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MINI REVIEW

Heat shock proteins and kidney disease: perspectives of HSP therapy

Natalia Chebotareva[1] · **Irina Bobkova**[1] · **Evgeniy Shilov**[1]

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Abstract Heat shock proteins (HSPs) mediate a diverse range of cellular functions, prominently including folding and regulatory processes of cellular repair. A major property of these remarkable proteins, dependent on intracellular or extracellular location, is their capacity for immunoregulation that optimizes immune activity while avoiding hyperactivated inflammation. In this review, recent investigations are described, which examine roles of HSPs in protection of kidney tissue from various traumatic influences and demonstrate their potential for clinical management of nephritic disease. The HSP70 class is particularly attractive in this respect due to its multiple protective effects. The review also summarizes current understanding of HSP bioactivity in the pathophysiology of various kidney diseases, including acute kidney injury, diabetic nephropathy, chronic glomerulonephritis, and lupus nephritis—along with other promising strategies for their remediation, such as DNA vaccination.

Keywords Kidney diseases · Molecular chaperones · Tissue protection · DNA vaccines · T cell regulation

Introduction

In 1999, Kitamura et al. formulated a new concept of kidney self-defense, which was based on a well-known phenomenon of enhancement of local tissue defense in response to environmental stresses. The authors hypothesized that after initiation of an inflammatory process, the kidney tissue may acquire a potential for protecting itself from further activation and injury. "Thermotolerance" is one example of such a tissue defense. In various tissues and cultured cells, the exposure to thermal stress induces activity of a number of stress proteins, so-called heat shock proteins (HSPs), thereby affording tolerance against subsequent insults. The activity of HSPs (chaperones) is one of the most effective kidney protection mechanisms.

The HSPs or stress proteins are highly conserved molecules that play a range of functions, including cytoprotection, intracellular assembly, protein folding, and translocation of oligomeric proteins (Hightower 1991). HSPs can play an important role in the intra- or extracellular defense of the kidney tissue. In addition to being constitutively expressed (up to 5–10% of the total protein content under normal growth conditions), the synthesis of these proteins can be induced (up to 15% of the total cellular protein content) by a range of cellular insults (Welch 1993). The constitutively expressed intracellular HSPs control maturation and turnover of intracellular proteins and play significant role in the maintenance of cellular integrity. Intracellularly, HSPs facilitate the formation of the secondary and tertiary structure of other proteins and also participate in the processes of repair or removal of damaged denatured protein molecules or their toxic aggregates. The inducible HSPs are synthesized in response to environmental perturbations, such as inflammation, ischemia, and oxidative stress, as defending molecules that protect tissues from further injuries (Lindquist and Craig 1998; Pockley 2003). They mainly act as intracellular chaperones, protecting protein structure and folding under stress condition. HSPs are also able to assist with numerous reparative processes including the refolding of denatured proteins and removal of irreparably damaged proteins (Kampinga and Craig 2010). Under certain

✉ Natalia Chebotareva
natasha_tcheb@mail.ru

[1] I.M. Sechenov First Moscow State Medical University, 2-4 Bolshaya Pirogovskaya st., Moscow, Russia 119992

circumstances, these proteins can be released from cells into the extracellular space, where they exhibit a range of immunoregulatory activities.

HSF1 is a transcription factor, which plays a critical regulatory role in HSP expression with the promoter element for the HSP genes described by Voellmy (1994). HSF1 exists in the cellular cytoplasm as a latent monomer molecule. Cytotoxic influences increase the intracellular levels of newly synthesized protein precursors, which have not been properly folded into physiologically functional conformations. Such "unfolded" molecules stimulate HSF1 phosphorylation by mitogen-activated protein kinase with the formation of three-dimensional HSF1 structure (Kim et al. 1997). This trimer translocates to the nucleus, binds to DNA of HSP gene promoter, and enables the transcription of the corresponding protein (Pockley 2003). HSPs are subdivided into families according to their molecular weight in kilodaltons (kDa). There are small HSPs (16–40 kDa) belonging to HSP40, HSP60, HSP70, and HSP90 families. Many HSPs are expressed in normal kidney tissue, and their expression is changed after an injury (Beck et al. 2000) (Table 1 and Fig. 1).

Small (low molecular weight) HSPs

Small HSPs are a group of proteins highly heterogeneous in molecular weight, which ranges from 16 to 40 kDa. The low molecular weight HSPs play a role in the polymerization/depolymerization of actin (Lavoie et al. 1993). HSPs inhibit the aggregation of proteins by interaction with hydrophobic regions of the proteins involved in the formation of globular structure (Lee et al. 1997). Among the low molecular weight proteins, HSP25/27 plays an important role in the protection of renal tissue from damage (HSP27 in humans and rats and HSP25 in mice). HSP27 exists in the cell in the form of large oligomers functioning as chaperones, and smaller oligomers combined with actin microfilaments (actin-associated protein) stabilizing actin fibers in the cells under stress especially under the influence of reactive oxygen species and TNF-α (Huot et al. 1996; Mehlen et al. 1997; Preville et al. 1998). At the same time, the most potent protective activity is provided by non-phosphorylated HSP27 oligomers, after phosphorylation by p38 MAP kinase losing their ability to bind to the actin microfilaments and promoting remodeling of the actin network in the cell.

HSP27 in normal kidney tissue

The low molecular weight HSPs can perform various protective functions in all regions of the kidney. The normal human kidney shows a significant staining for HSP27 in the endothelium, strong apical staining of proximal tubules, and the medullary papillae of the terminal collecting ducts or the ducts of Bellini (O'Neill et al. 2013).

In cells of the medulla, which express HSPs at high levels, the protection by these molecules functions primarily to inhibit osmotic damage via effects of hypertonic medium (Neuhofer et al. 1998). High expression of HSP27 in intrarenal arterial vessels suggests the involvement of HSP27 in a vascular contraction–dilatation cycle (Muller et al. 1996). Intense staining of HSP25/27 in the brush border of proximal tubules may reflect the effect of this protein on the remodeling of actin filaments in the cellular domain (Schober et al. 1998).

HSP27 in acute kidney injury

HSP25 is a part of generalized stress response in renal proximal tubular cells, which may play a role in recovery from ischemia-induced actin filament disruption (Smoyer et al. 2000). After the acute ischemic kidney damage, an increased HSP27 expression is observed in the kidney tissues peaked at 6 h post-reperfusion in rats (Guo Q et al. 2014). In addition, the chaperon function HSP27 causes autophagy and inhibits apoptosis that is shown in vitro and in renal tubular cells in ischemia/reperfusion acute kidney injury (AKI) model (Matsumoto et al. 2015). HSP27 can inhibit apoptosis by decreasing intracellular reactive oxygen species and the mitochondrial caspase-dependent apoptotic pathway (Tian et al. 2016). Kim et al. (2010) have shown selective renal overexpression of HSP27 in mice through intrarenal lentiviral gene delivery that provides renal protection against the ischemic renal injury. Selective expression of HSP27 improves the renal function and reduces necrosis, inflammation, apoptosis, and preservation of the F-actin cytoskeleton after ischemia reperfusion injury.

Vidyasagar et al. hypothesized that HSP27 plays an active and protective role during renal fibrogenesis in rat and human obstructive nephropathy. They indicated that overexpression of HSP27 in tubular epithelial cells preserved E-cadherin protein levels during an epithelial–mesenchymal transition. Expression of HSP27 was associated with reduced oxidative stress and fibrogenesis in transgenic kidneys due to decrease of activated (phosphorylated) p38 MAPK, collagen III, α-smooth muscle actin (α-SMA), and lipid peroxidation (Vidyasagar et al. 2013).

HSP27 accumulation in the cytoplasm of proximal tubule cells in toxic tubular injury in rats contributed to cell survival and regeneration (Fujigaki et al. 2010). According to Djamali et al. (2005), immunohistochemical analysis revealed a "shift" in HSP27 from the medulla to the cortex in allografts with chronic allograft nephropathy (CAN). Lower medullary HSP27 in CAN could result from a relative redistribution of blood flow toward the medulla, with attenuation of local hypoxia.

In a more recent work (O'Neill et al. 2013), an increased expression of HSP27 was observed in the tubular cells of the

Table 1 HSP expression in various kidney diseases

HSPs	Type of cells with intracellular HSP expression	Renal diseases associated with HSP overexpression	References
HSP27	Actin network of the podocytes, tubular cells, and endothelial cells	Acute kidney injury (AKI): ischemic and toxic	Matsumoto et al. (2015)
		Diabetic nephropathy	Sanchez-Nino et al. (2012)
		Lupus nephritis	Tsagalis et al. (2006)
		Obstructive nephropathy	Vidyasagar et al. (2013)
HSP 70	Mesangial cells, tubular cells, macrophages	AKI	Guo et al. (2014)
		Diabetic nephropathy	Barutta et al. (2008)
		Chronic glomerulonephritis	Venkataseshan and Marquet (1996)
		Lupus nephritis	Tsagalis et al. (2006)
		Tubulo-interstitial nephritis	Venkataseshan and Marquet (1996)
HSP 60	Podocytes, tubular cells of outer medulla, macrophages	AKI	Hernandez-Pando et al. (1995)
		Diabetic nephropathy	Barutta et al. (2008)
		Transplant rejection	O'Neill et al. (2013)
HSP 47	Fibroblasts, myofibroblasts in the zones, glomerulosclerosis, interstitial fibrosis	AKI	Hegazy et al. (2016)
		Diabetic nephropathy	Ohashi et al. (2004)
		IgA nephropathy	Razzaque et al. (1998)
		Cyclosporine nephrotoxity	Abe et al. (2000)
		Obstructive nephropathy	Moriyama et al. (1998)
		Transplant rejection	Abe et al. (2000)
HSP 90	Podocytes, pariethal epithelial cells, proximal tubular cells, endothelium, mesangial cells	AKI: ischemic and toxic	Morita et al. (1995)
			Ohtani et al. (1995)
		Crescentic nephritis	Komatsuda et al. (1996)
		Glomerulonephritis	Pieper et al. (2000)
HSP 32	Podocytes, endothelium, tubular cells, mesangial cells, macrophages	AKI	Shimizu et al. (2000)
		Diabetic nephropathy	Pagnin et al. (2016)
		Obstructive nephropathy	Chen et al. (2016)
		Chronic glomerulonephritis	Datta et al. (1999)
		Lupus nephritis	Takeda et al. (2004)
		Transplant rejection	Agarwal et al. (1996)
			O'Neill et al. (2013)

distal convoluted tubules in acute cellular rejection, cyclophilin nephrotoxicity, and less frequently, in CAN. The cases of cyclophilin nephrotoxicity and type II acute cellular rejection did show evidence of HSP 27 and 70 within the parietal epithelium of Bowman's capsule.

HSP27 in podocytes

Increased intracellular HSP27 inhibits actin polymerization and aggregation, stabilizes actin cytoskeleton of the cells, and increases resistance to damage. Therefore, HSP27 has emerged as a dynamic protein with diverse roles in the regulation of actin cytoskeletal remodeling, apoptosis, oxidative stress, and renal fibrogenesis. Localization of HSP27 within the glomeruli revealed that it was almost completely restricted to podocytes, which have a well-developed actin microfilament system. The structure of the pedicels of podocytes is an integral part of the kidney filtration barrier, which depends directly on the actin microfilaments condition and their polymerization processes and is regulated by HSP27. Smoyer et al. (1996, 2002) have demonstrated a significant expression of HSP27 in podocytes within the glomerular capillary loops of normal rats. Induction of experimental nephrotic syndrome resulted in both increased expression and enhanced phosphorylation of glomerular HSP27. Phosphorylation of HSP27 in podocytes leads to aggregation and redistribution

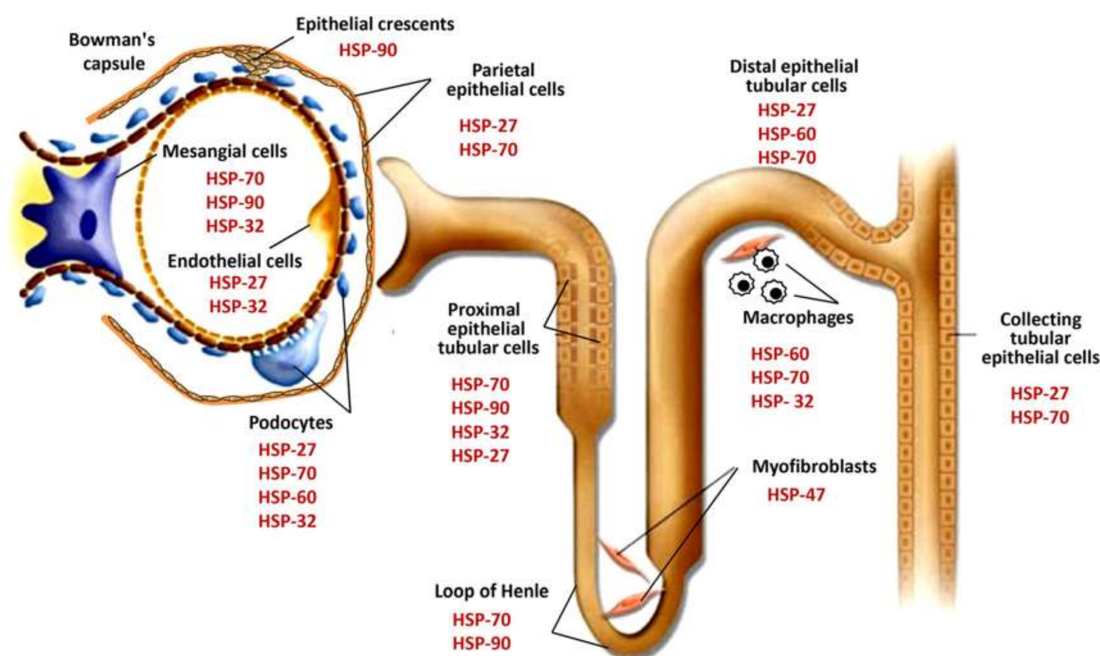


Fig. 1 Expression of HSPs in various parts of kidney

of the actin filaments, the cytoskeleton destruction, the loss of normal structure of the filtration barrier, and the development of proteinuria. So, the loss of pedicels of podocytes in puromycin aminonucleoside nephrosis (PAN) is closely linked to hyperphosphorylation of HSP27. Thus, HSP27 may regulate actin polymerization in the foot processes of podocytes, and thus have an important role both in the maintenance of normal foot process structure and during development of the nephrotic syndrome. An increased glomerular HSP27 expression was observed using immunohistochemistry measurements in nephropathy associated with proteinuria and nephrotic syndrome, such as human diabetic nephropathy (DN), *focal segmental glomerulosclerosis* (FSGS), and hypertonic nephropathy (Sanchez-Nino et al. 2012). The phosphorylated form of HSP27 was enhanced in the glomerular podocytes of diabetic animals and in vitro exposure of podocytes to stretch-induced HSP27 phosphorylation via a p38-MAPK-dependent mechanism (Barutta et al. 2008). Furthermore, HSP27 upregulation in the presence of diabetic nephropathy protected human podocytes from a stress induced by high glucose and angiotensin II (Sanchez-Nino et al. 2012).

Tsagalis et al. (2006) demonstrated an important role of HSP 27 in cellular defense in lupus nephritis. The increased expression of HSP27 was noted primarily in residential (glomerular and proximal and distal tubular) cells, and not in the inflammatory kidney tissue cells, suggesting activation of protective intrarenal reserves in this case. The expression was especially high in diffuse proliferative nephritis (with the most pronounced inflammatory processes and cell proliferation) and correlated with histological indices of nephritis activity and with the serum creatinine level. In a less severe inflammation (lupus nephritis of classes III and V), no HSP27 expression in glomeruli was detected. The cytoprotective response in nephritis is believed to depend on the severity of the injury (Tsagalis et al. 2006).

The increased HSP27 serum and urine levels in chronic kidney disease (CKD) of various etiologies on stages 3 to 5 were detected (Lebherz-Eichinger et al. 2012; Musiał and Zwolińska 2012). The authors suggested that the increased urine HSP27 level resulted from the compensatory renal reaction to elevated serum concentrations as well as from the increased cell damage in the kidney itself (Lebherz-Eichinger et al. 2012). Serum levels of HSP27 were significantly elevated in dialyzed patients compared to the predialysis period and healthy subjects, and this effect was likely associated with an additional activation of chronic inflammation and enhanced apoptosis in progressing CKD (Musiał and Zwolińska 2012).

HSP70 family

HSP70 has a wide spectrum of functions common to all chaperone proteins and participates in shaping the structure of newly synthesized native proteins, restoring of partially denatured proteins, and degradation of irreversibly damaged protein molecules. HSP70 can interact with cytoskeletal structures and participate in the transport of proteins through intracellular membranes into the organelles and in the cleavage of protein aggregates (Beck et al. 2000). The HSP70 family consists of 73-kDa HSP and 72-kDa HSP. HSP73 (also known as a 70-kDa heat shock cognate protein, HSC70) is the main constituent protein of the family, which is normally expressed

in all areas of renal tissue. The extensive investigation of renal localization and function of HSP70 family started in 1990s.

HSP73 in normal renal tissue

Thus, Komatsuda et al. (1992) studied HSP73 localization in a normal rat kidney tissue. The protein was expressed in kidney tissue of experimental rats, specifically in podocytes, Bowman's capsule cells, tubular epithelial cells of the proximal tubules, collecting tubules, papillary epithelium, and interstitium. The ubiquitous presence of HSP73 can be attributed to the need, also of non-stressed cells, for assistance in protein folding, trafficking, and controlled degradation. In the puromycin aminonucleoside induced nephrosis, the intracellular expression of HSP73 is increased in mesangial cells, tubular cells of the Henle loop, distal tubules, and collecting tubules, probably due to increased protein reabsorption, and this effect reflects a protective response to the damaging components of proteinuria. In kidneys with the puromycin aminonucleoside induced nephrosis, HSP73 accumulates in the cytoplasm at a level higher than in the nucleus in association with the severity of renal dysfunction and proteinuria (Komatsuda et al. 1992). Somewhat different localization of HSP70 expression in normal human kidney was demonstrated by Venkataseshan and Marquet (1996) and Dinda et al. (1998). HSP73/72 showed a uniform fine granular cytoplasmic staining of visceral glomerular epithelial cells and epithelia of distal convoluted tubules and collecting ducts without localization in proximal tubules.

HSP73 after renal ischemia

Morita et al. (1995) described the effect of increased HSP 73 levels after renal ischemia. HSP73 was rapidly induced in the cytoplasm of injured epithelial cells of the proximal tubules that were the main site of injury. It was again induced in the cytoplasm of regenerative cells in this segment and involved in the process of post-ischemic cellular recovery. After the gentamicin-induced acute tubular damage, HSP73 leaves the nucleus of tubular cells, enters the cytoplasm and accumulates in the lysosomes, and is probably involved in degradation of structurally damaged proteins (Komatsuda et al. 1993). Furthermore, the expression of HSP73 increases the resistance of cells to apoptosis when exposed to oxidative stress (Yokoo and Kitamura 1997).

HSP72 in normal kidney tissue

HSP72 is an inducible protein; however, its expression is also detected in normal kidney. In the early 1990s, it was demonstrated that HSP72 expression was increased in cultured kidney cells (MDCK) in response to an increase in extracellular osmolality due to selected osmotic agents (Cohen et al. 1991; Cowley et al. 1995). The osmolality-dependent reorganization of the cytoskeleton and expression of heat shock proteins may be components of the regulatory systems involved in the adaptation of medullary cells to osmotic stress (Beck et al. 1998). O'Neill S et al. (2013) identified HSP72 in the renal cortex (only in individual collecting duct cells) and medulla. All tubules were stained weakly in the outer medulla, while an intense staining was noted in the papilla collecting duct epithelium and in the urothelium lining the papilla. Features of its distribution along the cortico-papillary areas suggest the involvement of this protein in the adaptation of medullary cells to a high extracellular concentration of salts, that is, to hypertonic stress. HSP72 stabilizes intracellular proteins and thus reduces the denaturing effect of hypertensive environments including a high concentration of urea (Neuhofer et al. 2001).

Immunohistochemical analysis revealed an overexpression of HSP72 in the diabetic outer medulla, whereas no differences were seen in the glomeruli. The increased hypertonic and hypoxic stress in the diabetic outer medulla may induce an overexpression of HSP localized specifically to this area, which may result in cytoprotection and counterbalance in diabetes-induced cell (Barutta et al. 2008).

HSP72 in acute kidney injury

Expression of the protein increases sharply in cell injury that has been found in many studies in ischemic and toxic renal failure (Emami et al. 1991; van Why et al. 1992; Schober et al. 1997; Aufricht et al. 1998; Wang et al. 2009). HSP72 plays an important role in AKI induced by renal ischemia in animals and humans (Harrison et al. 2008; Guo et al. 2014). The experimental results indicate that HSP72 complexes with aggregated cellular proteins in an ATP-dependent manner and suggest that enhancement of HSP72 function assists in refolding and stabilization of Na–K–ATPase or aggregated elements of the cytoskeleton (Aufricht et al. 1998). The observation that HSP72 is transiently induced in cortex and outer medulla, but not in inner medulla after renal ischemia, may be explained by the fact that while all kidney cells are exposed to ischemic stress, only inner medullary cells experience a major post-ischemic attenuation of osmotic stress (Schober et al. 1997). Zhang et al. (2008) demonstrated that when the kidney was subjected to ischemia–reperfusion injury, the heat shock proteins were among the gene products that responded to the highest degree from more than 30,000 genes analyzed. The HSP70 gene was upregulated more than 43-fold compared to control non-ischemic kidneys after renal ischemic insult in rats. Non-proximal tubules possess high levels of HSP70 regardless of their location in the cortex or the medulla. It seems likely that normally high levels of heat shock proteins

are cytoprotective in non-proximal tubules when the kidney is subject to ischemic or toxic injury. Thus, HSP70 provides a sensitive molecular marker for renal ischemia–reperfusion injury. Over the last few years, an *increasing number of studies* have been conducted to investigate the role and functions of HSPs in the ischemic renal injuries, and the results of these works pave the way to the development of targeted therapeutic approaches to HSP modulation (Kim et al. 2014; Yeh et al. 2010; Wang et al. 2011; O'Neill et al. 2012, 2015).

A variety of protective mechanisms of HSP72 action in AKI are discussed. HSP72 is involved in the degradation of irreversibly damaged proteins, restoration of the structure of partially denatured proteins, recovery of the cytoskeleton, and cell polarity. In addition, the induced HSP72 expression significantly limits tubular cell apoptosis by controlling the activity of Akt kinase and glycogen synthase kinase 3β that regulate the activity of a pro-apoptotic protein Bax. Lentiviral-mediated HSP70 repletion decreases mitochondrial Bax accumulation, the pro-apoptotic protease caspase 3, and rescues HSP70 knockout cells from death (Wang et al. 2011). HSP70 also limits pro-inflammatory NF-κB signaling in kidney ischemic renal injury by inhibiting NF-κB p65 translocation to the nucleus (Wang et al. 2011) (Fig. 2a). HSP72 influences the chronic tubulointerstitial fibrosis by mechanisms that are independent of its effect on tubular apoptosis. HSP72 inhibited tubular epithelial–mesenchymal transition in response to TGF-1 (Fig. 2b), decreased the number of SMA-positive myofibroblasts, collagen I deposition, and reduced tubulointerstitial fibrosis (Mao et al. 2008). The induction of HSP70 expression is thought to play a protective role from toxic injuries. In that case, HSP72 can play by means of the MEK/ERK signaling pathway and by inhibiting oxidative stress, providing the cell survival (Zhipeng et al. 2006; Wang et al. 2009). On the other hand, HSP70 inhibits phosphorylation of the stress kinases (JNK and p38 MAPK) that leads to inhibition of both apoptosis and synthesis of pro-inflammatory Th1-cytokines (Fig. 2c).

HSP70 in renal transplantation

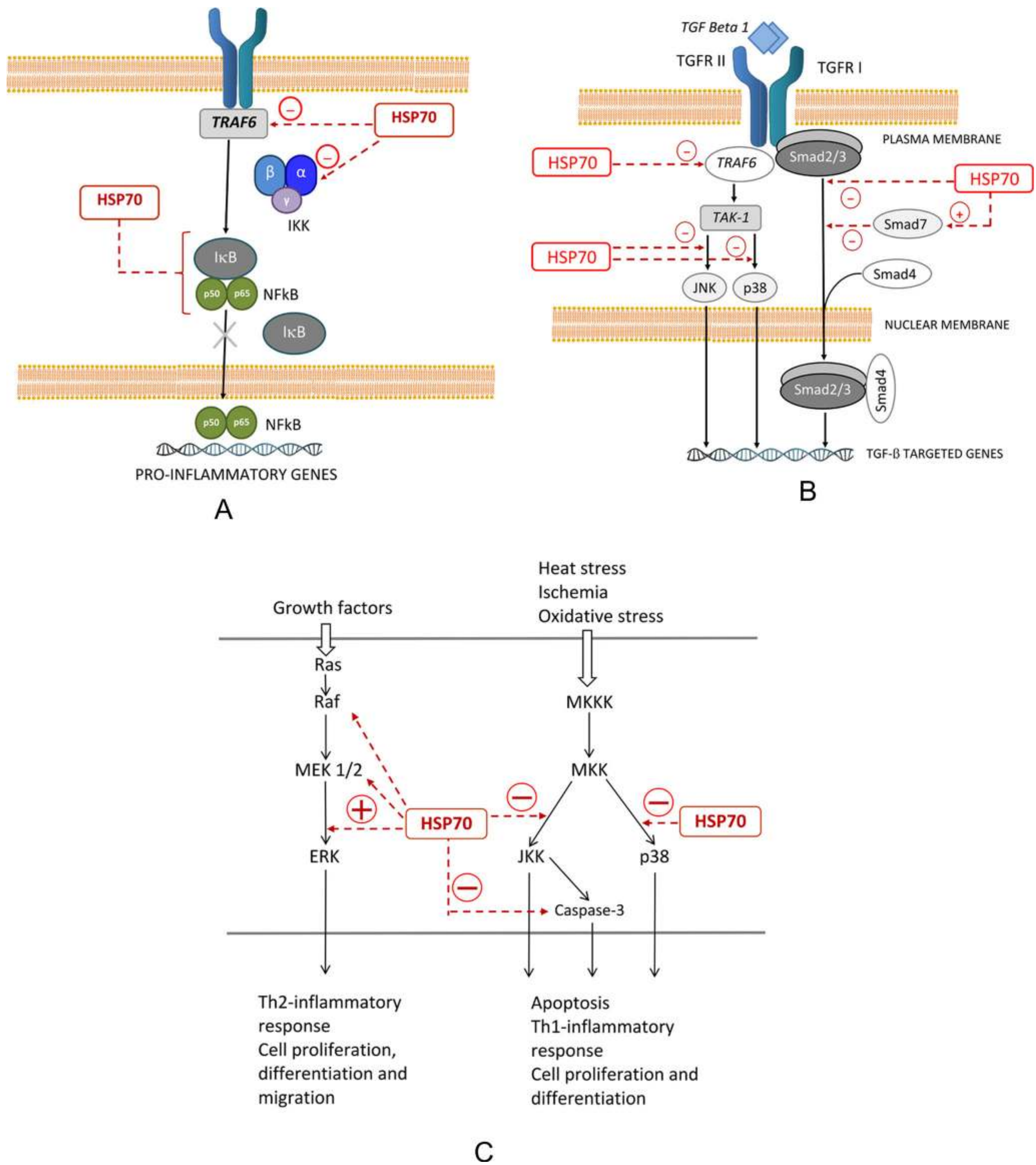
The inducible HSP70 showed a most significant induction within distal tubules in acute rejection and cyclophilin toxicity. HSP70 expression was more pronounced in type II acute rejection and increased within all cortical tubules including the proximal convoluted tubules and collecting ducts. In chronic allograft nephropathy, HSP70 was induced in the distal tubules. The cases of type II acute cellular rejection and cyclophilin toxicity also had evidence of HSP70 induction within the parietal epithelium of Bowman's capsule. A constitutively expressed HSP72/73 was found in the tubular cells in acute cellular rejection. It was most marked within cortical distal tubules but not markedly increased from expression in normal allografts. There was no increase in HSP72/73 in acute cyclophilin toxicity or chronic allograft nephropathy (O'Neill et al. 2013).

HSP70 as a biomarker of kidney injury

HSP70 is released into the extracellular space and circulation (Multhoff and Hightower 1996; Bassan et al. 1998), and it can also be found in the serum and plasma. Increased expression of HSP72 in the kidney tissue is accompanied by increased excretion of the protein in the urine; therefore, the urinary HSP72 can be used as a noninvasive biomarker of kidney damage. So, the urinary HSP72 detection has been shown to be a sensitive and early AKI biomarker up to 3–4 days before the diagnosis in critically ill patients. This protein was not only able to detect early AKI but it could also reflect the tubular recovery processes that occur after the epithelium is exposed following ischemic/reperfusion insult (Morales-Buenrostro et al. 2014). The urinary Hsp72 levels were sensitive enough to monitor therapeutic interventions and the degree of tubular recovery following an I/R insult in rats (Barrera-Chimal et al. 2010). Yilmaza A. et al. (2016) showed that the urine HSP70 may be a useful biomarker to detect early phases of diabetic kidney injury and may indicate progression of diabetic kidney injury with time.

The sharp increase in HSP72 urinary excretion is also observed in patients during the first hours after kidney transplantation, in the first urine of renal allografts, reflecting the violation of the integrity of the tubular epithelium and possibly indicating the degree of kidney damage after renal ischemia (Mueller et al. 2003). However, Ramires-Sandoval et al. (2014) showed that the urinary level of HSP72 did not increase significantly in kidney transplant recipients with prerenal AKI and immunological rejection. In this study, a small increase in HSP70 level was noted at patients with other factors of AKI (obstructive uropathy, calcineurin-inhibitor drug toxicity, recurrence of primary glomerular disease, and NSAID use) (Ramires-Sandoval et al. 2014).

In patients with the end-stage renal disease on dialysis, a significant increase in intracellular HSP72 in the tubular cells was shown; in addition, excretion of HSP70 in urine in patients with CKD stages 4 and 5 was significantly elevated (Lebherz-Eichinger et al. 2012). The increased expression of HSP with hemodialysis might be secondary to stress caused by dialysis in addition to alteration of *end-stage renal disease* (ESRD). Dialysis may cause the introduction of several potentially toxic exogenous chemicals (Dinda et al. 1998).



HSP60 family

HSP60 in normal kidney tissue

HSP60 family also includes molecular chaperones cross-linking monomeric proteins and combining them into oligomeric complexes (Beck et al. 2000). Normally, HSP60 is located predominantly in proximal tubule cells, but also with lower staining intensity in cells of the distal convoluted tubules in rats. HSP60 could not be detected in Bowman's capsule or in blood vessels. In the outer medulla, HSP60 is detected in thick ascending limbs of the Henle's loop. Barely noticeable amounts of HSP60 are present in the medullary collecting ducts. In the inner medulla, HSP60 appears

◀ **Fig. 2** The role of Hsp70 in signal transduction pathways. **a** Role of Hsp70 in signal transduction pathways of NF-κB. Intracellular HSP70 may also involve in preserving I-κB complex by interacting with IKK (Uchinami et al. 2002). HSP70 forms a complex with IκBα, attenuating NF-κB activity. HSP70 might bind IκBα to prevent its phosphorylation by IκB kinase, or HSP70 might inhibit IκB kinase directly, thereby inhibiting the degradation of I-κB and the subsequent activation of the NF-κB pathway (Shimizu et al. 2002). NF-κB activation induced by various stimuli is mediated by members of the TNF receptor-associated factor (*TRAF*) adapter family (le Luong et al. 2013). Intracellular HSP70 was demonstrated to inhibit NF-κB activation by binding TRAF6 via the TRAF-C domain and preventing its ubiquitination, thus resulting in inhibition of inflammatory mediator production (Cao et al. 1996). **b** Role of Hsp70 in signal transduction pathways of TGF signaling. HSP70 inhibits TGF-β signal by Smad-dependent and Smad-independent pathways. Upon TGFβ stimulation, Smad2 and Smad3 are phosphorylated by the activated TGFβ type I receptor kinase, forming a stable complex with Smad 4 in cytoplasm and then accumulating in the nucleus to regulate transcription of target genes. Moreover, in renal cells, TGF-beta direct or via TRAF6 stimulates rapid phosphorylation of the TGF-beta-activated kinase (TAK)1 and TAK1-binding protein, in turn activating MKK, which appears to function upstream of JNK and p38 (Schnaper et al. 2009). In contrast, Smad7 inhibits the TGFβ receptor type I-dependent Smad2/3 activation. Intracellular HSP70 interrupting Smad2/3 protein phosphorylation and its nuclear translocation and accumulation increases Smad7 protein expression, binds TRAF6, and reduces the phosphorylation of JNK and p38 MAPK, providing a protective effect (Zhou et al. 2010). **c** Role of Hsp70 in stress kinases (MAPK) signal transduction. The relative extent of MAPK activities, including JNK, p38, and ERK, has been proposed to determine cell fate after injury. Hsp70 downregulates also the activation of stress kinases (JNK and p38), and suppresses activation of caspases in renal cells (Suzuki et al. 2005) The activity of the MEK/ERK pathway that is upregulated by HSP70 may be relevant to renal protection. HSP70 provides most of the protective effects by activation of Raf, MEK, and ERK phosphorylation and cell survival (Wang et al. 2009, Park et al. 2002). Abbreviations: *TGF-β* transforming growth factor beta, *MAPK* mitogen-activated protein kinase, *JNK* c-Jun N-terminal kinase, *ERK* extracellular signal-regulated kinases, *MEK* MKK–mitogen-activated protein kinase kinase, *MKKK* mitogen-activated protein *kinase kinase kinase*, *Raf* a family of serine/threonine-specific protein kinases

exclusively in the papillary tip in the cytoplasm of collecting duct cells (Muller et al. 1996). The normal human kidney cortex shows mild HSP60 staining in most proximal tubules, with occasional intensely staining tubules. Distal convoluted tubules show moderately intense staining. In the medulla, the ascending thick limb shows strong staining, with thin limbs of Henle showing mildly intense staining (O'Neill et al. 2013). In glomeruli, HSP60 is expressed only by podocytes (Hernandez-Pando et al. 1995).

HSP60 in acute renal injury and renal transplantation

In experimental toxic renal damage, the HSP60 expression increased in all cortical tubules correlating with the degree of the damage (Hernandez-Pando et al. 1995). There was a significant increase in HSP60 expression in the outer medulla of renal tissue in early and advanced experimental diabetes (Barutta et al. 2008). Cisplatin-induced tubular damage in experimental model could be delayed through an early induction of cytosolic HSP60 by preventing the Bax-mediated apoptosis (Tsuji et al. 2009). HSP60 induction within distal tubules occurred in cases of type I acute rejection, chronic allograft nephropathy, and cyclophilin toxicity. In type II acute rejection, HSP60 expression within cortical distal tubules was more pronounced (O'Neill et al. 2013).

Role of HSP70 and HSP60 in the T cell regulation of chronic inflammation

Increasing expression of HSPs inside the cells provides stabilization and recovery of damaged proteins as well as optimal balance between the synthesis, structure formation, and degradation of proteins. It results in enhanced cell resistance to cellular stress. At the same time, HSPs can release into the extracellular medium or express on cell surface (Tytell et al. 1986; Basu et al. 2000), and in that case, their specific protective role is to control the inflammatory immune response.

HSP60 and HSP70 are the immune-dominant molecules, and the peptide sequences of microbial HSP60 and 70 are the major epitopes stimulating an anti-infective immune response. Prokaryotic (bacteria) and eukaryotic (mammalian and human) cells in HSP have a high degree of homology reaching, for example, 50–60% in HSP60 family (Kaufmann 1990a. One explanation is that HSPs are potential candidates for molecular mimicry and can be recognized by the immune system as being potentially pathogenic antigens; as a result, they can play a role in the development of both anti-infective response and autoimmunity (Lydyard and van Eden 1990). This hypothesis is evidenced by the increased serum levels of HSP60 and 70, as well as the respective antibodies, in several autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, scleroderma, diabetes, nephritis, and after organ transplantation **(**Dhillon et al. 1991; Georgopoulos and McFarland 1993; Birnbaum et al. 1998; Jorgensen et al. 1998; Lang et al. 2005; Trieb et al. 2005; Wu and Tanguay 2006). However, the first evidence of the protective role of HSP in inflammatory diseases was the fact that HSP60 infusion to experimental animals with autoimmune adjuvant arthritis provided an anti-inflammatory effect and inhibited the development of the disease (van Eden et al. 1988). Later, the regulatory effect of microbial HSPs has been established in other models of autoimmune diseases, including autoimmune encephalomyelitis, collagen-induced arthritis, and type I diabetes (Elias et al. 1997; Birnbaum et al.1998; Jorgensen et al. 1998). Kim et al. (2014) demonstrated that in heat preconditioning, upregulation of HSP70 in CD11c+ dendritic cells was responsible for Treg-mediated renoprotective effect and subsequent conversion of immune response toward tolerance or anti-inflammation in ischemia/reperfusion acute kidney injury.

Intracellular heat shock proteins can be expressed in cellular inflammation and damage on the cells surface or released into the extracellular space (Multhoff and Hightower 1996; Bassan et al. 1998). The epitopes of the proper HSPs expressed in the inflammation sites are recognized by T cells with the formation of anti-inflammatory phenotypes of regulatory T cell (Anderton et al. 1995), namely T-helper type 2 (Th2) phenotype producing IL-10 and IL-4, T regulatory cell 1 (Tr1) producing IL-10 and TGF-β, and CD4+CD25+ regulatory cells (Treg) (de Kleer et al. 2003, 2004; Zanin-Zhorov et al. 2005, 2006). The anti-inflammatory IL-10 is one of the first cytokines expressed by regulatory cells in inflammatory site and is a major stressor cytokine mediating many immunoregulatory effects of HSP. So, the preimmunization of experimental animals by HSP60 and HSP70 leads to an increase in the number of IL-10-producing T regulatory cells in the inflammatory site (Zanin-Zhorov et al. 2006). A change in the phenotype of T cells exposed to HSPs is found to occur after the activation of a signal from the Toll-like receptors (TLRs). HSP60 or 70 released from the cells into the extracellular space can activate CD4+CD25+ regulatory cells, acting on TLR-4 (Vabulas et al. 2001; Ferat-Osorio et al. 2014). The interaction of HSP60 or its peptide p277 (437–460) with TLR2 on T cells leads to "switch" of Th1 phenotype on Th2 one with the decrease in the inflammatory (TNF-α and IFN-γ) and the increase of anti-inflammatory (IL-10 and IL-4) cytokine secretion (Paul et al. 2000; Wendling et al. 2000; Zanin-Zhorov et al. 2003; Zanin-Zhorov et al. 2005) (Fig. 3).

HSPs increase the production of anti-inflammatory cytokines not only in T cells but also in the mononuclear cells, such as monocytes and dendritic cells (Detanico et al. 2004). For example, peripheral T cells and transplant-infiltrating lymphocytes, as well as peripheral blood mononuclear cells of patients with chronic post-transplant nephropathy, can produce IL-10 under the influence of HSP60 (Caldas et al. 2006).

The role of HSPs in the process of removal of activated immune cells from inflammatory site and reduction of the inflammatory infiltration is being actively discussed. The HSP60 and 70 natively expressed on the surface of inflammatory neutrophils are recognized by the HSP-specific T cells (γδ T cells) characterized by the production of cytokines IFN-γ, IL-10, and TNF-α as well as by the immediate cytotoxic activity against neutrophils and macrophages (Hirsh and Junger 2008). In the immune inflammation, HSPs are expressed on the surface of the activated T cells and can be recognized by T cell receptors (TCR) of regulatory T cells (CD4+ or CD8+) involved in the elimination of abnormal activated T cell clones from inflammatory site (Ferris et al. 1988).

The HSP expression in an inflammatory site and the ability of HSPs to induce the production of IL-10 by mononuclear cells affect the extent of anti-inflammatory action of these proteins and can be influenced by genetic factors (Miyata et al. 1999; Xiao et al. 2004). The decreased cellular HSP expression ability can cause the loss of resistance to chronic inflammatory diseases (Rao et al. 1999). The role of HSPs in the regulation of chronic immune inflammation in the human kidney is poorly studied.

Increased HSP expression is found in patients with various forms of nephritis including minimal change glomerulonephritis, FSGS, membranous nephropathy, and acute interstitial nephritis in the loci of acute interstitial infiltration (Venkataseshan and Marquet 1996). Marzec et al. (2009) revealed the decreased HSP72 expression on the surface of peripheral blood monocytes of patients with CKD as compared with the control. This decrease of HSP72 expression by monocytes was observed in patients with terminal CKD and with the development of systemic inflammation. In patients with lupus nephritis, the HSP72 expression in renal tissue (in the cytoplasm of cells of the proximal and distal tubules and collecting ducts) was normal (Tsagalis et al. 2006). However, Venkataseshan and Marquet (1996) showed a significant increase in the HSP70 expression by tubular cells in the areas of acute interstitial inflammation in glomerulonephritis and interstitial nephritis, whereas no increase of HSP70 was observed in chronic interstitial inflammation and fibrosis.

We can assume that the expression of these proteins on the surface of the cells corresponding to the inflammation activity is important in the resolution of the inflammation, especially since they have a protective effect in chronic inflammatory diseases with different and sometimes unknown autoantigens.

T cells reactive to HSPs have also been found in healthy human (Pockley et al. 1998, 1999). The HSPs are found to be expressed by the cells into the extracellular space and on the cell surface even in the absence of any damage (Multhoff and Hightower 1996; Bassan et al. 1998). The normal immune response to the HSPs is needed to maintain immune homeostasis, and it can also participate in controlling the inflammatory diseases. The absence of autoimmune response to the expression of the genuine HSPs is probably due to the formation of a regulatory or tolerant phenotype of autoreactive T cells. The T cells reactive to cross-epitopes of HSPs are known to avoid removing in the thymus and obtain tolerance by the peripheral immune organs. So, the autoreactive T cells of intestinal lymphoid tissue can recognize the highly homologous HSPs of normal microflora and differentiate into regulatory anti-inflammatory phenotypes producing IL-10 and TGF-β. These HSP-specific regulatory T cells can migrate to the site of immune inflammation and control the pathogenic T cell clones (Chen et al. 1994; Samson 2004).

Thus, to the late 1990s, the role of HSP60 and HSP70 in regulation of chronic immune inflammation was determined. A number of authors (Pockley 2003; Hauet-Broere et al. 2006; de Kleer 2003, 2004) developed a concept which stated that the reactivity to self-heat shock proteins rather than promoting disease can downregulate the chronic disease process. HSPs prevent or arrest inflammatory damage and promote

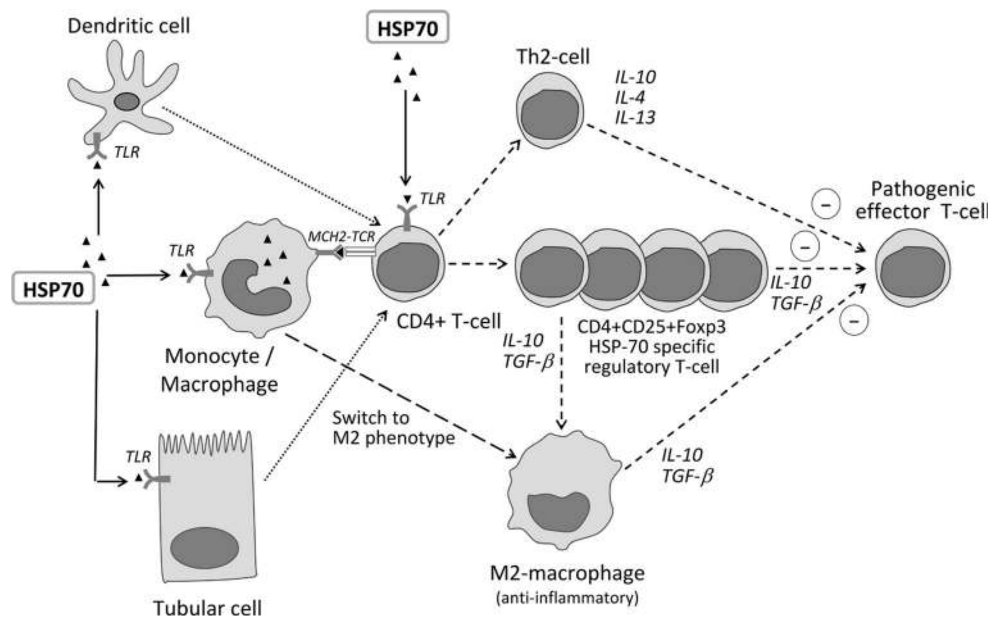


Fig. 3 Role of Hsp70 in immune inflammation. HSP70-induced beneficial protective effect is caused not only by intracellular produced HSP70 but also by HSP70 in immune cells and subsequent regulatory function toward anti-inflammation in immune and non-immune renal diseases. Extracellular Hsp70 binds with the Toll-like receptors (TLR) 2 and 4 on the antigen-presenting cells (APCs): dendritic cells (CD11c), monocytes/macrophages, and tubular cells in site of inflammation or injury. Other transmembrane receptors such as CD91 and LOX-1 may be the receptors for HSP 70. APCs present HSP 70 epitopes with help of MHC-II to HSP-specific CD4+ T cells, ultimately leading to expansion of CD4+CD25+ (T regulatory cells) with subsequent anti-inflammatory or immunomodulatory effect via IL-10 and TGF-β production (Kim et al. 2014). Moreover, HSP70 may directly bind to the TLR2/4 of CD4+ T cells, and activate the expansion of Tregs. HSP70 may also converse inflammatory macrophage (M1) phenotype to the anti-inflammatory (M2) macrophage providing the resolution of inflammation. *TCR* T cell receptor, *MHC-II* major histocompatibility complex class II

production of anti-inflammatory cytokines indicating immunoregulatory potential through expansion of Tregs. Therefore, in addition to their original function as a chaperone, HSP-induced immunomodulation is thought to be another important mechanism of renoprotection in various pathologies including I/R-induced AKI. A better understanding of HSP–immune cell interaction could facilitate the discovery of new targets or drug development in the prevention or treatment of AKI (Kim et al. 2014). Moreover, taking into account the protective role of HSPs in chronic immune inflammation, a targeted modulation of HSP60 and HSP70 seems to be a prospective approach in chronic glomerulonephritis. However, this area still requires further theoretical and practical investigations.

HSP47

Heat shock protein (HSP) 47 is a specific chaperone of procollagen. HSP47 is a 47-kDa glycoprotein that is mostly present in the endoplasmic reticulum (ER) of collagen-producing cells. HSP47 binds to the triple helical procollagen and stabilizes its higher-order structure. It prevents the premature secretion of procollagens from the ER into the Golgi apparatus and concentrates them within the ER before finishing their maturation process. HSP47 seems to dissociate from the procollagens, which is then rapidly secreted from the cell (Tasab et al. 2000). The protective role of many chaperones in the renal tissue is well documented; at the same time, HSP47 expression in kidney cells promotes development of post-injury profibrogenic transformations. Increased glomerular expression of the collagen-specific chaperone protein HSP47 is likely to be involved in overproduction of collagens that ultimately promotes glomerular sclerosis. HSP47 is strongly expressed in glomerulosclerotic lesions in parallel with increased expression of collagens I and IV in DN. Advanced glycation end products are a key factor in the synthesis of the increased expression of both HSP47 and collagens in vitro and in vivo (Ohashi et al. 2004). HSP47 may be involved in the initial stage of fibrosis via the TGF-β1-induced transdifferentiation of fibroblasts to myofibroblasts, as well as at the later stage of fibrosis, the collagen synthesis in already transdifferentiated myofibroblasts (Hong et al. 2012). HSP47 increases the expression of collagen type I, collagen type IV, fibronectin, and tissue-type plasminogen activator inhibitor in human proximal tubular epithelial (HK-2) cells, suggesting the functionality of HSP47 in regulating ECM synthesis and degradation in processes related to renal tubulointerstitial fibrosis (Xiao et al. 2012).

A similar induction of HSP47 expression with excessive accumulation of collagens is also noted in other experimental models of renal fibrosis. Overexpression of HSP47 was closely associated with increased deposition of interstitial collagens in toxic kidney injury (Cheng et al. 1998; Hegazy et al. 2016)

and in rats with radiation-induced tubulointerstitial nephritis (Liu et al. 2002). However, this effect may be related to its powerful antioxidant properties that prevent generation of free radicals and removed the stress induced by toxic agents in tubular cells (Hegazy et al. 2016).

In addition, HSP47 may play an important role in the excessive assembly of collagens resulting in glomerulosclerosis and interstitial fibrosis found in DN and immunoglobulin A nephropathy (IgAN) patients. Increased deposition of collagens was present in relation to a strong expression of HSP47 in glomeruli and the tubulointerstitium of these patients (Razzaque et al. 1998). HSP47 might play a significant role in the excessive assembly of collagens and could subsequently contribute to the expansion of mesangial matrix found in *anti-thymocyte serum glomerulonephritis* in rats (Razzaque and Taguchi 1997). Using anti-sense oligonucleotides against HSP47, it was shown that attenuation of sclerotic lesions and expression of collagen in glomeruli coincided with a reduction of HSP47 expression (Sunamoto et al. 1998). In the earlier studies, the potential role of HSP47 in the pathogenesis of interstitial fibrosis in the obstructed kidneys was suggested. The early and persistent upregulation of HSP47 was determined during the progression of interstitial fibrosis in mouse unilateral ureteral obstruction (UUO) kidneys (Moriyama et al. 1998). Recently, interesting data were obtained by researchers from Japan. They found that amlodipine may inhibit the expression of HSP47 and type IV collagen by reducing phosphorylation of c-jun-N-terminal kinase and ameliorating the renal interstitial fibrosis in mice (Honma et al. 2016).

The level of HSP47 expression in the interstitial area correlated with the histological degree of fibrosis in chronic allograft rejection and cyclophilin toxicity. The fibroblasts and renal tubular epithelial cells are the predominant sites of collagen production and HSP47 in the tubulointerstitium of chronic rejection renal tissue (Abe et al. 2000).

HSP90 family

While ubiquitously expressed in unstressed normal cells, the HSP90 complex assists in the folding and function of a variety of proteins, which are called client proteins. There are over 175 client proteins involved in a multitude of cellular processes such as cell cycle control, apoptosis, proliferative signaling, and malignancy (Richardson et al. 2011; Peng et al. 2007). The client proteins include tyrosine kinases (e.g., Akt and MEK), transcription factors (androgen receptor, estrogen receptor, and p53), structural proteins (tubulin, actin), and hypoxia-inducible factor 1α (HIF-1α) (Goetz et al. 2003; Neckers and Ivy 2003). The mechanism of action of HSP90 includes the stepwise recruitment of cochaperones, including HSP70, $p50^{cdc37}$, HOP, and p23 (Pearl and Prodromou 2000).

The HSP90 protein contains three functional domains, the ATP-binding, protein-binding, and dimerizing domain, and each of these domains plays a crucial role in the functioning of the protein. The ATPase-binding region of HSP90 is currently under intense study because it is the principal binding site for drugs targeting this protein (Chiosis et al. 2006). The HSP90 protein can adopt two major conformational states. The first is an open ATP-bound state, and the second is a closed ADP-bound state. Thus, ATP hydrolysis drives what is commonly referred to as a “pincer-type” conformational change in the protein binding site (Grenert et al. 1997). On ATP-binding, the HSP90 client complex associates with co-chaperones to facilitate client stabilization (Isaacs et al. 2003). In contrast, in its ADP-bound form, HSP90 associates with different co-chaperones such as HSP70, resulting in enhanced proteasomal degradation of the HSP90 client proteins. HSP90 inhibitors targeting this section of HSP90 include the antibiotics geldanamycin (Goetz et al. 2003; Pratt and Toft 2003), herbimycin, radicicol (Oh et al. 2007), derrubone (Hadden et al. 2007), and macbecin (Martin et al. 2008) and suppress the progression of the HSP90 complex toward the stabilizing form and shift it to the proteasome-targeting form, which results in ubiquitin–proteasome degradation of the client (Kamal et al. 2003). HSP90 interacts with many cellular proteins, including protein kinases and steroid receptors, in a manner which regulates their activity and kinetics (Beck et al. 2000).

HSP90 in normal renal tissue

The normal kidney tissue expresses HSP90 mainly in the distal tubules and the cortical and medullary collecting ducts, which corresponds to the distribution of mineralocorticoid and glucocorticoid receptors, determining the importance of the complex HSP90/steroid receptor in the signal transduction (Farman et al. 1991). After binding the hormone, the HSP-receptor complex becomes disintegrated, and the activated receptor is translocated into the nucleus. Also, some HSP90 expression is observed in the loop of Henle, podocytes, parietal epithelium of the Bowman’s capsule, and in endothelial and interstitial cells, which indicates that the HSP90 has a wide range of functions in various kidney cells (Matsubara et al. 1990). HSP90 is involved in the maintenance of normal renal blood flow and affects the glomerular filtration rate (GFR) by regulating the synthesis of nitric oxide-dependent on endothelial NO-synthase. Ramirez et al. (2008) showed that inhibition of HSP90 resulted in a reduction in renal blood flow and GFR, and significantly decreased urinary excretion of nitrates and nitrites.

HSP90 in acute kidney injury

Following ischemic damage and in toxic AKI, the expression of HSP90 is increased in tubular cells in the late regeneration phase. In gentamicin-induced acute renal failure, it was found in the proximal tubules and in cisplatin-induced renal failure—in the epithelium of the loop of Henle (Morita et al.

1995; Ohtani et al. 1995). Thus, HSP90 is a component of the protective system providing regeneration of the damaged and differentiation of new tubular cells. In crescentic nephritis in humans, the expression of HSP90 is increased in the cytoplasm of proliferating crescent cells. (Komatsuda et al. 1996). A recent study has identified TGF-β1 receptor and TGF-βII receptor as HSP90 client proteins. HSP90 inhibitor (17-allylamino-17-demethoxygeldanamycin (17-AAG)) can also prevent the development of renal fibrosis via blocking the interaction between HSP90 and TGF-β type II receptor (TβRII) and promoted ubiquitination of TβRII, leading to the decreased availability of TβRII (Noh et al. 2012).

HSP90 in renal transplantation

In the first study of Maehana et al. (2016), high serum HSP90α levels were obtained from patients whose graft vascular tissues were damaged by acute rejection, such as those with acute antibody-mediated rejection and type II acute T cell-mediated rejection. In contrast, the serum HSP90α levels were not elevated in other conditions such as chronic rejection and calcineurin inhibitor nephrotoxicity (CIN). It was speculated that vascular cells damaged by allorejection could be a source of increased serum free HSP90α in kidney recipients. Other cells in the kidney, including renal tubular cells and infiltrating immune cells, can also be a source of free HSP90α because the serum HSP90α level was high in two cases of type IB acute T cell-mediated rejection, which must have had only interstitial infiltration of lymphocytes and tubulitis. The results of this study suggest that the serum HSP90α level can predict acute rejection distinct from CIN before it is proven by biopsy. It can be helpful for assessment of the effect of anti-rejection therapy and early detection of steroid-resistant rejection (Maehana et al. 2016).

HSP32 (heme oxygenase-1)

Heme oxygenase (HO) is a ubiquitously expressed microsomal enzyme which catalyzes the cleavage of unreacted heme to biliverdin, free iron, and carbon monoxide (CO). HO-1 (also called HSP32) is an inducible isoform whose expression is induced by the substrate (heme) availability and action of stressors such as heat, heavy metal ions, cytokines, and reactive oxygen species (Maines 1997). In human cells, HO-1 is involved mainly in the protection against the adverse effects of oxidative stress (Toru et al. 2006). But it can also be induced by inflammatory stimuli, such as the addition of IL-1β. The protective value of HO-1 is the inhibition of synthesis of inflammatory factors (IL-1, IL-6, IL-8, TNF-α), increasing anti-inflammatory cytokines (IL-10) (Nakao et al. 2003), heme degradation products, and their metabolic derivatives. CO reduces the production of inducible NO-synthase (iNOS), cyclooxygenase-2, related inflammatory mediators NO, and prostaglandins (Nakao et al. 2003). Biliverdin converts into bilirubin, and iron stimulates synthesis of ferritin exhibiting antioxidant properties (Morse and Choi 2002).

da Silva et al. (2001) demonstrated that the basal levels of HO-1 expression in the normal kidney in rats were relatively low. The immunohistochemical localization performed with anti-HO-1 antibodies indicated mainly tubular and arteriolar expression. In the cortex, HO-1 immunostaining was present in proximal and distal tubules. In the medulla, HO-1 staining was evident in collecting tubules and loop of Henle.

The increased HO-1 expression was observed in tubules and interstitium after UUO injury in WT mice. Overexpression of HO-1 counteracts multiple renal fibrosis-associated pathological processes, such as peritubular capillary (PTC) loss, tubular apoptosis, and proliferation of myofibroblasts (Chen et al. 2016). The protective role of HO-1 is demonstrated in ischemic and toxic kidney damage, rejection of kidney transplant, obstructive nephropathy (Agarwal et al. 1996; Mosley et al. 1998; Datta et al. 1999; Shimizu et al. 2000; Chen et al. 2016), and diabetic nephropathy (Pagnin et al. 2016).

Interestingly, HO-1 can contribute to T cells homeostasis, maintaining these lymphocytes in a non-activated state, and the pharmacological inhibition of HO-1 leads to T cell activation and proliferation. Choi et al. (2005) demonstrated that CD4+CD25+Treg cells constitutively expressed HO-1 and that this enzyme could be induced after FoxP3 expression in CD4+CD25− cells, conferring a regulatory phenotype to these cells. Thus, in animal models and in patients with low production of HO-1, mesangioproliferative glomerulonephritis develops frequently (Poss and Tonegawa 1997; Yachine et al. 1999; Ohta et al. 2000). On the contrary, the induction of endogenous HO-1 in experimental models of anti-BMP nephritis and lupus nephritis reduces the glomerular injury and immune deposits in the kidney tissue and results in a reduction of proteinuria (Datta et al. 2002; Takeda et al. 2004).

High glucose levels induced podocyte apoptosis through direct downregulation of HO-1 (Yang H et al. 2016). HO-1 inhibition promoted the increased albuminuria and reduced podocyte numbers in diabetic rats (Lee et al. 2009). The upregulation of HO-1 in obese, hypertensive rats with type II diabetes improved proteinuria levels and significantly decreased histological abnormalities. Moreover, the treatment also reduced the gene expression of profibrotic molecules transforming growth factor (TGF)-β (Ohtomo et al. 2008).

Thus, HO-1 is an important endogenous protecting factor in both inflammatory and non-inflammatory kidney damage. HSP renal expression data are presented in Table 1 and Fig. 1.

Interplay of HSPs in kidney diseases

Synthesis of HSPs in response to different types of tissue injury, including endogenous inflammatory processes, is a major intracellular protective mechanism for inhibiting cell damage

(Welch 1992). Chaperones never work alone, but form large complexes with each other and with their cochaperones. In these associates, one of the basic principles of the protein folding is observed, namely, the ordered cooperative effect of different classes of chaperons on the growing client (substrate) protein. Co-expression of HSP 27, HSP70, HSP90, and HSP60 in kidney cells and tissues was observed in in vitro and in vivo experiments under normal and pathologic conditions (Morita et al. 1995; Donnelly et al. 2013; Dihazi et al. 2011; Schober et al. 1997; O'Neill et al. 2013). According to current models of protein folding in the cytoplasm, HSP70 is an important molecular chaperone that regulates protein quality control through a conserved mechanism of ATP hydrolysis. The capacity of cytoplasmic HSP70 to perform these diverse tasks requires ATP binding and hydrolysis, which is facilitated by other chaperones or cofactors (i.e., "co-chaperones"). These co-chaperones include HSP40, HSP60, and HSP90 (Fink 1999). Aberrant or misfolded client proteins bind to HSP40 and HSP70 to prevent aggregation. The HSP70–HSP40–client complex can recruit HSP90, a central regulator of protein homeostasis that also influences protein folding via an ATP-dependent hydrolytic cycle (Kampinga et al. 2016). Formation of HSP70/HSP40/HSP90 "intermediate complexes" may be augmented by the HSP70/HSP90 organizer protein (HOP), which connects the C-termini of HSP70 via tetratricopeptide repeat (TPR) domains to promote productive folding. On the other hand, quality control of misfolded HSP70- and HSP90-bound clients can be managed by a different TPR domain-containing cochaperone, the C-terminus of HSC70 interacting protein (CHIP). The mechanism of multichaperone complex formation is presented in Fig. 4.

The highly coordinated interactions of HSP70 and HSP90 resulting in formation of HSP70/HSP40/HSP90 intermediate complexes are required for the folding and conformational regulation of a variety of proteins, including the renal tissue cell proteins. The thiazide-sensitive NaCl co-transporter (NCC) in renal cell forms complexes with the core chaperones HSP90, HSP70, and HSP40. Two cochaperones, CHIP and HOP, are associated with NCC (Donnelly et al. 2013). Dihazi et al. (2011) showed that the exposition of the kidney cells to osmotic stress (NaCl, glucose) resulted in an enhancing of co-expression of HSP70 and HSP90. Moreover, Morita et al. (1995) investigated the inductions and intracellular localizations of HSP70 and HSP90 in rat kidneys after unilateral ischemia following reflow. Both HSP70 and HSP90 were rapidly induced in the cytoplasm of injured epithelial cells of the proximal tubules during the degenerative and regenerative phases of the post-ischemic injury. In the study of Coskun et al. (2016), the members of HSP70 and HSP90 families were detected in the preservation solution of the pretransplanted kidney by proteomic analysis. Furthermore, the levels of HSP90β and HSP70 were correlated with ischemia time and donors' age.

HSP90, by itself and/or associated with multichaperone complexes, is a major repressor of heat shock transcription factor-1 (HSF1), which binds to upstream regulatory sequences in the promoters of heat shock genes (Zou et al. 1998). Under non-stressed conditions, HSP90 binds to HSF-1 and maintains the transcription factor in a monomeric state. Denatured proteins bind to HSP70 and HSP90, thus resulting in the displacement of HSF1. Activated HSF1 translocates to the nucleus and induces the transcription of a number of HSP genes, including HSP70 and HSP40. HSP90 inhibitor geldanamycin (GA) targets HSP90 fairly specifically by binding to and inhibiting the ATP binding pocket (Hadden et al. 2006) and inhibits HSP90 ATPase activity, affecting the dissociation of HSP90/HSF-1 complex, while HSF-1 translocates to the nucleus and initiates the production of HSPs such as the chaperones HSP70 and its activator, HSP40 (Murata et al. 2003; Wang et al. 2014). This effect of HSP90 inhibitors is used for targeted treatment of renal injuries in animal models (Harrison et al. 2008; Noh et al. 2012; Lazaro et al. 2015; O'Neill 2015).

Interactions of small HSPs such as HSP27 with HSP70 in kidney are also of significant interest, since these HSPs may interact with cytoskeletal structures and participate in translocation of proteins across membranes into organelles and in the disassembly of protein aggregates within the *actin-rich* renal cells, podocytes, and tubular epithelial cells. It was shown that toxic metals exposure alter phosphorylation of HSP25/27 along with induction of HSP70 in cultured tubular renal epithelial cells and podocytes (Bonham et al. 2003; Eichler et al. 2005), in a model of ischemic renal injury (Schober et al. 1997), and also in patients with renal obstruction (Valles et al. 2003) and lupus nephritis (*Tsagalis* et al. 2006) In various pathologies associated with kidney transplantation in humans, including acute and chronic rejection and cyclophilin nephrotoxicity, an increased cytoplasmic immunopositivity for HSP27 and HSP70 was shown in the same sites of injury (O'Neill et al. 2013).

Sreedharan et al. (2011) demonstrated that in cultured proximal tubule cells (LLC-PK1), suppressing the endogenous stress response as well as abolishing specific HSP70 induction decreased the resistance to injury afforded by overexpression of HSP27. Furthermore, specific blockade of HSP70 induction eliminated the cytoprotection provided by HSP27 overexpression. Thus, HSP27 and inducible HSP70 might work in the renal cells, cooperatively, as co-chaperones to other disrupted cell proteins important to maintaining cell integrity. It was hypothesized that an individual and specific function for each HSP is necessary but not sufficient to prevent breakdown of cell structure. Although HSP27 is not dependent on induction of HSP70 for its association with actin, stabilization of the membrane associated protein Na–K–ATPase requires HSP70. So, overall protection of cell architecture cannot be achieved by overexpression of HSP alone, but requires coordinated work of HSPs in tandem.

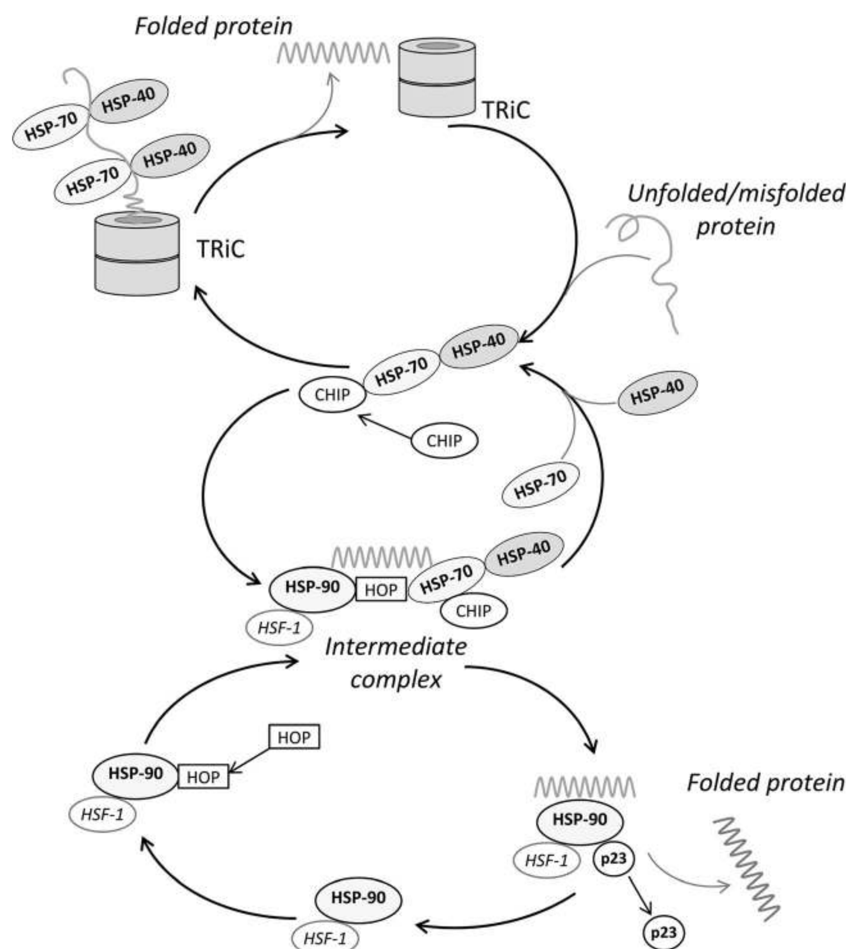


Fig. 4 Interplay of HSP70, HSP 90, and HSP60 in renal cells. The unfolded or misfolded (client) protein is initially recognized by the Hsp70/40 system with CHIP (carboxy-terminus of Hps70 interacting protein) and, subsequently, transferred to HSP90. CHIP is a Ubox E3 ubiquitin ligase that associates with Hsp70 or Hsp90 via its TPR domain and ubiquitinates misfolded substrates (Murata et al. 2003). HSP90 forms a multicomponent complex with cochaperones including Hsp40, Hsp70, HOP (Hsp70 and Hsp90 organizing protein), and p23 that serve to recognize client proteins and assist their binding to the Hsp90 heteroprotein complex (Dickey et al. 2007,Hernández et al. 2002). Subsequently, the cochaperone p23 interacts with the Hsp70/40-HOP-Hsp90-substrate complex resulting in the release of Hsp70/40 and HOP. The folded protein, HSP90, and cochaperone p23 released from the complex and could be participated in the next cycle of protein folding action (Wang et al. 2014). HSP70, HSP40, and TCP-1 ring complex (TRiC) also form a high molecular mass complex that mediates protein folding in ATF-dependent process. HSP70 and HSP 40 bind first to the nascent chain and subsequently mediated the interaction of the growing polypeptide with the TRiC cylinder. As translation proceeds, ATF-dependent folding of an N-terminal domain of the client protein occurs within the central cavity of the TRiC cylinder, while the C-terminal regions remain associated with HSP70/HSP40 in an unfolded conformation (Frydman et al. 1994)

It has also been argued that HSP27, HSP70, and HO-1/HSP32, which are upregulated in rat model of ischemia–reperfusion injury, play consolidated roles in preconditional cytoprotection in ischemia/reperfusion injury (IRI) (Zhang et al. 2008; Guo et al. 2014). According to Ishizaka et al. (2002), staining of serial renal sections in rats undergoing long-term administration of angiotensin II clearly demonstrates that HSP70, HSP25, and HO-1/HSP32 are induced in proximal renal tubular epithelial cells from the same segments and play a role against angiotensin-II-induced nephrotoxicity including hypertonic nephropathy.

The induction of HO-1/HSP 32 and HSP70 by means of NO-mediated modification in intracellular antioxidants levels is a novel alternative anti-apoptotic mechanism. NO can oxidize intracellular reduced glutathione and thereby change the antioxidant levels within the cell, resulting in oxidative or nitrosative stress (Mazzei et al. 2015).

In the eukaryotic cell, about 10% of newly synthesized cytosolic proteins, including actin and tubulins, are co- or post-translationally passed on to the chaperonin TCP-1 ring complex (TRiC), which belongs to chaperonins of the HSP-60 family (Vabulas et al. 2010). The substrate transfer to TRiC is also mediated by HSP70/HSP40, which is consistent with a general sequence of chaperone interactions in the cytosolic folding pathway (Fig. 4). HSP70, HSP40, and double-ring chaperonin TRiC also form a high molecular mass complex

that mediates protein folding in an ATP-dependent process (Frydman et al. 1994).

It was shown that HSP70 and HSP60 co-existed in sites of severe damage (i.e., cortical tubules) during the necrotic phase of acute tubular necrosis induced by inorganic mercury (Hernádez-Pando et al. 1995). Since mercury promotes protein denaturation and aggregation, it is tempting to speculate that an enhanced expression of HSP60 and HSP70 in $HgCl_2$-induced acute renal failure accelerates the reconfiguration of "disordered" proteins. Co-expression of HSP70, HSP60, and HSP27 in the tubular compartment was also detected in renal graft rejection (O'Neill et al. 2013; Trieb et al. 2001). The chaperone interaction scheme is shown in Fig. 4.

The studies on the mechanisms of chaperone interactions in the renal cells represent both theoretical and practical interests, since the modulation of the key stages of the multichaperone complexes formation may open promising approaches to HSP-targeted therapy.

Prospects of HSP therapy

Considering a wide variety of protective functions of HSPs, there are rich possibilities associated with the induction of their expression in kidney cells in various kidney diseases. HSPs are therefore the promising therapeutic candidates to be used in the context of predictable injury. The most common experimental paradigm for evaluation of the potential cytoprotective effects of HSPs is the preconditioning experiment (Table 2). The cells in culture or the whole organisms are first conditioned by exposure to a mild or moderate stress that is sufficient to stimulate accumulation of HSPs but does not result in a significant level of cell death. A period of several hours after the moment of conditioning stress is then required to achieve the elevated HSP levels. Then, the cells or organisms are subjected to a more severe test stress that typically causes a significant cell death. The result is that the preconditioned specimen shows a significantly improved survival as compared to a specimen exposed only to the severe stress (Tytell and Hooper 2001). Recently, there were reports on a protective impact of the mild systemic thermal stimulation of the progression of renal injury in a mouse model of renal ablation through increased level of HSP27, reduced apoptosis, and oxidative stress in remnant kidney (Iwashita et al. 2016).

HSP70 is one of the important candidates due to its multiple protective effects, wide tissue distribution in renal tissue, and potential anti-inflammatory properties (Aufricht 2005). Induction of HSP70 in high-risk patients in post-operative AKI may benefit from HSP70 induction prior to surgery. However, the physical preconditioning approaches often involve an additional thermal or ischemic injury potentially associated with some negative consequences (O'Neill et al. 2014). An alternative approach is related to the use of pharmacological agents capable of increasing the level of HSP70 locally in the kidney prior to the onset of ischemia/reperfusion injury. As an illustration, a liposomal delivery form of HSP72 prevented the ischemia-induced renal tubular cell apoptosis by inhibiting NF-κB activation and TNF-α production. The authors suggested that the impact on this mechanism can underlie therapeutic interventions that minimize renal dysfunction and accelerate recovery from AKI (Meldrum et al. 2003).

Development of a viable pharmacological strategy to reduce AKI, including the pathologies induced by renal transplantation, is highly desirable. The ultimate aim is to improve the function and longevity of transplanted organs by administering a single dose of an agent to an organ donor prior to organ retrieval. In addition, it may be beneficial to treat the organ ex vivo with a drug delivered by machine perfusion prior to the implant procedure (O'Neill et al. 2013). Recent research has begun to focus on pharmacological induction of HSP70, but so far only in experimental models (Tsuji et al. 2009; O'Neill et al. 2014). The treatment with an HSP70 inducer geranylgeranylacetone (GGA) before ischemia results in increased renal cortical HSP70 content, decreased BUN levels, more rapid renal recovery, preserved tubular morphology after injury, and improved animal survival (Wang 2011). The HSP90-binding agent geldanamycin and its analogs (17-AAG and 17-dimethylaminoethylamino-17-demethoxygeldanamycin, alvespimycin (17-DMAG)) are known to upregulate HSPs. The treatment with these agents results in increased expression of HSP70 in human cells in vitro and murine cells in vivo. This expression pattern is associated with cell protection from oxidative injury and decreased morphological and functional injury following ischemia/reperfusion injury in a mouse model (Harrison et al. 2008); attenuated renal fibrosis through degradation of TGF-β-receptor in the unilateral ureteral obstruction model (Noh et al. 2012); improved renal function; decreased albuminuria and renal lesions, such as mesangial expansion, leukocyte infiltration, and fibrosis, in diabetic mice (Lazaro et al. 2015). Geldanamycin, herbimycin, and then radicicol were the first natural Hsp90 inhibitors discovered; however, their instability and hepatotoxicity limited any clinical potential (O'Neill et al. 2012). A geldanamycin analog 17-allylamino-17-demethoxygeldanamycin (17-AAG) was well tolerated and assessed in a clinical trial. 17-DMAG is another water-soluble geldanamycin analog, which can be administered both intravenously and orally (Kim 2009). However, due to the fact that the exact mechanisms of protective action of HSPs and potential side effects in renal diseases are not established yet, the use of these drugs is limited in human studies. O'Neill (2015) recently studied a new small molecule HSP90 inhibitor (AT13387) in an established renal IRI model to assess efficacy of this agent in reducing renal IRI. Following renal IRI, AT13387 significantly reduced serum creatinine, tubular necrosis, TLR4 expression, and NF-κB-dependent chemokines in mice. AT13387 also has

Table 2 The pleiotropic effects of HSPs in the kidney

HSPs	Effects	References
HSP27	• Inhibits actin polymerization and aggregation, stabilizing actin cytoskeleton • Maintenance of foot process structure of podocytes (in normal cells and nephrotic syndrome) • Prevent apoptosis via decrease of caspases activity • Protects against the oxidative stress • Rescued endothelial dysfunction • Inhibits renal fibrogenesis • Preserved E-cadherin during an EMT • Inhibits osmotic damage in medulla	Smoyer et al. (1996) Mehlen et al. (1997) Neuhofer et al. (1998) Preville et al. (1998) Schober et al. (1998) Smoyer et al. (2000, 2002) Kim et al. (2010) Vidyasagar et al. (2013) Matsumoto et al. (2015) Tian et al. (2016)
HSP70	• Shaping the structure of newly synthesized native proteins • Restoring of partially denatured proteins • Degradation of irreversibly damaged protein molecules • Transport of proteins through intracellular membranes into the organelles • Cleavage of protein aggregates • Prevent apoptosis • Supress pro-inflammatory NF-κB signaling • Protects against the oxidative stress • Suppresses of stress kinases (JNK and p38), caspases, and activates of the MEK/ERK pathway • Supress TGF-1 signal, decreased the number of SMA-positive myofibroblasts, collagen I deposition, reduced tubulointerstitial fibrosis • Mediates anti-inflammatory response • Interplays with co-chaperones—HSP40, 90, 60, 27 for more effective protein refolding	Frydman et al. (1994) Aufricht et al. (1998) Beck et al. (2000) Park et al. (2002) Shimizu et al. (2002) Uchinami et al. (2002) Suzuki et al. (2005) Jo et al. (2006) Wang et al. (2009)(Mao et al. (2008) Schnaper et al. (2009) Marzec et al. (2009) Wang et al. (2011) Sreedharan et al. (2011) Kim et al. (2014) Kampinga et al. (2016)
HSP60	• Folding of newly synthesized native proteins • Refolding damaged protein molecules • Preventing the Bax-mediated apoptosis • Promotes protein translocation into mitochondria • Mediates anti-inflammatory response	Frydman et al. (1994) Stuart et al. (1994) de Kleer et al. (2003) Zanin-Zhorov et al. (2003, 2006) Tsuji et al. (2009)
HSP90	• Folding of a variety of client proteins: tyrosine kinases (e.g., Akt and MEK), transcription factors, structural proteins (tubulin, actin), HIF-1α, and TGF-β receptors • Forms of "intermediate complex" with co-chaperones—Hsp70, p50 (cdc37), HOP, and p23 resulting in enhanced degradation of the client proteins • Binds to HSF-1 and maintains the transcription factor in a monomeric state • Regulates the synthesis of NO-dependent on endothelial NO-synthase, normal renal blood flow and glomerular filtration rate	Zou et al. (1998) Pearl and Prodromou (2000) Murata et al. (2003) Goetz et al. (2003) Neckers and Ivy (2003) Ramirez V. et al. (2008) Noh et al. (2012) Wang et al. (2014)
HSP47	• Binds to the triple helical procollagen and stabilizes its structure • Promotes excessive assembly of collagens • Increases of collagen type I, IV, fibronectin, and t-PAI expression • Promotes glomerulosclerosis and interstitial fibrosis	Razzaque and Taguchi (1997) Tasab et al. (2000) Xiao et al. (2012)
HSP32 (HO-1)	• Protects against the oxidative stress • Prevent apoptosis • Limits production of NO by iNOS • Mediates anti-inflammatory response • Reduces TGF-β expression	Albakri and Stuerh (1996) Nakao et al. (2003) Choi et al. (2005) Toru et al. (2006) Ohtomo et al. (2008) Wei et al. (2011)

ROS reactive oxygen species, *EMT* epithelial–mesenchymal transition, *SMA* smooth muscle actin, *NO* nitric oxide, *iNOS* inducible nitric oxide synthase, *HIF-1α* hypoxia-inducible factors, *HOP* Hsp70/Hsp90 organizer protein, *HSF-1* heat shock factor protein 1, *t-PAI* tissue-type plasminogen activator inhibitor

a low toxicity profile and better translational potential than 17-DMAG, and therefore, it may be possible to more rapidly translate this therapy into a clinical trial. Thus, preventive treatment with AT13387 could be administered in individuals at high-risk of acute ischemic kidney injury (patients with preexisting kidney disease, diabetes, or previous toxic drug and radiological contrast exposure) (O'Neill 2015).

Zhang (2009) demonstrated that pretreatment of animals with a single dose of glutamine i.v. (0.75 g/kg) 1 h in advance was effective in IRI in rats. Ischemia–reperfusion renal injury

and cell apoptosis in the glutamine group were significantly milder than those in control group. HSP70 expression was higher in the glutamine group, and the peak of HSP expression was much earlier. The mechanism of glutamine in reducing renal IRI is partially due to the induction of HSP70 expression, through which anti-inflammatory, anti-injurious, and anti-apoptotic action work.

In addition to the protective function as a chaperone molecule, HSP70 and HSP60 can modulate chronic immune inflammation by regulation of the immune activity of Tregs and other infiltrating inflammatory cells in immune diseases, such as chronic glomerulonephritis. The introduction of bacterial HSPs is attempted as factors contributing to the determination of the cross-reactive epitopes and to the formation of regulatory T cell activity in experimental animals (Shi et al. 2014) and in patients with autoimmune diseases. The protective effect of immunization by bacterial HSP is ensured by the high degree of homology of certain HSP epitopes of bacteria and humans (mostly of intermediate and C-terminal peptides). The induction of regulatory protective T cell phenotype is associated only with the cross (homologous) peptides, whereas bacterial (existing exclusively in bacteria, and non-homologous) epitopes induce the development of inflammatory response (Pockley 2003). To clarify the factors that contribute to the determination of cross-reactive epitopes and the formation of regulatory T cell activity in immunization by bacterial HSPs, further research is needed. However, attempts were made to use bacterial HSPs for prevention and inhibition of autoimmune diseases in an experiment and in a clinical setting. The use of OM-89 (*Escherichia coli* extract purified from endotoxin and containing HSP60 and HSP70) in one study and dnaJP1 (HSP40 bacterial peptide) in another study has not been accompanied by the development of side effects and resulted in a good clinical result (Vischer 1990; Rosenthal et al. 1991; Prakken et al. 2004). The immune modulatory effect consisted of "switching" of pro-inflammatory T cell phenotype (Th1) to anti-inflammatory one (Treg). The dnaJP1 peptide was safe and well tolerated. In response to treatment with dnaJP1, there was a significant reduction in the percentage of T cells producing tumor necrosis factor α and a corresponding trend toward an increased percentage of T cells producing interleukin-10 (Koffeman et al. 2009). Subcutaneous injections of p277 peptide (HSP60 peptide) to type I diabetes patients provided a favorable clinical effect based on the immune switching of Th1 response to the anti-inflammatory Th2 one (Raz et al. 2001; Huurman et al. 2008). Of significant interest are findings by Kim et al. (2014) that the heat preconditioning significantly expanded the intrarenal CD4+ CD25+ Treg population following renal IRI in comparison with control injured kidneys. Heat preconditioning induces renoprotection that is Treg dependent and associated with increased expression of HSP70.

An elegant clinical approach was described by McCarty and Al-Harbi who vaccinated patients, which have been subjected to heat shock in the early 1990s in Kuwait, with human mononuclear cells (McCarty and Al-Harbi SA 2013). Mahmoud FF (1996, 2010) documented anomalous immune cell activation and deficiency (CD4+CD25+) of Treg cells among citizens of Kuwait following the 1991 Gulf War, contributing to increases in chronic illness and autoimmunity in this population. The mononuclear cells were incubated at 42 °C for 30 min, then at 37 °C for 24–48 h, which resulted in activation of the synthesis of heat shock proteins. Then, these cells were injected subcutaneously into the patients. This therapeutic procedure dubbed MAM-14 that was found to be therapeutically beneficial, low cost, and side effect-free in the autoimmune patients (McCarty and Al-Harbi SA 2013).

Although many models of kidney diseases have focused on the effect of HSP70, other strategies have been used to manipulate HSP and protect kidneys from injury. These include inhibition of HSP90, which may mediate protection through induction of HSP70 and selective expression of HSP27 and HO-1.

The intrarenal transfection of HSP90 protects against the renal damage induced by ischemia/reperfusion. Rats subjected to ischemia/reperfusion and transfected with HSP90 showed preservation of the tubular epithelium and no reduction in renal blood flow and abnormal proteinuria (Barrera-Chimal et al. 2014). Tanaka et al. (2013) showed that HSP90 inhibitor 17-dimethylaminoethylaminogeldanamycin (17-DMAG) significantly suppressed the proliferation of human aortic endothelial cells induced by anti-HLA IgG. HSP90 plays a role in endothelial cell proliferation induced by anti-HLA alloantibodies, and therefore, it can be a potential target for the treatment of the acute antibody-mediated rejection in kidney transplantation.

Kim et al. (2010) introduced HSP27-lentiviral constructs via injections into the kidneys 2 days prior to induction of ischemia in mice. HSP27 overexpressing mice demonstrated lower plasma creatinine, significantly lower apoptosis and necrosis, and lower induction of mRNAs of various pro-inflammatory cytokines and neutrophil infiltration. These mice also demonstrated better F-actin preservation in the proximal tubules, thus substantiating a therapeutic role for HSP27 as an actin remodeling protein during conditions of ischemic injury. It is supposed that kidney-directed local expression of HSP27 through lentiviral delivery is a viable therapeutic option in attenuating the effects of renal IRI.

Vidyasagar et al. (2013) demonstrated that overexpression of HSP27 was associated with decreased renal fibrosis after UUO. In their earlier study, the same authors suggested a therapeutic role for HSP27 delaying tubular injury by maintaining E-cadherin protein levels, possibly through the down-regulation of Snail. HSP27 was overexpressed in rat proximal tubular cells NRK52E by transiently transfecting with a plasmid-HSP27 cDNA construct (Vidyasagar 2008).

Studies on HO-1 and AKI support a therapeutic approach for human AKI based on the induction of HO-1. Administration of macrophages modified to overexpress HO-1 would protect from renal IRI. Using an adenoviral construct, HO-1 was overexpressed in primary bone marrow-derived macrophages. The injection of macrophages to mice resulted in serum creatinine reducing and promoted resolution of platelet deposition. The protective effects of these macrophages likely reflected their elicited anti-inflammatory actions and their enhanced capacity to phagocytose apoptotic cells (Ferenbach et al. 2010). Macrophages in which HO-1 is upregulated thus provide a strategy to reduce the risk for ischemic AKI in the elderly and other susceptible patient populations. In a study by Chen et al. (2015), preconditioning by HO-1 inducer (hemin) enhanced tubular recovery, which subsequently prevented further renal injury in a mouse model of renal IRI. Cheng et al. (2012) recently showed that adiponectin upregulated HO-1 could protect against IRI-induced renal damage. In an SLE (MRL/*lpr*) mice model, the induction of HO-1 with hemin resulted in decreased proteinuria, reduced glomerular immune complex deposition, and decreased levels of anti-dsDNA immunoglobulin (Takeda et al. 2004). Positive effects of HO-1 preconditioning, which resulted in the decreased renal injury, were obtained in the models of cisplatin-, cyclosporine-, and contrast-induced nephropathy (Agarwal 1995; Rezzani 2005; Goodman 2007).

The strategy based on application of HO-1 inducers, such as *Ginkgo biloba*, curcumin, and sour cherry seed extract, is not only safe but also low cost (reviewed by Haines et al. 2012). A source of HO-1-inducing phytochemicals is the biflavone component of seeds *Prunus cerasus*—the Lake Balaton sour cherry. Dietary administration of sour cherry seed kernel biflavones induces expression of physiologically relevant CO levels in selected tissue (Szabo et al. 2004). Sour cherry seed extracts and other phytochemical HO-1 inducers are likely to significantly expand the range of pathologies that may be treated at low cost and with minimal adverse effects (Haines et al. 2012). A polyphenol component of green tea, epigallocatechin-3-gallate, is an inducer of HO-1 capable of protecting kidneys from ischemia/reperfusion (IR) injury (Kakuta et al. 2011). Plant-derived compounds are non-toxic and may be used in patients with kidney diseases.

Recently, the introduction of DNA vaccines was attempted to prevent and treat autoimmune diseases. The effectiveness of HSPs for their prevention and inhibition pave the way to application of HSP-immunotherapy of kidney immune and inflammatory diseases. Mice vaccinated with DNA that encoded the membrane-bound or secreted forms of HSP70 showed significant increase in the frequency of IFN-γ-secreting T cells. Inclusion of these novel forms of HSP70 may increase the efficacy of DNA vaccines and opens up the possibility of use of human HSP70 as an effective adjuvant in DNA clinical trials (Garrod et al. 2014).

In recent years, several experimental studies of heat shock proteins DNA vaccination method were performed with success, mainly in adjuvant arthritis. A single intramuscular injection of vaccinal DNA provided cellular and humoral immune response to antigen and induction of memory cells (Gurunathan et al. 2000). The vaccination with HSP60 and 70 DNA has been shown to activate the specific T cell clones secreting anti-inflammatory IL-10 and TGF-β and to cause the inhibition of autoimmune disease in an experiment (Quintana and Cohen 2005). Moreover, the HSP70 vaccine induced a response not only to the genuine peptides but also to multiple HSP60 peptides, i.e., the development of immunological cross-phenomenon between structurally non-homologous molecules, though the mechanisms of this effect require further investigation (Quintana et al. 2004).

Conclusion

In kidney tissue, HSPs are an important part of the intracellular defense system, which is operated physiologically and activated by different types of cellular stress. The various HSPs inside the cell provide stabilization of cell structures, enhance cell resistance to apoptosis and necrosis, and preserve potential for further regeneration. The unique properties of HSP60s and HSP70s provide an important immunoregulatory function in human body. Expression of these proteins on the inflammation cell surface results in differentiation of specific regulatory phenotypes of HSP-specific T-lymphocytes (CD4+, CD25+, Th2, Tc1 cells). By regulating the phenotype of T cells and production of anti-inflammatory cytokines, HSPs form a microenvironment conducive to limit the inflammatory process. CKDs result in a violation of HSP function, which can lead to a violation of local kidney self-defense mechanisms with resulting progressive tissue damage. The study of HSPs in kidney tissue in normal and chronic diseases is very important, as HSPs are promising targets for the development of new approaches to the treatment of kidney diseases.

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