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REVIEW

HSP47 in human diseases: Navigating pathophysiology, diagnosis and therapy

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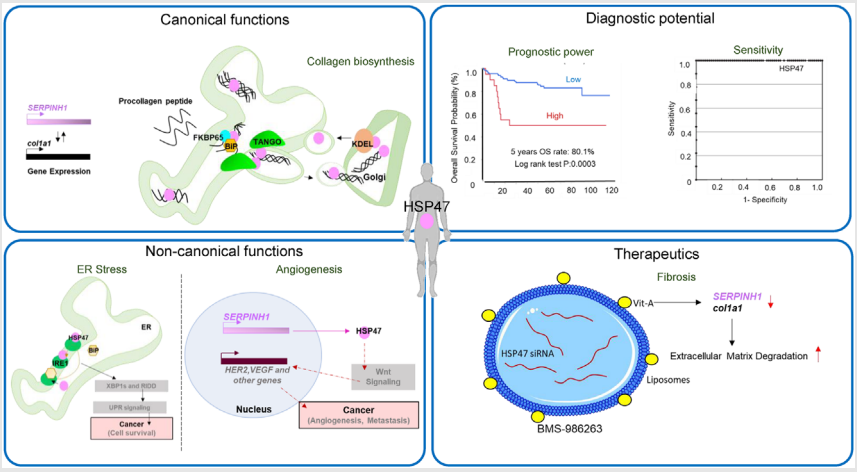
Graphical Abstract



- HSP47 plays a crucial role in collagen biosynthesis and tissue-specific functions, contributing to fibrosis and collagen-related disorders.
- Beyond collagen assembly, it is involved in diverse cellular processes like ER stress, angiogenesis, metastasis and thrombosis.
- HSP47 dysfunction is associated with various cancers, diabetes and neurodegenerative diseases.
- HSP47 serves as a versatile biomarker and therapeutic target across a wide range of pathologies.

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Abstract

Heat shock protein 47 (HSP47) is a chaperone protein responsible for regulating collagen maturation and transport, directly impacting collagen synthesis levels. Aberrant HSP47 expression or malfunction has been associated with collagen-related disorders, most notably fibrosis. Recent reports have uncovered new functions of HSP47 in various cellular processes. Hsp47 dysregulation in these alternative roles has been linked to various diseases, such as cancer, autoimmune and neurodegenerative disorders, thereby highlighting its potential as both a diagnostic biomarker and a therapeutic target. In this review, we discuss the pathophysiological roles of HSP47 in human diseases, its potential as a diagnostic tool, clinical screening techniques and its role as a target for therapeutic interventions.

KEYWORDS
biomarker, heat shock protein 47 (HSP47), human disorders, therapy

1 | INTRODUCTION

Molecular chaperones are essential for maintaining cellular proteostasis by intricately guiding proteins folding and refolding processes, delicately balancing the functionality of over 20 000 proteins in humans.[1] The aberrant function of these molecular chaperones is often characterized as either loss-of-function or toxic gain-of-function contributing to human diseases.[2] Heat shock protein 47 (HSP47), a molecular chaperone, unfolds a narrative far beyond its initial collagen-centric role.[3] It is traditionally understood as a collagen-specific molecular player involved in collagen folding, quality control and assembly inside the cells.[4,5] It has a constitutive expression with synthesized collagen, which helps in tissue-specific functions.[5,6] Aberrant expression or function of HSP47 is involved in collagenopathies.[4,5,6] It can either be linked to mutation in HSP47 itself leading to defective collagen production in diseases like osteogenesis imperfecta (OI) and epidermolysis bullosa or due to overexpression of collagen in fibrosis.[3] Beyond its canonical role, it interacts with other cellular processes, and new functions have been discovered in promoting various disease like cancers,[7–9] autoimmune diseases (diabetes type 1[10]) and neurodegenerative diseases.[11] Furthermore, recent reports highlight its diagnostic potential as a biomarker[12] and therapeutic target.[13] Here we shed light on the pathophysiological role of HSP47, discuss its diagnostic potential and techniques used to screen it for clinical implementation and its role in therapy.[1–13]

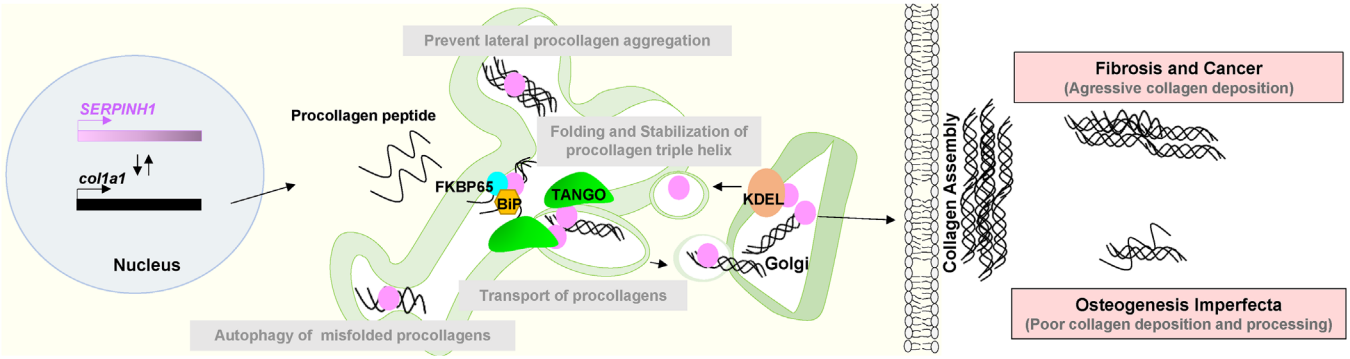

FIGURE 1 Heat shock protein 47 (HSP47) in collagen biosynthesis. HSP47 (Pink), a chaperone protein expressed by *SERPINH1*, facilitates collagen (COL1a1) folding and stabilization in the endoplasmic reticulum (ER).[3,4] Interacting with chaperones (FKBP65 (Blue), binding immunoglobulin protein (BiP) (Yellow)), it regulates collagen posttranslational modifications, prevents misfolded collagen aggregation and aids in procollagen transport to the Golgi via Transport and Golgi Organization (TANGO1) interaction.[23,26] Elevated HSP47 levels promote aggressive collagen deposition in fibrosis[48,49] and cancer,[59] whereas low levels cause poor collagen processing in osteogenesis imperfecta.[83]

2 | ROLES OF HSP47 IN PATHOPHYSIOLOGY

2.1 | Canonical roles of HSP47

2.1.1 | Collagen as a classical client

HSP47 functions as a collagen-specific molecular chaperone.[3,4] It is involved in various essential functions related to collagen biosynthesis and maturation, comprehensively explained elsewhere (Figure 1).[3,14,15] Once procollagen peptides enter the endoplasmic reticulum (ER) and the initial triple helices form, HSP47 binds to the triple-helical structure, stabilizing and further folding the protein.[16,17] Alongside other chaperones, it prevents procollagen aggregation, thereby promoting quality control of misfolded protein.[16,18–20] HSP47 facilitates the transport of folded procollagen from the ER to the Golgi apparatus, dissociates procollagens and is then recruited back to the ER via KDEL receptors.[5,21] Constitutive expression of HSP47 with collagen synthesis has been shown to contribute to tissue-specific functions.[3,6,10,13] Although the mechanism of how HSP47 regulates collagen expression or vice versa is poorly understood, it acts as a critical player in folding and regulating collagen homeostasis.

2.1.2 | Interaction with co-client of collagen during ER exit

HSP47 plays a crucial role in the dynamic interplay with key proteins that helps in the collagen folding and transport machinery. During procollagen folding, it engages in a molecular duet with proteins like FKBP265 (a member of the FK506-binding protein family) and Transport and Golgi Organization (TANGO).[22] Recent reports suggest that FKBP65 and HSP47 cooperate in collagen maturation during normal bone development, but this interaction is impaired in mutant HSP47 OI cells.[23] Additionally, HSP47, FKBP65 and binding immunoglobulin protein (Bip) modulate the activity of lysyl hydroxylase 2 (catalyse hydroxylation of lysines on collagen), contributing to the regulation of connective tissue quality through collagen modification.[24]TANGO1 is involved in loading large extracellular matrix (ECM) proteins like collagens into COPII vesicles for intracellular transport.[25] It indirectly interacts with collagens through its Src homology 3 domain binding to HSP47, guiding procollagens to COPII vesicles.[26] In summary, HSP47's role in collagen packaging transcends mere escort duty, positioning it as a central player in collagen biosynthesis.

2.2 | Non-canonical roles of HSP47

Recently, new interactions of HSP47 have been discovered beyond its role in collagen assembly in unfolded protein response (UPR), angiogenesis and platelets-induced thrombosis and haemostasis. These novel interactions may have implications for various cellular processes.

2.2.1 | ER stress

The UPR is a dynamic signalling network that helps maintain the proper functioning of the ER.[27] Inositol-requiring enzyme 1 (IRE1), a crucial part of the UPR acts as a sensor to manage the protein-folding balance in the ER.[28] Under normal conditions, a chaperone protein called BiP keeps IRE1 in an inactive state. However, when there is stress in

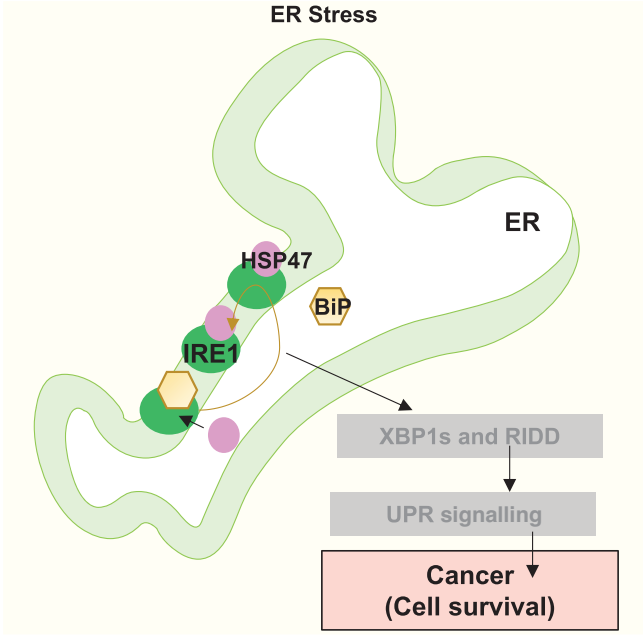

FIGURE 2 HSP47 regulates unfolded protein response(UPR) in ER stress. It binds toInositol-requiring enzyme 1 (IRE1), kicking off BiP, and helps IRE1 cluster and activate, which aids in managing ER stress. In cancer, it interacts with calreticulin and IRE1α to help the cells survive and resist chemotherapy by escaping ER stress.[30]

the ER due to misfolded proteins, BiP releases IRE1, allowing it to become active. Studies have shown that HSP47 has a strong affinity for IRE1 and displaces BiP in a tug-of-war, allowing IRE1 to cluster and become active.[7,29] In breast and pancreatic cancer, Hsp47 promotes chemoresistance by interacting with calreticulin and IRE1α, thus escaping ER stress[30] (Figure 2). In simpler terms, HSP47 regulates IRE1, and this interaction is a flexible and adaptive part of the UPR pathway, helping cells cope with ER stress.

2.2.2 | VEGFR2 signalling mediated angiogenesis

Vascular endothelial growth factor (VEGF) plays a focal role in the formation of blood vessels (vasculogenesis and angiogenesis).[31] Excessive VEGF disrupts intracellular barriers, increases leakage of the choroid plexus endothelia, evokes oedema and activates the inflammatory pathway in disorders like cancer[32] and cardiovascular diseases.[33] In glioblastoma, silencing HSP47 showed a reduction in the VEGF, HIF1α, PLCγ, ERK1/2 and Src and angiogenic gene expressions. It had a vice versa effect on its up-regulation, indicating a possible role of HSP47 in enhancing angiogenesis in glioma angiogenesis through the HIF1α-VEGFR2 signalling[34] (Figure 3).

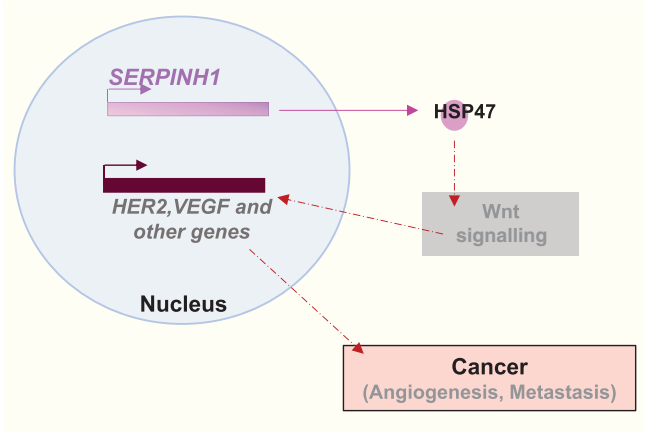

FIGURE 3 HSP47in cancer associated angiogenesis. It promotes angiogenesis via Wnt-Vascular endothelial growth factor (VEGF)-HSF-1 signalling.[34,66]

In head-and-neck squamous carcinoma, there is an increase in both HSP47 and VEGF expression under hypoxia. However, when treated with a stress kinase inhibitor, this increase reversed.[35] ERK pathway activation combined with C–C motif chemokine ligand 2 induction promotes HSP47-induced angiogenesis in bladder cancer.[36] Moreover, HSP47 inhibitors have also been shown to reduce VEGF-induced fibrovascular retinal fibrosis.[37] Therefore, these findings highlight the role of HSP47 in angiogenesis.

2.2.3 | Platelets and thrombosis

Thrombosis refers to the process of blood clot formation. It is initiated by platelets adhering to the injury site and releasing molecules like thromboxane A2 and ADP which promotes platelet aggregation through fibrinogen and fibrin clot formation.[38] Dysregulation of these processes contributes to pathologies like atherosclerosis, where platelet-driven thrombosis can lead to serious cardiovascular events.[39] Studies have revealed that HSP47 is exposed on the surface of activated human platelets.[40] It has been identified to help platelet collagen-binding to promote platelet aggregation, highlighting its significance in platelet function and coagulation processes41 (Figure 4). Interestingly, HSP47 has been shown to promote cancer metastasis by enhancing collagen-dependent cancer cell-platelet interaction.[8] Therefore, HSP47 may be one of the important players in the platelet paradigm and its physiological processes.[42]

Altogether, Hsp47 demonstrates functions extending beyond collagen assembly, engaging in diverse cellular mechanisms. Nevertheless, the underlying mechanisms governing these functions remain to be fully elucidated.

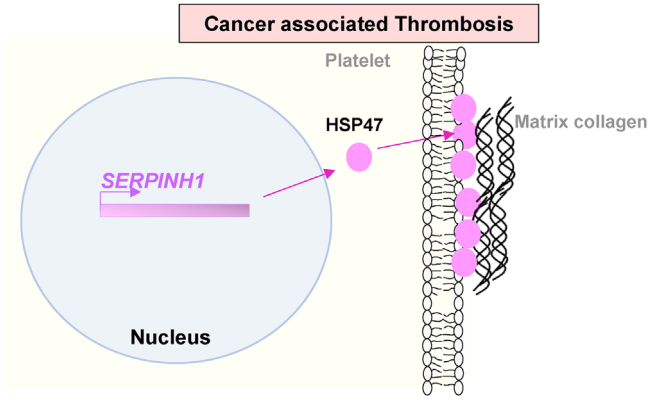

FIGURE 4 HSP47in cancer associated thrombosis. Cell membrane-bound HSP47 helps platelets stick to the collagen matrix, promoting platelet aggregation and blood clotting in cancer.[40,41]

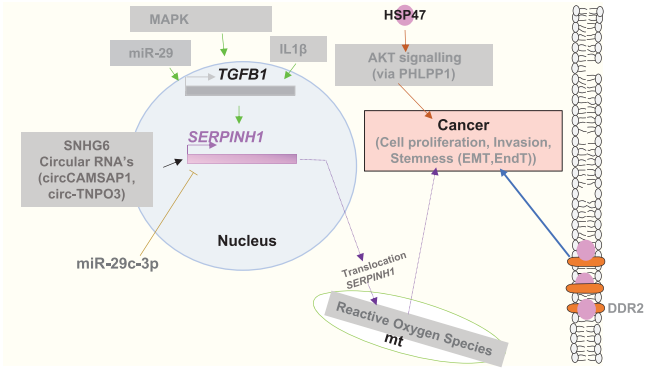

FIGURE 5 HSP47 linked to fibrosis and cancer stemness, proliferation and survival. HSP47 is up-regulated in fibrosis and cancers through TGFβ1 signalling,[60] circular RNAs[62] or small nucleolar RNA Host Gene 6 (SNHG6)[61] or cancer survival and metastasis (via AKT-PHLPP1 signalling[65]). Translocation of the HSP47 gene causes mitochondrial (mt) stress and reactive oxygen species (ROS) to induce cancer.[67] HSP47 bound discoidin domain receptor tyrosine kinase 2 (DDR2) on cell surface promotes cancer.[68]

3 | HSP47 IN HUMAN DISEASES

Given the emerging functions of HSP47 in diverse biological processes, it is not surprising that its expression and abundance are increasingly linked to disorders, encompassing both collagenopathies (fibrosis[43]) and non-collagenopathies (neurological disorders[11]). In the following, we present a few examples that document the broad spectrum of such disorders associated with HSP47.

3.1 | Fibrosis

Fibrosis is attributed to excess deposition of ECM components majorly collagen defined by the hardening, overgrowth and scarring of various tissues leading to organ dysfunction and eventual death.[44] The severity of the disease varies depending on the type of tissue affected.[45] Myofibroblasts, activated cells that produce aberrant collagen, are key mediators of fibrosis.[45] They are generated through processes such as epithelial/endothelial-mesenchymal transition (EMT/EndMT)[46] and from circulating fibroblast-like cells called fibrocytes, derived from bone marrow stem cells.[47] A cycle of myofibroblast accumulation occurs due to their resistance to apoptosis, influencing EMT through increased matrix stiffness and positive feedback on TGF-β1 activation.[44] HSP47 expression is up-regulated by unsolicited TGF-β1 activation through the MAPK signalling pathway or by IL1β alone or in combination with TGF-β[48,49] (Figure 5). Both mediators enhance HSF 1 trimerization, increasing its affinity for the heat shock element[48] and leading to HSP47up-regulation causing deposition of defective collagens in tissues, contributing to a fibrotic environment that further amplifies HSP47 up-regulation.[43] Clinical data shows that Hsp47 is up-regulated in various tissue-specific fibrosis and can act as a molecular signature to assess the disease progression.[50–56] Elevated HSP47 in fibrosis is also associated with myocardial infarction,[57] atherosclerotic arteries[57] and scleroderma patients.[58] In conclusion, HSP47 emerges as a critical player in fibrotic processes across diverse tissues, and its up-regulation has a diagnostic potential for assessing disease progression.

3.2 | Cancers

Fibrotic diseases and cancer share several characteristics; both pathologies are characterized by uncontrolled cell proliferation, genetic and cellular alterations, and tissue invasion. In the last decade, accumulating evidence suggests the role of HSP47 in the progression of various cancers. The *SERPINH1* (HSP47 gene) is located on chromosome 11q13, a region usually amplified in human cancers.[59] Up-regulation of HSP47 is associated with increased cancer progression and its expression in the tumour-associated stroma.[12] TGF-β signalling appears to play a crucial role in regulating HSP47 expression to promote HSP47-induced tumour progression and stemness in glioblastoma.[60] Small nucleolar RNA host gene 6 up-regulation has also been shown to activate HSP47 expression by competitive binding to miR-139-5p to promote hepatocellular carcinoma.[61] Recently, circular RNA has been shown to enhance HSP47 expression by binding to its mRNA and promoting various cancer progressions. For instance, in nasopharyngeal carcinoma, splicing factor-derived circular RNA (circCAMSAP1) has accelerated tumourigenesis via the HSP47/c-Myc positive

feedback loop.[62] Another circular RNA, circ-TNPO3, binds to Insulin-like growth factor 2 mRNA-binding protein 2, destabilizing HSP47 mRNA and inhibiting clear cell renal cell carcinoma metastasis.[63] High levels of HSP47 have been linked to various cancer promoting cascades getting activated. For example, HSP47 promotes cell migration and invasion through the AKT signalling pathway in non-small cell lung cancer.[64] It has also been shown to promote the growth of colorectal cancer (CRC) tumours and suppress the efficacy of chemotherapy via modulation of AKT-PHLPP1 signalling.[65] It also regulates the EMT of gastric cancer metastasis through the Wnt/β-catenin signalling.[66] Additionally, translocation of HSP47 has shown the generation of mitochondrial reactive oxygen species in human neuroblastoma.[67] Moreover, HSP47 sustains the membrane localization and stability of discoidin domain-containing receptor 2, promoting EMT in breast cancer.[68] Clinical data suggest that HSP47 has a role in the prognosis of laryngeal squamous cell carcinoma by inhibiting cell viability and invasion and promoting apoptosis.[69] Preoperative HSP47 levels identify CRC patients with lymph node metastasis and poor prognosis.[12] HSP47 is regulated by miR-29 during breast cancer progression. The underlying possible mechanism is through the HSP47/Smad3 signalling pathway.[70–72] Tumour-suppressive microRNA-29a inhibits invasion and cancer cell migration via targeting HSP47 in cervical squamous cell carcinoma.[73] These findings highlight the multifaceted role of HSP47 in cancer and related pathological conditions (Figure 5), positioning it as a promising target for further research and potential therapeutic interventions.

3.3 | Osteogenesis imperfecta

OI, also known as brittle bone disease, is a phenotypically and molecularly heterogeneous group of inherited skeletal disorders, which is characterized by irregular connective tissue morphology and mineralization.[74,75] OI can be broadly classified into two types. Dominant OI forms (90% of all cases) are generally induced by mutations of type I collagen itself, whereas recessive OI forms originate due to alterations in collagen posttranslational modification machinery.[76] HSP47 deficiency in recessive OI fibroblasts has been shown to promote inadequate collagen deposition causing inefficiently mineralized bone fragility.[77,78] Homozygous missense mutation, point mutation or deletion in *SERPINH1* (c.233T > C, p.L78P,[79] c.338_357del22,[80] c.314_325del p,[81] (c.149 T > G, p. L50R,c.1214 G > A, p. R405H[82]), p.(R222S)[83]) has been reported to cause HSP47 deficiency manifesting severe OI with blue sclerae and dentogenesis imperfect. Moreover, a functional single nucleotide polymorphism in the promoter of *SERPINH1* has been associated with increasing the risk for preterm rupture of membranes.[84] OI patients carrying bi-allelic variants of KDELR2 (KDEL ER protein retention receptor 2) were identified to impair the KDEL receptor binding to HSP47, hindering HSP47's dissociation from collagen and release into the ECM space.[85] In summary, HSP47 mutation or deficiency impairs posttranslational modification, trafficking and deposition of ECM collagen in recessive OI patients.

3.4 | Diabetes mellitus

Diabetes mellitus is a long-term metabolic condition characterized by elevated blood glucose levels due to low insulin production or the body's inability to use insulin effectively.[86] Type 1 diabetes mellitus is often classified as an autoimmune disorder.[87] In this form of diabetes, the immune system mistakenly targets and destroys the insulin-producing beta cells in the pancreas.[88] The autoimmune attack leads to a significant reduction or complete absence of insulin production, resulting in elevated blood glucose levels.[87,88] The exact cause of this autoimmune response is not fully understood, but a combination of genetic and environmental factors is believed to play a role.[87–89] In diabetic nephropathy, advanced glycation end products increase the expression of HSP47 in association with collagens through TGF-β.[90] Hsp47 up-regulation in the later stages (sclerotic phase) of streptozotocin-induced diabetic nephropathy is associated with glomerulosclerosis and tubulointerstitial fibrosis.[91] High glucose in retinal Müller cells induces HSP47 up-regulation and the secretion of inflammatory factors through the IRE1α/XBP1/HIF-1α pathway in diabetic retinopathy.[91] HSP47 also induces diabetes-related kidney disease in children, positioning it as a potential target for diabetic therapeutic interventions.[92] Therefore, HSP47 is an important chaperone that contributes to disease progression in diabetes.

3.5 | Neurodegenerative diseases

Neurodegenerative diseases refer to a group of disorders characterized by progressive degeneration of the nervous system.[93] Common neurodegenerative diseases include Parkinson's disease, Alzheimer's disease (AD) and Huntington's disease.[94] The exact causes of neurodegenerative diseases are complex and involve a combination of genetic, environmental and age-related factors.[94] Work by the group of Ferdinando Di Cunto revealed an association of HSP47 with the β-amyloid precursor protein, a common component enriched in amyloid plaques primarily

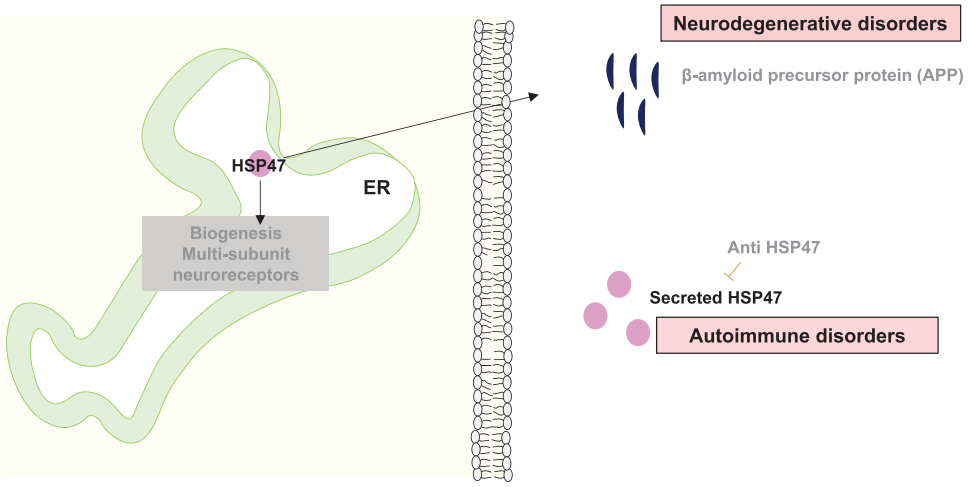

FIGURE 6 HSP47 in autoimmune and neurological disorders. HSP47 interacts with multi-subunit neuroreceptors and promotes β amyloid precursor protein (APP) secretion in neurodegenerative diseases[11,95] and contributes to autoimmune disorders through unsolicited secretion.[97]

found in AD mouse models and patients.[11] Inhibition of HSP47 reduced the levels of secreted Aβ peptides, implying HSP47 is a prominent target for preventing the formation and growth of amyloid plaques in AD patients. Moreover, HSP47 has been associated with the biogenesis of multi-subunit neuroreceptors in the ER, indicating its role in neurological processes[95] (Figure 6). These findings collectively emphasize the significance of HSP47 in neurological diseases and highlight its potential as a therapeutic target for conditions involving collagen synthesis and ECM remodelling.

3.6 | Rheumatic autoimmune diseases

Autoimmune rheumatic diseases (ARDs) are primarily associated with the joints, bones, muscle and connective tissue defects that are challenging to diagnose during early stages, presenting nonspecific symptoms and signs.[96] Sera of patients with ARDs such as rheumatoid arthritis (RA), Sjögren's syndrome, systemic lupus erythematosus and mixed connective tissue disease (MCTD) have significantly high amounts of HSP47 protein and autoantibody levels[97] (Figure 6). Notably, the sera of MCTD patients have elevated levels of HSP47 antigen and anti-HSP47 autoantibodies, which is considered a useful marker. In RA patients, up-regulated levels of HSP47 in synovial fibroblasts have been reported as a reliable marker for synovial fibroblasts quantification.[98]

The above-mentioned examples linking Hsp47 expression to various diseases highlight the significance of Hsp47 in diverse pathophysiology. Although Hsp47 may not be the cause for the progression of all the disease entities, it could perpetuate and potentially worsen the underlying pathophysiology. In either scenario, the prevalence and correlation of Hsp47 with diseases make it compelling for diagnostics.

4 | Diagnostic potential of HSP47

HSP47 has garnered significant attention for its potential as a diagnostic biomarker across various diseases, particularly in collagen-related disorders such as fibrosis, making it a promising diagnostic biomarker.[5,16] In Crohn's disease (CD), HSP47 has been shown to differentiate between fibrotic and non-fibrotic forms, presenting itself as a prospective diagnostic marker for treating CD-related fibrosis.[99] Furthermore, serological assessment of HSP47 has been identified as a signature of the fibrosis stage in early compensated alcohol-related liver disease (Figure 7A), emphasizing its diagnostic relevance.[100] Additionally, HSP47 serves as a prognostic marker in various cancers as it is over-expressed in most tumours (Figure 7B). In lung squamous cell carcinoma, it has been shown to distinguish between histopathological grades.[101] In CRC, HSP47-positive cells in the cancer stroma are proposed as a predictive biomarker for lymph node metastasis and poor prognosis[12] (Figure 7C). In pancreatic ductal adenocarcinoma, HSP47 expression is almost universally intense in ductal adenocarcinoma-associated stromal desmoplasia, underscoring its potential diagnostic implications.[102]In ulcerative colitis (UC), where there is an elevated risk of colorectal carcinoma, HSP47 overexpression stands out as a unique signature for grading different UC-associated carcinomas[103] (Figure 7D). Furthermore, the use of HSP47 as a marker for increased collagen metabolism has been instrumental in comparing

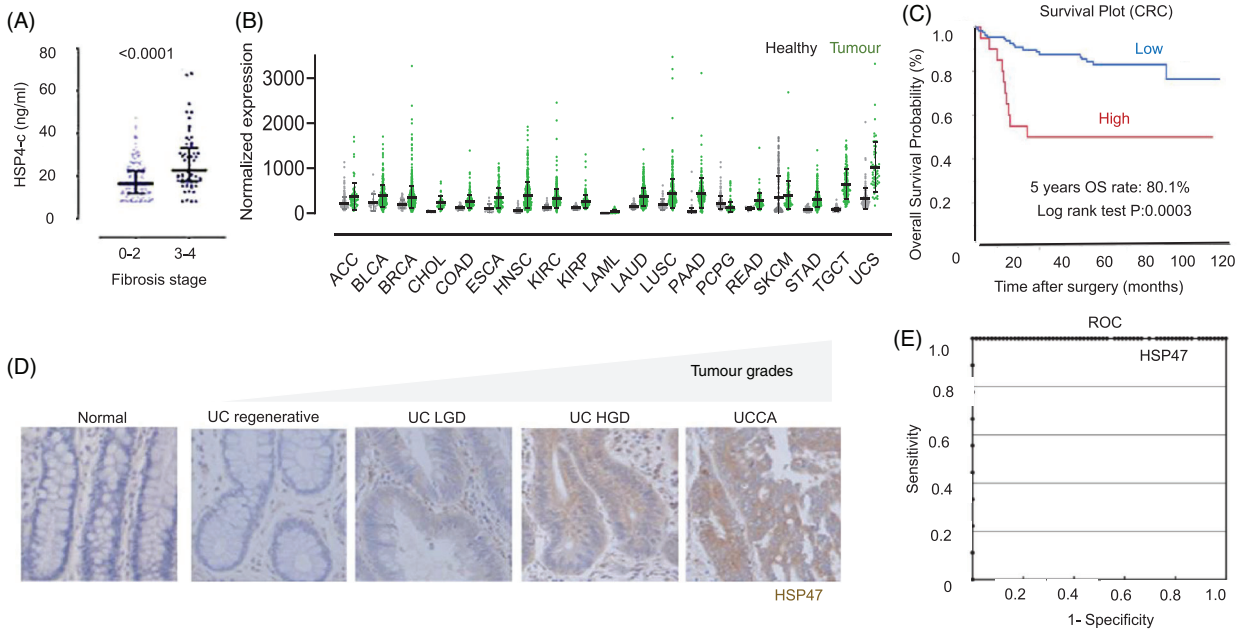

FIGURE 7 HSP47 as a potent biomarker. (A) HSP47-c levels as a prognostic determinant for alcohol-related liver disease patients divided into two cohorts based on histological fibrosis stage, F0-2 and F3-4.[100] (B) HSP47 in human tumours (green) compared to their healthy counterparts (grey). (C) High-level HSP47 (Red) is associated with lower survival probability in colorectal cancer.[12] (D) HSP47 expression used for grading different ulcerative colitis (UC)-associated carcinomas as a biomarker. UCLGD (UC low-grade dysplasia); UCHGD (UC high-grade dysplasia); UCCA (UC-associated adenocarcinoma).[103] (E) Highest diagnostic accuracy for HSP47 which discriminated between acute interstitial pneumonia (AIP) and the other IIP patients and healthy volunteers with 100% sensitivity, 98.5% specificity and a diagnostic accuracy of 98.7% assessed by measuring serum HSP47 level with area under the curve of 1.000.[105] *Source*: All figure parts are reproduced with permission. (B) Data of patients obtained from https://oncodb.org/index.html.

different treatments for bladder cancer, shedding light on its potential utility in assessing treatment responses.[104] Beyond cancers, patients diagnosed with acute interstitial pneumonia exhibit significantly elevated serum levels of HSP47 compared to those with cryptogenic organizing pneumonia (COP), nonspecific interstitial pneumonia, idiopathic pulmonary fibrosis and healthy volunteers. The diagnostic performance, evaluated using the ROC threshold, demonstrated exceptional sensitivity (100.0%), specificity (98.5%) and an overall diagnostic accuracy of 98.7%[105] (Figure 7E). Furthermore, HSP47 expression, influenced by its intron or synonymous variants, is linked to increased body fat traits, determining the extent of body adiposity and suggesting its potential as a diagnostic marker in obesity.[106] Taken together, HSP47 holds promise as a versatile biomarker and potential therapeutic target across a wide range of pathological conditions.[13]

5 | TECHNIQUES USED FOR SCREENING HSP47

To date, a variety of techniques, including immunohistochemistry (IHC), Western blotting (WB),[17] ELISA[105] and q-PCR,[10] have been employed to study HSP47 and its associated processes (Table 1). Although each technique provides unique insights into HSP47 expression and function, not all are readily adaptable for clinical use. In a clinical context, IHC WB and ELISA are commonly used in research laboratories and could potentially be adapted for diagnostic purposes, provided standardized protocols and quality control measures are established. IHC allows for the visualization of HSP47 expression in tissue samples, offering insights into its localization within specific tissues with limited quantitative information.[6] WB, on the other hand, facilitates the quantitative assessment of HSP47 protein levels in cell lysates, enabling the determination of HSP47 abundance but with Hsp47 antibody having high quality and specificity.[17] Other approaches like fluorescence microscopy,[17] flow cytometry[9] and in situ hybridization[107] offer valuable insights into HSP47's subcellular distribution, single-cell expression and mRNA localization, and their clinical implementation may pose challenges due to the need for specialized equipment, cost and expertise.

ELISA shows promise for clinical use, allowing quantitative measurement of HSP47 in biological fluids, potentially indicating its presence systemically. From a diagnostic point of view, it is likely the preferred non-invasive method for real-time detection of HSP47 compared to

TABLE 1 Techniques for diagnosing heat shock protein 47 (HSP47).

Diagnostic technique	Pros	Cons	Potential clinical benefits
Immunohistochemistry (IHC)[6]	Visualizes HSP47 expression in tissue samples	Limited quantitative data	Identifying HSP47 overexpression in specific tissues
Western blotting[17]	Quantitative assessment of HSP47 protein levels	Requires high-quality antibodies for specificity	Determining HSP47 abundance in various cell lysates
ELISA (enzyme-linked immunosorbent assay)[108]	Allows quantitative measurement of HSP47 in biological fluids	Limited to extracellular or secreted HSP47	Assessing HSP47 levels in blood or urine for systemic indications
qPCR[109]	Detects HSP47 mRNA levels, providing insight into transcriptional regulation	Limited information on posttranslational modifications	Examining gene expression changes in response to stimuli
Fluorescence microscopy[17]	Enables visualization of HSP47 localization within cells	Limited resolution for certain cellular structures	Identifying subcellular localization and organelle interactions
Flow cytometry[17]	Quantifies HSP47 expression at the single-cell level	Requires dissociation of tissues for single-cell analysis	Characterizing HSP47 levels in distinct cell populations
In situ hybridization (ISH)[107]	Visualizes the localization of HSP47 mRNA in tissues	Limited quantitative data	Correlating HSP47 expression with tissue-specific pathology

biopsy tissues analysis. However, this technique is only limited to detecting ECM or secreted HSP47 unless cell lysates are used.[108] q-PCR, used to detect HSP47 mRNA levels, may be employed in a clinical setting for evaluating gene expression profiles associated with HSP47, particularly in diseases like cancer.[109] Taken together, biochemical techniques for detecting HSP47 are available, but their clinical implementation requires careful optimization, protocol standardization and quality control measures for reliability. These techniques offer a comprehensive understanding of HSP47's functional importance and diagnostic potential in human disorders, potentially revealing insights into its role in pathologies affecting cells with limited regenerative potential. Given HSP47's involvement in various cellular processes like protein folding, cell membrane display, secretion and tissue homeostasis, perturbations in its biology could have detrimental effects. Further advancements in HSP47 detection technologies could offer new insights into its activities and consequences. Ideally, generalized guidelines are essential for their clinical applications. For instance, standardized ELISA and qPCR assays, with established normal ranges for HSP47 levels, distinguishing between ECM and intracellular isoforms of HSP47 with defined positive and negative controls is a necessity.

6 | HSP47 IN THERAPY

HSP47 is an established therapeutic target for treating fibrosis and cancer.[110–112] Here, we discuss a few examples of available therapeutic concepts for targeting HSP47 (Table 2). Small molecule inhibitors are one of the most accessible drug molecules that bind to proteins and interfere with their biological functions.[113] Small-molecule inhibitors targeting HSP47 have shown potential for controlling fibrosis and metastasis at low micromolar concentrations.[110,112] Using chemical inhibitors, it is possible to reduce the levels of secreted Aβ peptides by targeting HSP47 expression or interfering with its activity.[11] HSP47 Inhibitor (Col003) reduced collagen-induced platelet activation against brain damage induced by ischemic stroke.[111] Pirfenidone, a commercially available drug, is effectively reduces murine bleomycin-induced pulmonary fibrosis by attenuating HSP47 expression.[114] Aspirin has shown a protective effect against renal damage under stress conditions by targeting HSP47-mediated pathways in poultry.[115,116] SB203580 (4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-imidazole) is a stress kinase inhibitor that inhibits p38 MAPK by blocking MAPKAPK-2 activation and HSP phosphorylation.[117] Its treatment has shown down-regulation of collagen XVIII, CBP2/Hsp47 and VEGF expression induced by liver fibrosis and hypoxia.[118,119] Another approach is to use peptide drugs that have shown great potential for targeting HSP47.120 Engineered LDS affinity peptide with lanthanide-doped SPIO nanoparticles treatment has shown effective targeted therapy in cancer cells.[120] Natural compounds and derivatives, identified through in silico methodology, have shown a potential to modulate HSP47. Compounds like silymarin and curcumin have been shown to block the HSP47-procollagen complex, demonstrating therapeutic applicability in conditions such as liver fibrosis, keloids and pulmonary fibrosis.[121,122] Furthermore, calcium

TABLE 2 Therapeutic strategies used to target heat shock protein 47 (HSP47).

Therapeutic approach	Pros	Cons	Potential clinical benefits	Phase
Small-molecule inhibitors[110–112,114]	Broad applicability with potential for oral administration	May have off-target effects on other cellular processes	Inhibiting HSP47 function in various fibrotic diseases	Preclinical trail
Peptide-based inhibition[120]	Targeted disruption of HSP47-procollagen interaction	Limited tissue penetration for certain peptides	Blocking collagen secretion and fibrosis progression	
Natural compounds and derivatives[121,122]	Potential therapeutic agents with diverse mechanisms	Variable bioavailability and efficacy among compounds	Modulating HSP47 levels using natural anti-fibrotic agents	
Calcium channel blockers[123,124]	Impact on HSP47 expression through alternative pathways	Systemic effects on calcium homeostasis and other processes	Regulating fibrosis by modulating calcium signalling	
Receptor antagonists (Nintedanib)[127,128]	Inhibition of crucial signalling pathways involved in fibrosis	Side effects and tolerability concerns in some patients	Slowing disease progression in conditions like IPF	
siRNA targeting[131]	Specific suppression of HSP47 expression	Delivery challenges for effective siRNA uptake	Attenuating fibrosis by reducing collagen synthesis	BMS-986263, Phase2 clinical trail(2022) (NCT03420768)[132]

channel blockers, such as meloxicam, have demonstrated the potential to reduce fibrosis by down-regulating the expression of HSP47 and collagen genes in animal models.[123,124] Tetrandrine treatment in BDL rats has shown a decrease in HSP47, collagen 1, α-SMA and Pcol1A1 in fibrotic rat livers.[125,126] Receptor tyrosine kinase inhibitors like Nintedanib have also shown promise in down-regulating the expression of HSP47 and collagen genes, offering potential therapeutic benefits in fibrotic diseases.[127,128] Moreover, vitamin A-coupled liposomes containing HSP47 siRNA are effective in treating skin fibrosis in chronic graft-versus-host disease.[129] ND-L02-s0201, an HSP47 siRNA lipid nanoparticle, has been shown to reverse interstitial pulmonary fibrosis in preclinical rat models.[130] HSP47 siRNA with NOX4-modulating mesoporous silica-based nanoparticles has shown promising dermal delivery for treating fibrosis.[130] Using a preclinical model, an RNA ligand-tethered lipid nanoparticle (AA-T3A-C12) has shown about ~65% silencing of HSP47, leading to a significant reduction in liver fibrosis.[131] In 2022, a Phase 2 trial investigated the efficacy of BMS-986263, aimed at reducing hepatic fibrosis in HCV-SVR patients by targeting HSP47 mRNA.[132,133] Although there were slight improvements in METAVIR and Ishak scores at Week 12, further research is necessary to fully understand its potential benefits, despite the generally manageable adverse events reported.

Considering these broad spectra of therapeutic approaches targeting HSP47, it is evident that there is a rich landscape of potential treatments for fibrosis and cancer. However, there is still much to be explored. Future research should focus on optimizing existing therapies, discovering new compounds and investigating combination therapies to enhance the efficacy of HSP47-targeting treatments while minimizing adverse effects. Furthermore, although HSP70, HSP90 and HSP47 have received significant attention,[110,134] exploring other HSP in clinical trials could provide valuable insights into accelerating the development of effective treatments for numerous disease entities.[135]

7 | CONCLUSION

With the advent of new functions of HSP47, it is no surprise that this chaperone protein is implicated in various diseases, including fibrosis, cancer and neurodegenerative disorders accentuating its significance as a diagnostic biomarker and therapeutic target. Its dynamic expression patterns serve as an indicator of disease progression and therapeutic response. Targeting HSP47 offers promising interventions, particularly in conditions involving excessive collagen deposition and fibrosis. Advanced detection

techniques like immunoassays have enabled precise quantification and localization of HSP47 that can guide personalized treatment strategies. Overall, exploiting HSP47's multifunctional roles holds promise for improving clinical management and developing therapeutics for enhanced healthcare.

AUTHOR CONTRIBUTIONS

Essak. S. Khan: Conceptualization; literature survey; figures preparation; writing original draft; review and editing. **Tobias Däinghaus**: Literature Survey; writing original draft and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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