unique targeting and drug-release characteristics [186,187].

## Conclusion and future perspective

HSP47 is frequently upregulated in a variety of cancers and plays an important roles in tumor progression. Higher HSP47 mRNA levels in patients with several cancers are significantly correlated with poorer OS. Various factors directly or indirectly affect HSP47 expression in cancer progression. Overall, understanding the relationship between HSP47 expression and cancer progression may contribute to the development of novel therapeutic strategies. However, there are still many challenges in validating the effectiveness of a therapeutic drug targeting HSP47 for the treatment of cancer. The first challenge is the development of drugs that can efficiently inhibit the overexpression of HSP47 at the specific sites of lesions in different cancers and the issue of drug delivery. The second challenge is the potential for off-target effects resulting from the selective inhibition of HSP47. Despite these issues, which need to be addressed in future research, HSP47 targeted therapy is considered a promising approach for treating cancer and is a worthwhile endeavor.

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### Conflicts of interest

There are no conflicts of interest.

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