The role of heat shock proteins in kidney disease

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ABSTRACT

Heat Shock Proteins (HSP) belong to the family of intracellular proteins that are constitutively expressed and are upregulated by various stressors including heat, oxidative and chemical stress. HSP helps in reparative processes, including the refolding of damaged proteins and the removal of irreparably damaged proteins that would initiate cellular death or apoptosis. A growing body of evidence has expanded the role of HSP and defined their role in diseases such as neurodegenerative disorders, cancer, ischemic heart disease and kidney diseases. The protective role of HSP in ischemic renal injury has been described and HSP impairment has been noted in other forms of kidney injuries including post-transplant situation. Further research into the role of HSP in prevention of kidney injury is crucial if translation from the laboratory to patient bedside has to occur. This article aims to be a review of heat shock protein, and its relevance to kidney diseases.

Key words: heat shock protein, apoptosis, ischemia reperfusion injury, dialysis

INTRODUCTION

Heat Shock Proteins (HSP) belong to the family of intracellular proteins that are phylogenetically highly conserved. HSPs are constitutively expressed and are markedly upregulated by various stressors including heat, oxidative and chemical stress. The expression of HSP helps in numerous reparative processes, including the refolding of damaged proteins and the removal of irreparably damaged proteins that would accumulate and initiate cellular death or apoptosis.^[1,2] A growing body of evidence has expanded the role of HSP, which have been regarded as intracellular chaperones beyond their cytoprotective function. The main goal of the chaperones discussed extensively in the recent reviews [3, ^{4]} is to preserve cell survival by controlling the three -dimensional structure of the synthesized proteins, preventing misfolding or degradation. Therefore, HSP regulates the response to any detrimental factors such as temperature, radiation, hypoxia, toxins or infectious agents. Stress response may also evoke the release of HSP outside the cell as an effect of an active transport or cell disintegration due to damage. The extracellular HSP thus released plays a pivotal role in innate adaptive immune responses. They also take part in many pathological processes. There are several HSP families, each with specific properties that have been well established (Table 1). HSPs have been classified according to their molecular weight into five groups: small HSP (include HSP 27), HSP 60, HSP 70, HSP 90 and HSP 110. Among these, HSP 60, 70 and 90 have been studied extensively. [3] In each of these groups, two types of HSPs can be found: stress-induced isoforms (HSP 60, 70 and 90 alpha), as well as those constitutively and independent of stress conditions (HSP 70, HSP 90ß).

Role of extracellular HSP: Although the existence of extracellular HSP has been known for close to two decades, [5,6] there is still much uncertainty and controversy regarding the role of the extracellular form of these proteins. Extracellular HSP has been considered as a danger signal, [7] where the molecules are released under pathological or physiological stress giving a warning to the immune system. The cellular response comes from the antigen-

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Table 1: Summary of HSP families		
Mammalian HSP family	Location	Main established function
HSP 90	Cytosol	Chaperone for a regulator of protein complex formation
HSP 70	Cytosol/nucleus/mitochondria	Protein trafficking, anti-apoptotic properties and degradation of denatured proteins under stress
HSP 60	Mitochondria	Mitochondrial protein folding and assembly
HSP 27	Cytosol	Preventing unfolded protein aggregation

HSP: heat shock protein

presenting cell (APC), which recognizes HSP through the Toll-like receptors (TLR). That interaction subsequently triggers the APC to release inflammatory cytokines and to activate the nuclear factor (NF-KB), thus initiating the adaptive immune response and presentation of antigens to the cytotoxic T-cells. HSP can also stimulate the production of cytokines by monocytes and macrophages, as well as the expression of adhesion molecules on endothelial cells. HSP 60 is certainly pro-inflammatory, while the ambiguous function of HSP 70, inducing pro-inflammatory IL-6, TNF-α and anti-inflammatory (IL-10) cytokines, creates some confusion.

ROLE OF HSP IN ACUTE KIDNEY INJURY

The incidence of acute kidney injury (AKI) is increasing and represents a significant health concern globally. In a hospital-based setting, AKI may result from multiple causes including hypoperfusion, surgery and sepsis. Apart from supportive therapy including providing renal replacement therapy when appropriate, no definite therapy exists for patients with AKI and present treatments include prevention of further renal insults by avoidance of nephrotoxic medications and effective treatment of sepsis. [9]

HSP and renal ischemia reperfusion injury

Ischemia reperfusion injury (IRI) is a complex event that involves numerous classes of cells, and involves various biological processes such as apoptosis, microvascular dysfunction, immunological activation and altered transcription.[10] There is a marked increase in renal HSP expression with the HSP 70 gene showing a 43-fold increase, and the HSP 27 showing a 12-fold increase. The concept that HSPs are cytoprotective after IRI is re-enforced by the evidence obtained from HSP-70-/mice.[11] HSP -/- mice have the worse kidney function, tubular injury and worse survival following renal IRI. The protective effect from renal IRI provided by the HSP 70 inducing agent geranylgeranylacetone is also abrogated in HSP 70 knockout mice. The main barrier to the translation of these treatments to clinical use is the lack of complete understanding how HSP 70 induction results in kidney protection. The putative modes of protection include cytoskeletal stabilization, anti-inflammatory effects, requirement in autophagy, anti-apoptotic properties, influence over macrophage phenotype and stimulation of regulatory T cells. In addition to potent ant-inflammatory effects, HSP 70 also potentially exert pro-inflammatory effects. It is thought that HSP 70 located in the cytosol reduces inflammatory signaling, however HSP 70 released into extracellular compartments displays immunestimulating properties.^[13] This however remains poorly understood and calls for further studies aimed at a more accurate characterization of HSP 70 and its overall effect on the inflammatory equilibrium. Future prospects for translational use of HSP 70 in the prevention of kidney ischemia reperfusion injury will be helpful in patients predicted to be at a high risk of developing post-operative AKI, such as after cardiac surgery or after ionic contrast use. This type of preconditioning strategy has potential since it would allow prevention of IRI at the earliest stage. Better predictive models about which group of patients would likely benefit the most from such a therapy are needed. This use of HSP will also be helpful prior to kidney transplantation, since in this situation, the delivery of the drug to an organ donor prior to organ procurement could facilitate protection from IRI insult, and may result in improved graft outcomes.

ROLE OF HSP IN CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is a complex condition characterized by a variety of underlying pathological causes and pathways, culminating in the common end result of glomerulosclerosis and interstitial fibrosis. The potential components of this stress cocktail include the putative uremic toxins, mediators of inflammation, reactive oxygen species, apoptosis, infections, etc. Therefore, the discussion of HSP in chronic kidney disease can be conducted in two parallel directions. The first one is the possible impact of HSP, either protective or deleterious on the progression of chronic kidney disease. After defining the role of HSP, possible therapeutic interventions such as administration of anti-HSP proteins, as well as modification in the biocompatibility of dialysis materials, will open up future treatment perspectives in optimizing renal replacement therapy and improving patient outcomes. The in vitro investigations performed in the late 1990's have shown increased HSP 72 expression in human neuroblastoma calls treated with urea at varying concentrations from 40-200 mg/dL. It was shown that HSP values rose after 30 min, obtained peak values after 10 hrs, and reduced to zero after about 48 h.[14] However, a similar experiment conducted with creatinine as a medium did not show any impact on HSP 72 expression. This probably reflects the selective influence of uremic toxins on the stress response, and suggests that an increase in the HSP 72 expression may protect against apoptosis and lead to cell adaptation to noxious conditions. However, these experimental conditions are of short duration and cannot exactly mimic the conditions responsible for chronic kidney damage. Therefore, the interpretation of adaptive response in the course of CKD should be viewed cautiously. Mao et al. [15] studied the impact of HSP on chronic kidney damage in rats with obstructive uropathy. The selective activation of HSP 72 given orally inhibited the proliferation an apoptosis in tubular cells and diminished the accumulation of fibroblasts and collagen- 1 generation in renal parenchymal cells, thus slowing the process of fibrosis. Research on HSP levels in humans with CKD is limited and very few studies have been done in this area. Mahgoub et al.[16] looked at HSP 27 levels in Type-2 diabetic patients with and without diabetic nephropathy and found serum HSP 27 levels significantly higher in patients with diabetic nephropathy compared to diabetic control patients. Marzec et al.[17] described HSP 72 expression in the peripheral blood monocytes from adult patients with predialysis CKD when compared to controls (359 \pm 83 AU vs. 405 \pm 51 AU, P < 0.01) and found negative correlations between HSP 72 protein and serum creatinine concentrations, thus suggesting exhaustion of adaptive mechanisms along with aggravated apoptosis and impaired immunity characteristic for CKD. However, when compared to adults with CKD, children have better preserved HSP 70 levels, thus favoring better preservation of cellular adaptive processes. The same study revealed diminished serum concentration of anti-HSP-70, a negative factor in cardiovascular complications, thereby increasing the risk of atherosclerosis.

HSP in ESRD patients on dialysis

In contrast to the scarce data concerning HSP in CKD patients on conservative therapy, a lot more work has been done in the field of dialysis. In hemodialysis, the data has focused mainly on the role of HSP as a potential marker of biocompatibility of materials used. The studies of HSP in hemodialysis have concentrated mainly on HSP 72. It was shown that in regard to peripheral blood monocytes, mRNA amount in adults on HD was significantly lower than in controls (293 \pm 62 AU vs. 405 \pm 51 AU, P < 0.001). Interestingly, the exposure of urea-treated macrophages harvested from healthy controls to heat stress (47 °C for 40 min) resulted in greater increase of HSP 72 expression

than after incubation with urea only. This suggested that the stress response although altered in CKD was not entirely abolished. However, the levels of HSP 70 in children differed from adult patients on dialysis. HSP 70 and anti-HSP 70 serum concentrations between children on hemodialysis and controls did not significantly differ. The two studies assessing the impact of a single dialysis session with polysulphone membrane on HSP revealed an increase in HSP 72 expression, high HSP 60, as well as decreased anti-HSP 60 and anti-HSP 70 concentrations after HD.[18,19] The HSP 72 activation was indicative of a stress induced reaction such as blood-dialysis contact activation. However, the decrease in antibody levels could have resulted from adsorption to the dialyser membrane surface, creation of HSP-anti-HSP complexes and elimination by dialysis itself. The clinical interpretation of these findings is still unclear.

HSP in peritoneal dialysis:

The investigation of HSP in peritoneal dialysis patients has mainly focused on the impact of peritoneal fluid as a stress factor on the function of the peritoneum. Induction of HSP 72 expression has been found in both mesothelial cells incubated with peritoneal dialysis fluid, and in macrophages from the dialysis effluent collected after a 14 dwell.^[20] HSP 72 can also be used as a possible marker of peritoneal fluid biocompatibility. In vitro exposure of human mesothelial cells to peritoneal dialysis solution (PDS) resulted in over-expression and shift of HSP 27 and HSP 72 from the noncytoskeletal to cytoskeletal fraction within the cell. Bender et al.[21] successfully improved the status of mesothelial cells by pharmacological manipulation of the PDS content in vitro by adding glutamine to PDS. This improved the viability of human mesothelial cells by inducing HSP 27 and HSP 72 expression. In the rate model, this addition also reduced the detachment of mesothelial cells and decreased the amount of protein lost in PDS. The question whether there is any difference between hemodialysis and peritoneal dialysis patients with regard to HSP is difficult to answer in adults. In children, however, it appears that HSP 60 and HSP 90α concentrations were similar in both groups.^[22] The above mentioned results have revealed the complexity of HSP response to stressful conditions and although HSP disturbances were more evident in the case of hemodialysis, this does not imply an explicitly negative opinion of hemodialysis when compared to peritoneal dialysis. Anti-HSP may become a useful marker of biocompatibility.

ROLE OF HSP IN KIDNEY TRANSPLANTATION

The transplanted kidney whether from cadaveric organ donor or from a living kidney donor undergoes ischemiareperfusion injury, and HSP plays an essential role in that process. Studies in children, after kidney transplantation, have suggested that the urinary excretion of HSP 72 is characteristically seen only in the early post-transplant period, while patients with stable grafts do not have detectable levels of HSP in urine. [23] Urinary HSP 72 may be a good marker of tubular cell integrity. In ischemic kidney rat models, over-expression of HSP 70 and HSP 90 and relocation of Na-K ATP-ase from the apical to the basolateral membrane domain of the proximal tubule cells has been documented. The observed translocation of HSP 27 from the medulla to the cortex is an adaptive response of the ischemic milieu. A major concern and application of HSP in organ transplantation is their potential role in preventing or delaying the process of rejection. Experimental data has shown that activation of heat shock protein makes cells preconditioned by subjecting them to sublethal stress to become resistant and survive subsequent otherwise lethal stimuli. A natural consequence of such results will imply that HSP stimulation in the transplanted kidney would preserve kidney function for a longer time. However, this has not been replicated in experimental data, and results from studies are ambiguous and have not shown any definitive protective effects. [24,25] Some studies have even shown unpredictable effects such as enhanced immunogenicity^[26] which can be dangerous in a transplant setting.

CONCLUSIONS

Knowledge of the role played by HSP in kidney disease is slowly increasing, although we are far from understanding their entire role and pathological implications. The intracellular forms of HSP, especially HSP 70 in cytoprotective action and delaying of apoptosis will be crucial. The increasing biocompatibility of dialysis membranes, as well as the peritoneal dialysis fluids will help in improving the quality of renal replacement therapy. Future investigation should concentrate on this aspect.

Conflict of Interest

None declared.

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