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Heat Shock Protein 27(HSP27) in Kidney Disease: Potentials for Diagnosis and Therapy

Shahenda Mahgoub

Biochemistry and Molecular Biology Department, Faculty of Pharmacy, Helwan University, Cairo, Egypt.

Cairo, Egypt, Tel.: +202-01005056094

E-mail address: shahenda.mahgoub@pharm.helwan.edu.eg; shahendamahgoub@gmail.com
scientifickitty2003@yahoo.com

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ABSTRACT

The small HSP27 is an actin-specific molecular chaperone involved in cytoskeleton architecture, cell migration, metabolism, survival, growth/differentiation, mRNA stabilization, and tumor progression. HSP27 is detected in nearly all cells with different expression levels. A variety of stimuli induce expression and/or phosphorylation of HSP27. HSP27 phosphorylation affects some of its cellular functions as phosphorylation affects HSP27 oligomerization, which in turn has an impact on some of HSP27 functions. HSP27 has been involved in different kidney diseases playing protective and counter-protective roles. HSP27 shows a protective role against several stressors as reactive oxygen species, hypoxia, osmotic stressors, etc. HSP27 and phospho-HSP27 protein levels are increased in stressed and diseased cells. The current review presents HSP27 in the pathogenesis of different kidney diseases as renal injury, fibrosis and renal cell carcinoma, highlights its role as a potential biomarker and offers new therapeutic options through manipulation of HSP27.

Keywords: HSP27, Kidney disease, Protective, Stress.

INTRODUCTION

Heat shock proteins (HSPs) are universally expressed across nearly all phyla and classified according to molecular weight. They affect several key biological processes such as cell division, survival¹, differentiation, actin cytoskeleton regulation, and resistance to injury resulted from reactive oxygen species (ROS), as well as other cell stressors². Thermal, oxidative, hemodynamic, osmotic, and hypoxic stresses³ induce HSP90, HSP70 (in human)/HSP72 (in rodents), HSP60 and HSP27(in human)/HSP25 (in rodents) expression, resulting in cytoprotection.⁴

HSP27 or HSP beta-1 (HSPB1) belongs to the family of small HSPs which includes nine other isoforms designated: HSPB2 to HSPB9⁵⁻⁷. HSP27, an actin-specific molecular chaperone, can be detected in the majority of examined cells, although the expression

levels seem to vary from undetectable or fairly low expressed levels in some cells to abundant expression in other cells.⁸⁻¹⁰ HSP27 expression can be induced by diverse conditions, including heat shock, oxidative stress (OS) with other stress conditions in addition to nerve injury, and differentiation.^{8,11,12}

Khan *et al* showed that elevated intra-renal HSP27 levels are normally expressed in the medulla¹³ a kidney region subjected to severe hypoxia^{14,15} and osmotic stress^{13,16} suggesting that HSP27 plays a defensive role against these two stresses.¹⁷⁻¹⁹ Moreover, HSP27 plays an important role in actin cytoskeletal remodeling in proximal tubules²⁰ as well as modulation of mesangial and smooth muscle cells contractions.^{21,22} HSP27, as a stress protein, has been reported to be a potential useful molecule in acute ischemic renal failure^{18,23,24} along with chronic obstructive nephropathy²⁵ through promoting cell regeneration and adaptation to stress conditions.

Crucial roles of HSP27 in response to different stresses

HSP27 acts by key mechanisms as protein folding, actin cytoskeleton remodeling, OS reduction and suppression of apoptosis diverse modes or other cell death forms. HSP27 up-regulation, a biomarker of some disease states, is probably the cell's try to survive by using HSP27 to prevent cell death or to decrease OS²⁶ which is considered a stress condition during which HSP27 acts as an antioxidant molecule, raising intracellular glutathione levels besides lowering intracellular iron levels so as to decrease ROS.²⁷ Moreover, during chemical stress, HSP27 shows an anti-apoptotic response through interacting with mitochondrial dependent and independent apoptotic pathways. HSP27 is above all involved in protection from programmed cell death via inhibition of caspase-dependent apoptosis²⁸, **Figure 1**. The anti-apoptotic properties of HSP27 in response to chemicals that create a chemical stress condition in the cells, has major consequences on the success of some chemotherapies such as doxorubicin and gemcitabine.^{29,30}

HSP27 response to stress conditions in kidney disease

Due to the diversity of complications and the complexity of the underlying disturbances, chronic kidney disease seems to be an ideal model of cell and organ responses to long-lasting multi-factorial stress conditions. Multiple factors act as the potential machinery of this stress mixture as uremic toxins, inflammatory mediators, ROS, apoptosis, infections, moreover, the dialysis itself which also act a stress factor.³¹

Furthermore, Lin *et al.* have shown that HSP27 expression in the aortas of rats that underwent subtotal nephrectomy was decreased.³² This deficiency was most evident in the advanced atherosclerotic lesions, which confirm the potential cytoprotective role of this HSP.³¹ Alternatively, the anti-apoptotic and protective roles of HSP27 reported by several studies in the ischemia-reperfusion injury showing the active adaptive changes following kidney transplantation.³³⁻³⁵

HSP27 and acute renal failure

One of the most common causes of acute renal failure is ischemia/ reperfusion (I/R) which causes formation of ROS, lipid peroxidation, DNA damage, in addition to protein dysfunction, leading to renal structural and functional impairment.³⁶ Studies revealed that HSPs, as molecular chaperones, promote cellular tolerance to I/R injury. Elevated post-ischemic expression of HSP27 may account for the reduced disruption of tubular epithelium cytoskeleton, attenuation of OS^{24,37,38}, plus stabilizing of microfilaments, preventing protein dysfunction³⁹ and

reducing ischemia induced membrane lipids degradation.⁴⁰⁻⁴² The lack of HSPs alongside degenerative lesions in the renal tubular epithelial cells may lead to electromechanical dissociation, resulting in acute renal failure.⁴³

HSP27 in diabetic nephropathy

Previous studies have reported an increase in the phosphorylated HSP25 (the rodent homolog of human HSP27) in the diabetic glomeruli.⁴⁴⁻⁴⁶ Phosphorylated HSP25 plays a crucial role in the regulation of actin cytoskeletal dynamics. In vitro data by Dai *et al.* demonstrated that podocyte exposure to stretch, mimicking glomerular capillary hypertension, induced a rapid and significant elevation in phosphorylated HSP27 levels. Simultaneously exposure of podocytes to high glucose level led to increased HSP27 phosphorylation.⁴⁴ HSP25 is phosphorylated by upstream p38 mitogen-activated protein kinase (p38MAPK).⁴⁷⁻⁴⁹

A study showed synchronized activation of the glomerular p38MAPK-HSP25 pathway, acutely after the induction of diabetes with streptozotocin (Stz-DM) in rats, together with conservation of the podocyte actin cytoskeleton and normo-albuminuria. However, when Stz-DM becomes chronic, activation of this pathway declines, cleavage of F-actin produces G-actin monomers, and podocyte effacement (retraction) and albuminuria occur.⁴⁴ With these associations, Ma *et al.* hypothesized that early activation of that pathway might be a functional adaptation that maintained podocyte structure and function and prevented glucose stressor induced albuminuria.⁵⁰

Furthermore, HSP27 up-regulation in response to injurious high-glucose or Angiotensin II-rich environment, as in diabetic nephropathy (DN), forbids podocytes apoptosis and improves their tolerance to those adverse stressors⁵¹. Recently serum HSP27 concentration was found to be related to the incidence of DN in type 2 diabetic patients and that serum HSP27 may be used as an early marker for diagnosis of DN.⁵²

Chronic allograft nephropathy (CAN) affecting expression of HSP27

CAN is a chronic stress state subsequent to kidney transplant which is mainly characterized by chronic inflammation. Stimulation of HSP25/27 and alteration in the expression pattern from the renal medulla to the cortex has been observed. Apoptotic markers such as: Bcl-2 [B-cell lymphoma 2]-associated X protein (Bax) and Fas Ligand as well as markers of hypoxia as: Hypoxia-inducible factor (HIF-1 α) and Manganese Superoxide Dismutase were observed besides the shift in HSP27 expression pattern. Accordingly, when conditions in the kidney become hypoxic, HSP27 is up-regulated as a protective response.⁵³

Abnormal HSP27 phosphorylation in kidney disease

Involvement of anomalous HSP27 phosphorylation in several diseases has been reported, still the molecular mechanisms explaining this implication is to be recognized.⁵⁴ Animal models of nephrotic syndrome and DN showed enhanced HSP27 phosphorylation compared to control animals.^{44,46,55} Abnormal HSP27 phosphorylation is also observed in renal cancers, as well as in other kidney diseases.⁵⁶ Furthermore, over-expression of HSP27 has been contributed to tumor progression in a variety of cancers including Renal Cell Carcinoma (RCC). Various HSP27 phosphorylation patterns were correlated with the aggressiveness of tumor phenotype. Moreover, increased HSP27 phosphorylation was reported to be associated with increased tumor progression in RCC. Up-regulation of kinases along with down regulation of phosphatase may be playing the main role in creating the environment of enhanced phosphorylation in over-expressed HSP27.⁵⁷ The correlation of HSP27 over-expression with poor prognosis of cancer through protecting malignant cells from undergoing apoptosis was illustrated by Vidyasagar *et al.*. Thus, HSP27 could be targeted for prevention and management of fibrosis and cancer.²⁶ Increased phosphorylated levels of HSP27 may also participate in the patho-physiology of kidney tubulo-interstitial fibrosis through up-regulation of E-cadherin which is a reported biomarker for epithelial to mesenchymal transition (EMT), thereby promoting EMT of tubular epithelial cells into myofibroblasts.⁵⁸

HSP27 and tubulo-interstitial fibrosis

Under stress conditions, resident fibroblasts expand by cell division generating pro-fibrotic molecules. Several fibroblasts associated diseases can arise from tubular epithelia at the injury site through EMT.⁵⁹ EMT is also linked to cell migration, actin reorganization, tubular basement membrane disruption, and profibrotic molecules generation.⁵⁹⁻⁶¹ EMT can be induced by OS, hypoxia, transforming growth factor β 1 (TGF- β 1), interleukin-1, and tissue-invasive mononuclear cells. During EMT, tubular epithelial cells are gradually changed into myofibroblasts.⁶²⁻⁶⁴ HSP27 produces its cytoprotective achieve through modulation of the actin cytoskeleton in addition to inhibition of OS and apoptosis.⁶⁵⁻⁶⁷ It also plays a role in inflammation, cell signaling, differentiation as well as proliferation.^{68,69} It is therefore logical to hypothesize that HSP27 is involved in the pathogenesis of induced EMT and chronic tubulo-interstitial fibrosis through its induction by growth factors as TGF β 1 and OS besides its role as an actin specific molecular chaperone and as an antioxidant molecule.⁵⁸

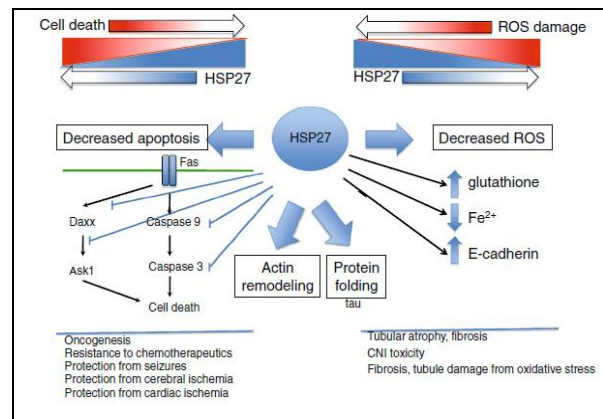


Figure 1 Some of the major mechanisms of HSP27 on disease states.²⁶ HSP27 acts on protein folding, actin cytoskeleton remodeling, reduction of oxidative stress and suppression of apoptosis or other kinds of cell death.

DAXX: Death-associated protein 6, ASK1: Apoptosis signal regulating kinase 1, Fas: a death receptor on the surface of cells that leads to apoptosis.

HSP27 in nephrotic syndrome

Nephrotic syndrome is characterized by retraction or effacement of the distal processes of glomerular epithelial cells (GEC) enclosing the capillary loops. These processes form a vital component of the kidney's filtration barrier. HSP27 phosphorylation is required for the polymerization of actin microfilaments which mainly control GEC distal processes structure. Enhanced HSP27 expression/phosphorylation in podocytes was reported in experimental nephrotic syndrome, suggesting that HSP27 may regulate polymerization of GEC foot process actin, maintaining normal foot process structure along with its implication in the pathophysiologic changes in these processes during development of the nephrotic syndrome.⁷⁰

CONCLUSIONS

The present review highlights some of the data considering HSP27 in its diagnostic and protective or therapeutic role in various kidney diseases. Despite increasing evidence to verify HSP27 as biomarker in many diseases, more studies are needed to evaluate its specific response. Another challenge lies in applying this knowledge towards therapy through understanding of HSP27 phosphorylation state in each disease condition. There are studies to utilize HSP27 as a therapeutic target in cancer. The future of HSP27 therefore ensures its development as a therapeutic agent and target.

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