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REVIEW – CANCER RESEARCH

The heat shock protein 47 as a potential biomarker and a therapeutic agent in cancer research

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Abstract

Heat shock protein 47 (HSP47) is an important chaperone required for the correct folding and secretion of collagen. Several studies revealed that HSP47 has a role in numerous steps of collagen synthesis, preventing procollagen aggregation and inducing hydroxylation of proline and lysine residues. HSP47 is encoded by the SERPINH1 gene, which is located on chromosome 11q13.5, one of the most frequently amplified regions in human cancer. The altered expression levels of HSP47 have been correlated with several types of cancer, such as cervical, breast, pancreatic and gastric cancers. Studies have shown that HSP47 promotes tumor angiogenesis, growth, migration and metastatic capacity. In this review, we highlight the fundamental aspects of the interaction between HSP47 and collagen and the recent discoveries of the role of this chaperone in different types of malignant neoplasias. We also discuss recent treatments using HSP47 as a therapeutic target, and present evidences that HSP47 is an essential protein for cancer biology and a potential molecular target for chemotherapy.

Keywords HSP47 · SERPINH1 · Collagen · Cancer · Therapeutic target

Introduction

The maintenance of cellular protein homeostasis (proteostasis) is essential for the proper function of the cell. The main compartment involved in the correct protein-folding process is the endoplasmic reticulum (ER), where a complex network of molecules assists with proteostasis (Dufey et al. 2015). At the core of this process are the chaperones, which support the correct maturation of new peptide chains (Brandvold and Morimoto 2015).

Heat shock protein 47 (HSP47) is an important chaperone required for the correct folding and secretion of various types of collagen (Natsume et al. 1994). This protein was first described in chicken embryo fibroblasts as an HSP that can bind to collagen type 1 (Nagata and Yamada 1986; Nagata et al. 1986). In 1991, with the determination of its nucleotide sequence, it was demonstrated that HSP47 belongs to the serpin family, despite the lack of serine protease inhibitory activity (Hirayoshi et al. 1991). However, the *HSP47* gene (SERPINH1) is transcriptionally modulated by a heat shock element (HSE) (Natsume et al. 1994).

In several types of cells, the expression of *HSP47* can be correlated with the expression of collagen. *HSP47* is highly expressed in cells such as chick embryo fibroblasts, which also express high levels of collagen (Hirayoshi et al. 1991). In addition, it has also been demonstrated that there are no detectable levels of HSP47 in cells that do not synthesize collagen type I, such as neuroblastoma and erythroleukemic cell lines (Clarke et al. 1993). In fibroblasts of chick embryos transformed by Rous sarcoma virus, the expression of both collagen I and HSP47 is decreased (Nagata and Yamada 1986). This effect is also observed in F9 teratocarcinoma cells. In these cells, the levels of *HSP47* and collagen type I and type IV are not detectable. However, when these cells are differentiated by treatment with retinoic acid, both *HSP47* and collagens show increased expression (TAKECHI et al. 1992).

Several types of cancer are associated with abnormal protein folding. In the last two decades, HSP47 has been described as an important chaperone in the control and maintenance of cellular proteostasis. In this paper, we review the importance of the interaction between HSP47

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and collagen and the role of this chaperone in different types of malignant neoplasias.

HSP47 and collagen maturation

Collagen is the most abundant protein in the body and the major component of the extracellular matrix (ECM). Collagen is composed of three α-chains, each with a triple-helix domain. These chains have three distinct domains: an N-terminal propeptide, a central collagen domain and a C-terminal propeptide. After translation, the C-terminal domains of the α-chains lead to recognition and the beginning of trimerization of the three α-chains. This process is accelerated by protein disulfide isomerase (PDI), which forms interchain disulfide bonds in this domain (Wilson et al. 1998). Subsequently, the molecule of collagen is transported and secreted via the ER–Golgi pathway (Fig. 1). When procollagen is in the extracellular environment, its N- and C-propeptide domains are cleaved by propeptidases, followed by ligation of collagen in the ECM (Layman and Ross 1973). HSP47 is capable of returning to the ER due to its RDEL ER-retention signal sequence and the KDEL receptors present in the Golgi membrane (Sauk et al. 1998).

HSP47 is essential for the correct folding of a collagen chain. During the formation of the collagen triple helix, regions of the molecule become hydrophobic. HSP47 binds to these regions and prevents aggregation of procollagens in the ER. The interaction between HSP47 and procollagens happens in a pH-dependent manner. In the range between pH 6.4 and 7, the fibril formation of type I collagen is inhibited by HSP47 ligation. When pH is decreased to a value of 6.3 or lower, fibril formation is increased. This occurs because the HSP47 structure is altered at lower pH, and this conformational change inhibits the ligation between HSP47 and collagen I (Thomson and Ananthanarayanan 2000). This explains why HSP47 is associated with procollagen in the ER, which has a neutral pH, and why it is dissociated from procollagen during the transport from the ER–Golgi compartment, which has a low pH (Nakai et al. 1992).

The central collagen domain is composed of 338 Gly–Xaa–Yaa repeats, where Xaa and Yaa are normally a proline or a hydroxyproline. In a previous work, in which various collagen model peptides were synthesized, it was revealed that the dominant binding site of HSP47 in collagen is formed by an Xaa–Arg–Gly triplet. In addition, it was demonstrated that HSP47 was able to bind to a procollagen molecule only when arginine (Arg) residues were incorporated in the Yaa position (Koide et al. 2002).

Several modifications are necessary for the correct formation and secretion of the collagen molecule. One key modification is hydroxylation of proline and lysine residues. These modifications only occur in unfolded chains and involve the three enzyme families prolyl 3-hydroxylases,

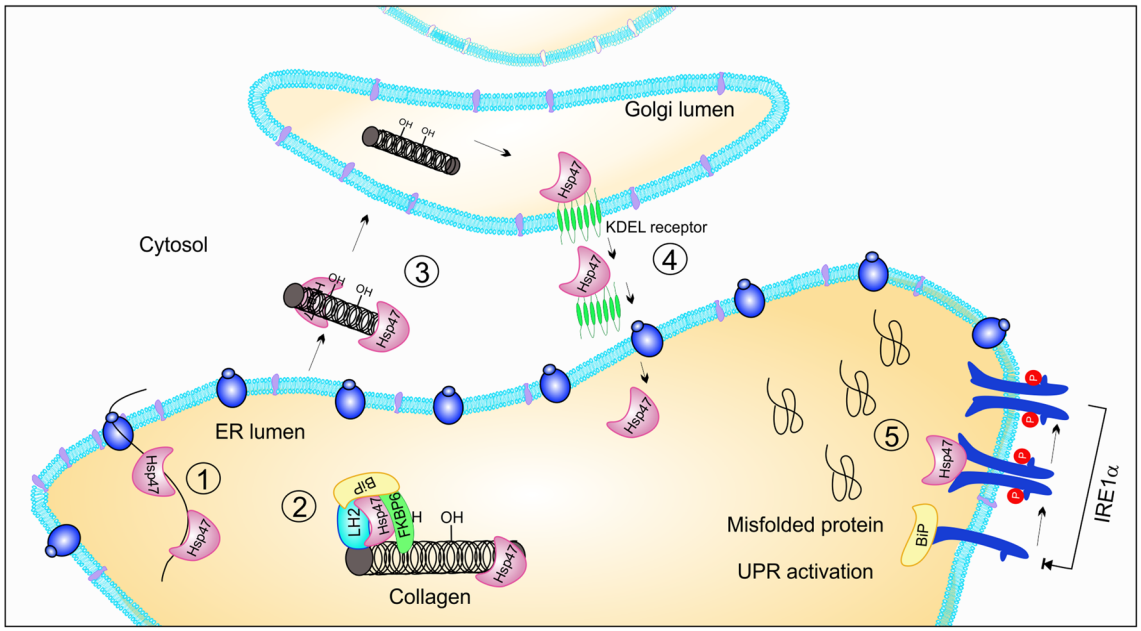

Fig. 1 Collagen synthesis and HSP47: a newly synthesized collagen is released into the ER, HSP47 binds to procollagen and prevents aggregation in the ER (1). A protein complex formed by LH2, FKBP65, HSP47 and BiP regulates lysyl hydroxylation (2). Then, the molecule of collagen is transported and secreted via the ER–Golgi pathway (3). HSP47 returns to the ER due to its KDEL ER-retention signal sequence (4). During ER stress, HSP47 binds with IRE1α, which reduces the association between IRE1α and BiP, leading to the activation of IRE1α (5)

prolyl 4-hydroxylases and lysyl hydroxylases. The activity of lysyl hydroxylase 2 (LH2) produces tissue-specific patterns of hydroxylation. These patterns modulate intra- and intercrosslinking between molecules and hence modulate the ECM (Walker et al. 2005). Alterations of these patterns can lead to changes associated with cancer metastasis (Chen et al. 2015).

In a recent work, Duran et al. (2017) described a chaperone complex that involved LH2 and HSP47. This complex regulated lysyl hydroxylation in type I procollagen, and it was composed of LH2, FKBP65, HSP47 and immunoglobulin heavy-chain-binding protein (BiP) (Fig. 1). BiP allows correct folding of nascent ER polypeptides and regulates the unfolded protein response (UPR). FKBP65 is a collagen chaperone resident in the ER, and the loss of its function leads to a decrease in lysyl hydroxylation. However, in cells with a reduction in HSP47 protein levels, there is an increase in lysyl hydroxylation of type I collagen (Lindert et al. 2015). Finally, the data from Duran et al. (2017) suggest that BiP participates in the formation of and affinity among the proteins in the complex. In addition, they also showed a balance between FKBP65 and HSP47 and that this balance is responsible for regulating lysyl hydroxylation (Duran et al. 2017).

Another important posttranslational modification that ensures collagen stability is glycosylation. Glycosyltransferases (GLT25D1 and GLT25D2) transfer galactose to the hydroxylysine residues of procollagen, preventing collagen from forming interchain crosslinks (Yamauchi et al. 1982).

HSP47 response to ER and Golgi stress

When misfolded/unfolded proteins accumulate in the ER, several signals lead to ER stress, triggering the UPR (Walter and Ron 2011). When the UPR is activated, expression of genes that improve protein folding is induced, and degradation of misfolded proteins is promoted as a way to re-establish ER homeostasis. A continuous ER stress state can lead to cell death, normally by apoptosis (Ma and Hendershot 2004). Chronic ER stress is a relevant factor in the development of pathological conditions, such as neurodegenerative diseases and cancer (Wang and Kaufman 2016).

Inositol-requiring enzyme 1 alpha (IRE1α) is an ER transmembrane protein and the most conserved ER stress signal transducer activated by the UPR. Activation of IRE1α leads to ER-associated degradation (ERAD), protein secretion and the expression of X-box binding protein 1 (XBP1), a transcription factor of genes involved in protein folding (Wang and Kaufman 2016). In a recent study, it was shown that HSP47 increases the activation of IRE1α by binding with the ER luminal domain of IRE1α and reducing the association between IRE1α and BiP (Sepulveda et al. 2018). The binding of BiP with the luminal domain of IRE1α preserves the inactive state of IRE1α (Kimata et al. 2003). Thus, a change in binding from BiP to HSP47 leads to activation of IRE1α (Fig. 1), and this results in ER stress attenuation (Sepulveda et al. 2018).

A major increase in protein secretion can cause insufficiency of Golgi apparatus functions and activation of the Golgi stress response. A disturbance in glycoprotein traffic by inhibition of O-glycosylation is an effective stimulus for the activation of the Golgi stress response (Sasaki and Yoshida 2015). To elucidate the role of HSP47 in the Golgi stress response, the expression of HSP47 was downregulated by small interfering RNA (siRNA) in NIH3T3 cells and treated with O-glycosylation inhibitor. The results showed that induction of Golgi stress in HSP47 knockdown cells caused cell death. HSP47-knockdown cells also exhibited an increase in cleavage of Golgi-resident caspase-2 and activation of mitochondrial caspase-9. Furthermore, the induction of Golgi stress also induced a UPR response. These discoveries could indicate that HSP47 protects the Golgi apparatus from the effects of O-glycosylation inhibition and protects cells from the Golgi stress response (Miyata et al. 2013).

Relationship among cancer, collagen and HSP47

ECM is essential to the support, resistance and organization of tissues. Moreover, it is responsible for numerous biochemical signals that modulate cellular function. The ECM comprises several components, such as collagen, laminin, fibronectin, glycoproteins, proteoglycans, and matricellular proteins. To develop cancer, an extensive reorganization of the ECM is necessary (Schedin and Keely 2011). This reorganization drives tumor progression through prosurvival and proliferative signals, promoting tumor metastasis. Deposition of collagen is higher in breast cancer cells than in nonmalignant mammary cells (Curran and Keely 2013). Furthermore, collagen was identified as a prognostic marker, and its expression is associated with cancer recurrence (Helleman et al. 2008).

HSP47 is encoded by the SERPINH1 gene, located on chromosome 11q13.5. This region is one of the most frequently amplified in human cancer (Schwab 1998). HSP47 promotes tumor growth and invasion, probably through regulation of the ECM network, and may be a possible biomarker and therapeutic target (Zhu et al. 2015). HSP47 has a 3′-UTR region in messenger RNA that is regulated by microRNA(miR)-29. Several works have demonstrated that miR-29 repressed the expression of HSP47, controlling the levels of this protein in cells (Yamamoto et al. 2013; Zhu et al. 2015). The downregulation of miR-29, leading to the upregulation of HSP47, has been correlated with several

types of cancer, such as cervical, breast, pancreatic and gastric cancer (Maitra et al. 2002; Hirai et al. 2006; Yamamoto et al. 2013; Zhu et al. 2015).

Gastric and colorectal cancer

Gastric cancer is the third most common type of malignant neoplasm (Ferlay et al. 2015). Good patient prognosis depends on several factors, and the stage of the tumor detection is critical. Thus, finding good biomarkers for early gastric cancer detection is essential and has been the subject of diverse scientific works that applied proteomic, transcriptomic and in silico analyses.

To determine novel biomarkers for gastric cancer, Zhang et al. (2010) performed an analysis with 22 genes imported into the public Affymetrix gene expression-profiling dataset. Of these genes, eight showed a significant difference ($p < 0.001$) in expression levels between the gastric cancer samples ($n = 22$) and healthy gastric tissue ($n = 8$), and *HSP47* was found to be upregulated in gastric cancer (Zhang et al. 2010).

Ulcerative colitis (UC) is a chronic condition that leads to inflammation and formation of ulcers in the colon and rectum. Patients with a longer disease duration seem to be at higher risk of neoplastic development (Ford et al. 2013). A proteomic approach for UC-associated cancer and sporadic colon cancer cell lines demonstrated elevated expression of HSP47 in UC-associated cancer compared with that in sporadic colon cancer. In addition, immunohistochemical analysis showed an increase in expression of HSP47 with the progression of cancer. Interestingly, HSP47 was also detected in the culture medium through a Western blot technique (Araki et al. 2009).

Association between HSP47 and colorectal cancer is also observed with the use of the isobaric tag for relative and absolute quantification (iTRAQ) method. In this study, Mori et al. (2017) identified proteins associated with lymph node metastasis in patients with colorectal cancer. A bioinformatic analysis demonstrated that HSP47 was the main potential biomarker. In addition to these data, they also validated their results through immunohistochemistry. The analysis also demonstrated that expression of HSP47 was significantly higher in lymph node metastasis than in colorectal cancer without metastasis (Mori et al. 2017). These data indicate a correlation between HSP47 and colorectal tumor aggressiveness, which can also be observed in obstructive colorectal carcinoma (OCC) (Xu et al. 2013).

OCC has a poor prognosis and a higher correlation with aggressive types of cancer (Fitchett and Hoffman 1986). The expression of HSP47 was strongly detected in obstructive carcinoma. OCC showed cancer cells with less differentiation and stromal myofibroblast proliferation leading to a fibrotic process. Coexpression of HSP47 with basic fibroblast growth factor (bFGF) in inflammatory cells may contribute to stromal fibrosis formation (Xu et al. 2013). A relation between HSP47 and fibrotic process is also observed in scirrhous carcinoma of the stomach and in cirrhotic human liver (Hirai et al. 2006; Poschmann et al. 2009). The effect of HSP47 on the fibrotic process may occur through the regulation of endothelin receptors A and B (ETBRA, ETBRB) by HSP47 (Zhao et al. 2017).

Pancreatic cancer

In a study with 57 cases of primary invasive pancreatic ductal adenocarcinomas, the expression of HSP47 was detected in all neoplastic samples. Interestingly, the expression of HSP47 was most intense in the tumor-associated stroma. Only a dispersed immunoreactivity was found in the fibroblast cells of ductal adenocarcinomas, and in 35% of cases, these cells did not express HSP47 (Maitra et al. 2002). In addition, in analyses of stroma of nonductal pancreatic neoplasms, all tested cases were positive for HSP47 (Cao et al. 2005). However, when HSP47 expression was analyzed in the cells of this neoplasm, the results were similar only in cases of pancreatoblastomas, with 75% of cases showing cells positive for HSP47. In acinar cell carcinomas and solid pseudopapillary tumors, the cells were positive for HSP47 in only 23 and 25% of cases investigated, respectively. Nevertheless, 100% of the cases analyzed of osteoclastic-like giant cells showed cells with HSP47 protein expression (Cao et al. 2005).

Gynecological cancers

Cancers in women's reproductive organs are referred to as gynecologic cancers and include cervical, ovarian, uterine, vaginal, and vulvar cancers (Tavassoli and Deville 2003).

In cervical squamous cell carcinoma (SCC), miR-29a is normally found to be downregulated (Li et al. 2011; Yamamoto et al. 2013). When its expression was restored in SCC cell lines, the migration and invasion capacity decreased. Luciferase reporter assays demonstrated that miR-29a acts by directly regulating HSP47 (Yamamoto et al. 2013). In addition to these results, analyses with cervical normal tissue, HPV16-positive SCCs, and HPV16-positive CIN2–3 (abnormal cells found on the surface of the cervix) also demonstrated a relationship between miR-29a and malignant transformation of cervical epithelial cells. Infection by human papillomavirus (HPV) is directly correlated with the development of invasive cervical cancer, and the results showed a small decrease in miR-29a in HPV16-positive CIN2–3 and a significant decrease in HPV16-positive SCCs when compared with that in normal tissue (Li et al. 2011).

17-AAG (17-allylamino-17-demethoxygeldanamycin) is a promising antitumor agent that acts through inhibition of

the molecular chaperone Heat shock protein 90 (HSP90). Despite the antitumor activity, treatment with 17-AAG increased expression of *HSP47* (Maloney et al. 2007). Conversely, 17-AAG disrupted the tumor suppressor pathway LATS–MST2–YAP. These findings may suggest that, although 17-AAG has antitumor activity, it is also involved in signaling pathways that promote tumorigenesis (Huntoon et al. 2010).

Breast cancer

Using gene coexpression network analysis, Zhu et al. (2015) discovered a coexpression network that participates in ECM remodeling from breast cancer tissues. In this network, *HSP47* appears as a nodal hub in the regulation of ECM, and their analysis showed that *HSP47* expression was activated during breast cancer development and progression. To determine the function of HSP47 in breast tumor progression, silencing of *HSP47* was carried out in breast cancer cell lines. Their results showed that HSP47 promotes cancer progression by increasing cell proliferation and invasion. In addition, silencing of HSP47 reduced the levels of collagen I and IV and fibronectin in the conditioned medium but did not alter the protein expression levels in cells, demonstrating the role of HSP47 in secretion of the ECM components (Zhu et al. 2015).

Human breast cancer cells silenced for HSP47 showed restricted tumor growth in xenograft assays. This probably occurs through a reduction in the secretion of collagen and fibronectin and hence their deposition in the ECM. Coexpression network analysis also revealed that levels of microRNA-29b and 29c are associated with expression of HSP47 and ECM network genes (Zhu et al. 2015). TGF-β expression was linked to several molecules that are part of the ECM (Xu and Mao 2011). Treatment with TGF-β also induced HSP47 expression in nonmalignant breast cell lines. In addition, blocking the TGF-β pathway with a TGFBR inhibitor reduced HSP47 expression in breast cancer cell lines. These results could indicate that HSP47 is regulated by the TGF-β pathway (Zhu et al. 2015).

The TGF-β pathway involves the activation of several molecules including SMAD3. SMAD3 is associated with the transcription activation of *GATA3* (Blokzijl et al. 2002), another protein correlated with HSP47 (Wang 1994).

GATA3 is a transcription factor that regulates luminal epithelial cell differentiation in the mammary gland (Kouros-Mehr et al. 2006). In breast cancer cells, there is a loss of GATA3 expression, and this fact is related to poor prognosis in patients. When expression of GATA3 was induced in breast cancer cells, there was suppression of metastasis, modification of the cellular microenvironment and increases in cellular differentiation. These effects are related to the induction of miR-29b expression through GATA3 (Chou et al. 2013). Interestingly, GATA3 is also related to the induction of HSP47 expression (Wang 1994). These data suggest a possible role for GATA3 in the balance of *HSP47* expression.

Lung cancer

Lung tumors are classified into small cell lung carcinoma and non-small cell lung carcinoma. This last group consists of squamous cell carcinoma (SCC), lung adenocarcinoma, and large cell carcinoma (LCC). Cells from normal human bronchial epithelium and squamous cell carcinoma tumors were analyzed in a comparative proteomic approach. The results showed that 32 proteins were differentially expressed between the two groups of cells and that HSP47 was overexpressed in squamous cell carcinoma. In addition to these data, immunohistochemical analysis of the different types of lung cancer revealed a significant coregulation between HSP47 and cytokeratins in squamous cell carcinoma (Poschmann et al. 2009).

Idiopathic pulmonary fibrosis is a chronic lung disease that can lead to lung cancer (Daniels and Jett 2005). Recent studies of miRNA expression demonstrated that miR-29a is downregulated in lung cancer and pulmonary fibrosis. Through a combination of gene expression analysis and in silico analysis of lung cancer cells and lung fibroblast cells lines, 24 possible targets of miR-29a were described. This microRNA is associated with the expression of LOXL2 and HSP47. When the expression of miR-29a is restored in lung cancer cell lines, the aggressiveness and the fibroblast migration capacity were repressed (Kamikawaji et al. 2016).

Osteosarcoma

Collagen I is the principal protein found in mature bone. In addition to the presence of a binding site for HSP47, collagen I also has a binding site for the serine protease inhibitor (serpin) pigment epithelium-derived factor (PEDF). This protein has shown anti-osteosarcoma properties with a protective effect against osteolysis and lung metastasis (Ek et al. 2007b). PEDF was also capable of decreasing the angiogenesis, migration and invasion capacity in experiments in vivo and in vitro with two osteosarcoma cell lines (Ek et al. 2007a). Nevertheless, it was observed that PEDF upregulates collagen I and HSP47 in osteosarcoma cells in vitro (Alcantara et al. 2014).

In a study by Uozaki et al. (2000), the expression of HSP27, HSP47, HSP60, HSP70 and HSP90 was analyzed by immunohistochemical staining in 70 cases of conventional osteosarcoma in the bones of the extremities. The overexpression rate of HSP47 (94%) was higher than that of other HSPs. However, the expression of HSP47 does not

demonstrate a relationship with poor prognosis in patients (Uozaki et al. 2000).

Glioblastoma

Grade IV glioblastoma multiforme (GBM) is the most aggressive form of brain tumor. Overexpression of HSP47 was described in analyses of tissues and glioma cell lines, and this expression was correlated with the grade of the disease (Wu et al. 2014, 2016; Zhao et al. 2014; Jiang et al. 2016). Knockdown of HSP47 using small interfering RNAs inhibited growth, viability, migration and invasion capacity in glioma cells lines in vitro and decreased tumor volume in vivo (Zhao et al. 2014; Wu et al. 2016). The relationship between HSP47 and these cellular mechanisms was also demonstrated through overexpression of *HSP47* by lentivirus infection. In this experiment, it was found that overexpression of *HSP47* promotes glioma formation, invasion and angiogenesis. The effect observed is probably caused by regulation of ECM components through the TGF-β pathway (Jiang et al. 2016).

In addition to the remodeling of the ECM, another fundamental mechanism for tumor growth and metastasis is angiogenesis (Sato 2003; Nishida et al. 2006). Thus, pericytes have an important role in tumor development (Hosaka et al. 2016). Analyses with pericytes in glioma tissues demonstrated that these cells express HSP47 (Wu et al. 2016; Hosono et al. 2017). Knockdown of HSP47 in human umbilical vein endothelial cells decreased the proliferation and migration of the cells and inhibited tube formation. A decrease in HSP47 expression reduced the microvessel density in vivo. Furthermore, gene array and Western blot analyses demonstrated that HSP47 promoted glioma angiogenesis via HIF1α-VEGFR2 signaling (Wu et al. 2016). Therefore, HSP47 can be considered as a potential therapeutic target of GBM.

Tumor immunotherapy treatment with directional targets for cytotoxic T lymphocytes (CTL) leads to tumor regression in several types of neoplasias (Azuma et al. 2016; Verma et al. 2016; Suekane et al. 2017; Wu et al. 2017). The tumor-associated antigen can be a highly differentially expressed gene. In a prospective study, Wu et al. identified two peptides of HSP47 that were candidate epitopes for CTL treatment. The T-cell immune response was analyzed in GBM patients by stimulation with the peptide mixture. The results showed that the GBM patients with a positive CTL response to HSP47 experienced a prolonged progress-free survival time and overall survival (Wu et al. 2014).

Head and neck cancers

Cancers collectively known as head and neck cancers typically begin in the squamous cells and, rarely, in the salivary glands (Huntoon et al. 2010). To understand the role of HSP47 in these types of cancers, analyses of HSP47 were performed in lines of human squamous cell carcinoma of the head and neck (SCCHN) in a comparative mode with a primary gingival fibroblast cell line. The expression of HSP47 was positive for all cell lines, but when the analysis was performed for cell surfaces only, the expression of HSP47 was detected only in SCCHN lines. The invasion capacity of SCCHN cells was evaluated using modified Boyden chambers. The results showed variance among the different cell lines, and this variance could be associated with the level of HSP47 expressed on the cell surface. Unexpectedly, cell lines expressing high levels of HSP47 revealed the lowest migratory index (Hebert et al. 1999).

To understand how HSP47 is anchored in the cell membrane, several immunoprecipitation assays were performed, and the immunoprecipitation assays using anti-CD9 and anti-HSP47 antibodies confirmed that these proteins precipitated together. Reimmunoprecipitation of the CD9 with anti-HSP47 confirmed the interaction between these two proteins in all SCCHN lines. These findings indicated that HSP47 may be anchored in the cell membrane in a complex with CD9 (Hebert et al. 1999). In a previous work, Sauk et al. showed that HSP47 could be recycled and is not permanently anchored to the cell surface (Sauk et al. 2000).

HSP47 as a therapeutic target in cancer

To investigate the potential of HSP47 as a molecular target for chemotherapy, a water-soluble polymeric drug delivery system containing an HSP47-binding peptide sequence and the chemotherapeutic agent doxorubicin (Dox) was tested in SCCHN cell lines. The HSP47-binding peptide sequence WHYPWFQNWAMA (Hebert et al. 2001) and the chemotherapeutic agent Dox were attached to the polymer via a tetrapeptide spacer. The treatment of SCCHN cell lines with the polymer-drug conjugate proved that the drug delivery system is recognized by the HSP47 receptors and that after its recognition, drug internalization and intracellular release occur (Nan et al. 2005).

In the same way, an *N*-(2-hydroxypropyl) methacrylamide (HPMA) copolymer was bound with a peptide sequence WHYPWFQNWAMA (Hebert et al. 2001) as a targeting ligand and synthesized by a simple synthetic route. Subsequently, 1,3-dimethylol-5-FU, derived from 5-fluorouracil (5-FU), was attached to the polymer. After polymer formation and internalization of the polymer, cytotoxicity and apoptosis assays were evaluated in an SCCHN cell line. All experimental results were compared to those of treatment with 5-FU and a copolymer without the peptide sequence from HSP47. The results showed that the polymer with the HSP47 peptide exhibited the highest cytotoxic efficacy,

the fastest internalization, and an increased apoptotic and necrotic induction of tumor cells when compared to the other conditions (Xiang et al. 2012).

In the development of new chemotherapies, HSP inhibitory molecules emerged as an important strategy. Inhibition of HSP47 is an attractive therapeutic intervention, because unlike other chaperones, HSP47 has collagen as a unique substrate. In this context, a screen with 2,080 compounds identified four molecules that have inhibitory activity against HSP47. After the definition of IC50 values, these compounds were tested in cell culture, and the inhibitory activity against HSP47 was proven (Thomson et al. 2005).

AK778 was described as an inhibitory molecule that competitively inhibited the interaction between HSP47 and collagen. When the cells were treated with AK-778, the molecule of collagen was destabilized. Further experiments demonstrated that AK-778 was degraded into two fragments named Col002 and Col003, and the inhibitory effect on HSP47 was due to Col003. Experiments also demonstrated that Col003 inhibited collagen secretion in vivo by binding with HSP47 in its collagen-binding region (Ito et al. 2017).

Pirfenidone is an antifibrotic drug commonly used for the treatment of idiopathic pulmonary fibrosis (Sharbeen et al. 2015). Pirfenidone exerts its antifibrotic effect by suppressing HSP47 and collagen I expression through downregulation of the TGFβ signaling pathway (Nakayama et al. 2008). Supported by positive clinicals studies, pirfenidone was approved for treatment of idiopathic pulmonary fibrosis. In a recent study by Polydorou et al., it was demonstrated that pirfenidone improves blood vessel perfusion and intensifies the antitumor efficacy of Dox, increasing the drug efficacy in chemotherapy (Polydorou et al. 2017).

Terutroban is a specific antagonist of the thromboxane receptor (TP) that has demonstrated a high antithrombotic efficacy (Siller-Matula et al. 2010). Gelosa et al. demonstrated that terutroban suppresses the expression of HSP47 in the aortic tissues of rats treated with this drug. In addition, quantitative PCR also showed a suppression of TGF-β expression (Gelosa et al. 2011). These discoveries suggest that terutroban could be a possible treatment for diseases that have altered HSP47 expression such as cancer.

Conclusions

HSP47 expression can be directly correlated with several types of cancer, and this protein is emerging as a possible biomarker and therapeutic target in malignant neoplasms. Nevertheless, the expression of HSP47 in different types of cancer has divergent effects. Although in some types of cancer, like glioblastoma and breast cancer, HSP47 is associated with aggressiveness (Zhu et al. 2015; Jiang et al. 2016), in osteosarcoma HSP47 has an indirect protective effect against osteolysis and lung metastasis (Alcantara et al. 2014; Kobayashi et al. 2014). Therefore, more studies are necessary to understand the influence of HSP47 in tumor development.

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Compliance with ethical standards

Conflict of interest Author Beatriz Dal Pont Duarte declares that she has no conflict of interest. Author Diego Bonatto declares that he has no conflict of interest.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

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