HSP70 Family in the Renal Inflammatory Response

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Abstract: Heat shock proteins (HSP) are a shock induced family of proteins, whose most prominent members are a group of molecules dedicated to maintaining the function of other proteins. Interestingly, after being exposed to heat shock typical proinflammatory agonists modify the heat shock-induced transcriptional program and expression of HSP genes, suggesting a complex reciprocal regulation between the inflammatory pathway and that of the heat shock response. The specific task of Heat shock protein 70 (Hsp 70), the most widespread and highly conserved HSP, is to protect against inflammation through multiple mechanisms. So, the expression of immune reactivity to Hsp70 in the kidney could be a cause of hypertension. Hsp70 modulates inflammatory response, as well as down-regulates the nuclear factor kappa-light-chain-enhancer of activated B cells. Also, a decreased expression of renal Hsp70 may contribute to activate the toll-like receptor 4-initiating inflammatory signal pathway.

In addition, several studies have revealed that Hsp70 is involved in the regulation of Angiotensin II, a peptide with pro-inflammatory activity. Increased inflammatory response is generated by nicotinamide adenine dinucleotide phosphate oxidase, following activation by Angiotensin II. Interestingly, Hsp70 protects the renal epithelium by modulation of nicotinamide adenine dinucleotide phosphate oxidase, a fundamental step in the pro-inflammatory mechanism.

This article aims to summarize our understanding about possible mechanisms improving the renal inflammatory process linked to Hsp70 expression. Finally, from a therapeutic point of view, the notion of antiinflammatory tools regulating Hsp70 could directly affect the inflammatory renal disease.

Keywords: Angiotensin II, heat shock protein 70, inflammatory renal disease, toll-like receptors, vitamin D.

INTRODUCTION

Organisms respond to environment and stress by inducing cell stress responses that protect physiologic processes such as DNA repair, protein folding, and clearance of damaged proteins. More specifically, the heat shock proteins (HSP) are a group of cellular modulators activated by various factors, most notably by the increase in cells temperature [1]. These responses are controlled transcriptionally. Furthermore, HSP, are crucial in the heat shock response (HSR), and respond primarily to heat shock factor (HSF) [2]. Since the discovery of the family of HSF the functional relevance of distinct members is now emerging, and recent studies have provided evidence for both cooperative and specific functions of HSF that expand beyond the HSR. Accordingly, the stimulation of protective mechanisms such as those mentioned above (HSF and HSR), may slow the damaging effects of oxidative stress and inflammation. Widespread research has identified innate immune recognition receptors and intracellular signaling pathways that culminate in inflammatory responses [3]. Interestingly, typical proinflammatory agonists modify the heat shock-induced transcriptional program and expression of HSP genes following exposure to heat shock, suggesting a complex reciprocal regulation between the inflammatory pathway and the HSR pathway [4]. In agreement, heat shock protein 70 (Hsp70) has anti-inflammatory potential [5]. Different kind of cells release HSP 70 that has an important signaling role especially in the inflammatory and immune response [6]. Also, proteins are helped to adopt native conformation or regaining function after misfolding by Hsp 70, a quite widespread and very much conserved HSP [7]. The Hsp70 family of HSP consists in molecular partners about 70 kDa, which play a critical role in protein function. Besides protecting the synthesis, maintenance and protein degradation, contributing to the homeostasis of the same [8]. Furthermore, of particular relevance to our knowledge, Hsp70 and their receptors protect against inflammation through multiple mechanisms [9, 10]. Therefore, the expression of salt-sensitive hypertension in the kidney is the immune reactivity to Hsp 70 [11, 12]. Hsp70 reduces inflammation, renal infiltration and consequent acute kidney injury (AKI). Renal oxidative stress as well as inflammatory response characterize AKI, a common problem [13]. In addition, Hsp70-renal cytoprotection has been partially attributed to CD4 + CD25 + T cells Foxp3 + regulatory T cells during AKI [14].

On the other hand, the pharmacological induction of HSP expression is an emerging pre-conditioning strategy aimed at reducing ischemia-reperfusion injury following renal transplantation. The disruption of the IκB kinase (IKK) complex leads to the potential down regulation of the nuclear

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factor kappa-light-chain-enhancer of activated B cells (NF-κB) [15]. On the other hand, the lesions in diabetic nephropathy are consequences of inflammatory processes at the tubulointerstitial levels. Of special interest, Toll-like receptors (TLRs) were established as moderators of inflammation [16], but as yet there is not a precise comprehension of their role in diabetic nephropathy [17]. However, a decreased expression of renal Hsp70 may contribute to activate the toll-like receptor 4 (TLR4) - initiating inflammatory signal pathway [18]. TLRs were discovered in 1997 and since then have been extensively studied, leading to the come out of a very detailed picture on how they act in the renal inflammatory disease [19]. Besides immunocytes, there is a wide distribution of TLRs in several types of cells, renal cells included, where they significantly contribute to various inflammatory pathologies [20].

Ultimately it is now a well-known fact that the activation of the rennin-angiotensin system (RAS) predisposes to cardiovascular and renal diseases, and that angiotensin II (Ang II) has major pro-inflammatory activity inducing the expression of multiples factors such as reactive oxygen species (ROS) [21]. It is interesting to note that Hsp70 relates to the regulation of the Ang II-induced NF-κB [22]. Previously, Ishizaka *et al*. demonstrated that Ang II infusion induces renal Hsp70 [23]. Later, lower oxidative stress in response to the Hsp70 expression is involved in the renal fibrosis protection by Losartan [24]. Furthermore, it is believed that Hsp70 in proximal tubule membranes would exert cellular protection by modulation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase subunits Nox4 [25]. Activation of NADPH oxidase is a fundamental step in the pro-inflammatory mechanism [26]. NADPH oxidase activity was reverted in mitochondrial fractions from vitamin D inducer-treated animals [27]. Indeed, vitamin D receptor-modulated Hsp70/Angiotensin II receptor, type 1 (AT_1) expression, may protect the kidneys of spontaneously hypertensive rats (SHR) at the structural and functional levels. Here, we propose that low AT_1 expression through vitamin D receptor induction could be a consequence of the HSR Hsp70-mediated cell protection [28] (Fig. **1**).

HEAT SHOCK RESPONSE IN RENAL INFLAMMATION

Cellular damage by environmental stresses have been ancestrally combated by processes such as HSR. More specifically, the heat shock proteins (HSP) are a group of cellular modulators activated by various factors, most notably by the heat shock [1]. The expression of the HSP is a key part of the HSR and is induced predominantly by heat shock factor (HSF) [2]. Specifically, the factor of heat shock-1 (Hsf1) is the central regulator of the HSR, and regulates a number of cytokines [29]. Besides, typical proinflammatory agonists modify the heat shock-induced transcriptional program and expression of HSP genes resulting exposure to heat shock, suggesting a complex reciprocal regulation between the inflammatory pathway and the HSR pathway [4]. In agreement Hsp70 has anti-inflammatory potential [5]. Thus, Hsp70 is released from cells particularly related to the inflammatory and immune responses [6]. Additionally Hsp70, one of the most promiscuous molecular chaperones, helps to maintain protein folding to favor cellular functions [7]. They also participates in maintaining protein homeostasis [8].

The protein folding regulated by Hsp70 is ATP/ADP dependent. The relatively stable complex consisting of ADP, Hsp70 and nonnative polypeptides prevents the incorrect interaction between protein domains. For the folding process to advance there has to be an interchange ADP/ATP, resulting in a complex that releases the substrate [30-32]. Cofactors (Hsp40, Hip, BAG) modulate the substrate polypeptides and Hsp70 interaction. These cofactors would regulate as well the ADP/ATP exchange or ATP hydrolysis [33] (Fig. **1**).

HSP70 EXPRESSION AND LOCALIZATION IN THE KIDNEY

The main representative chaperone of the Hsp70 family, constitutively expressed, is Hsp73 (70-kDa heat shock cognate protein). Hsp73 have been detected on cells along the whole kidney. With the exception of a few cell group, the immunoreactivity for Hsp73 is similar in the nucleus and cytoplasm. The involvement in protein folding of the unstressed cells, can be the cause for this ubiquitous presence of Hsp73 [34]. There is a steep increase of Hsp72 expression, the principal inducible member of the Hsp70 family, in the normal kidney. Hence, Hsp72 was only identified in the renal cortex. All tubules were stained weakly in the outer medulla, while it was noted an intense staining of the papilla collecting ducts and in the epithelium lining the papilla [34]. A hypothesis has emerged because of the renal Hsp72 expression, where Hps72 could participate in the modulation of extracellular tonicity.

HSP70 LINK TO INFLAMMATORY RENAL DISEASES

To highlight recent scientific research suggests that Hsp70 and their receptors protect against inflammation through multiple mechanisms [9, 10]. The immune response gets help to trigger off by Hsp70, an immunodominant molecule and its constitutive peptides that likewise play a role in autoimmunity [35]. Hsp70 gene polymorphic variants have been studied in hypertension [36]. In kidney and T lymphocytes, a higher Hsp70 expression was harvested from several models of salt-induced hypertension in experimental models of hypertension, developing a proliferative reaction when challenged with Hsp. So, there could be an involvement of Hsp70 in the development of autoimmune reactivity in the kidney and by that, impairing physiological mechanisms of sodium excretion that accompanies salt-sensitive hypertension [11]. Moreover, Hsp70 diminishes inflammation, renal infiltration and consequent AKI [13]. Several urinary biomarkers including neutrophil gelatinase-associated lipocalin (NGAL), N-acetyl-β-D-glucosaminidase (NAG) [37], Interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), liver fatty-acid-binding protein (L-FABP), and cystatin-C, have shown an ability to predict AKI days before an elevation in serum creatinine [38]. It is interesting to note that Hsp70 decreases apoptosis in AKI *via* regulation of the c-Jun N-terminal kinase phosphorylation [39]. Likewise, factors such as CD4+ CD25+ Foxp3 + regulatory T cells in

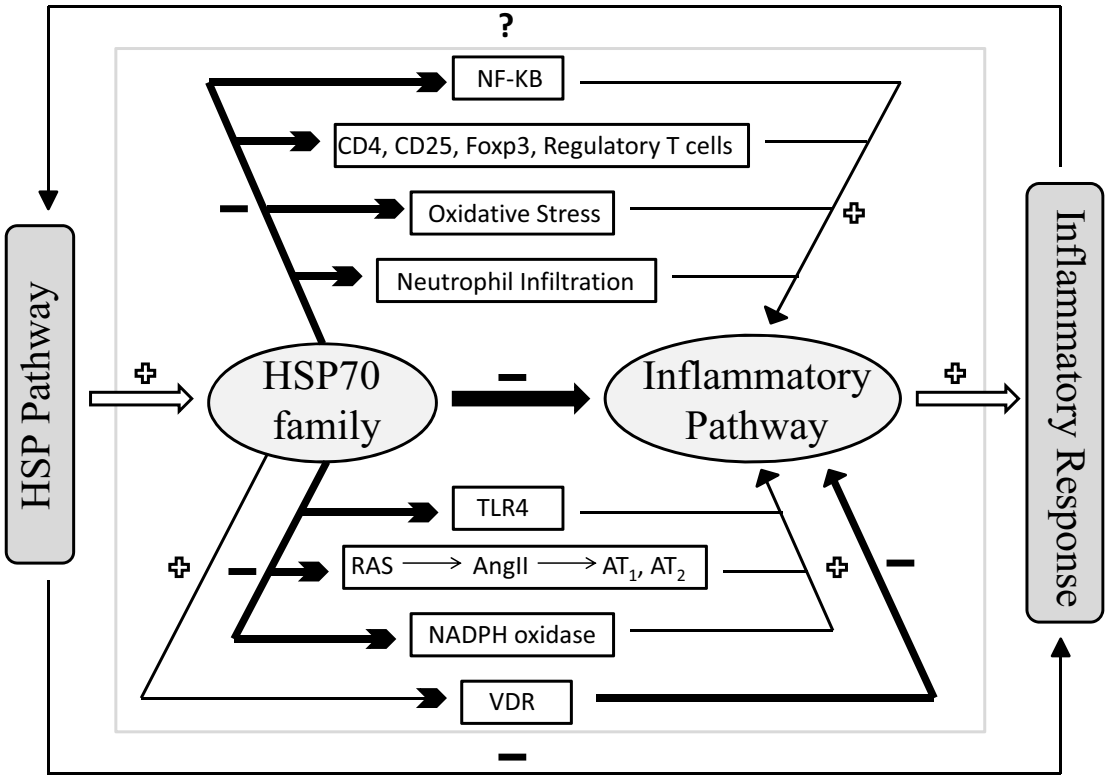

Fig. (1). Hsp70 family in the renal inflammatory response. A representative overview of the potential interaction between Hsp70 family and inflammatory pathway in the renal cells: target of regulation of Hsp70 to control inflammatory responses.

AKI, partially mediate the Hsp70-induced renoprotective effect [14]. Before serum creatinine elevation urinary Hsp70 increases significantly in patients with clinical AKI. Therefore, urinary Hsp70 would a biomarker for evaluation of AKI. Hence, urinary Hsp70 levels are sensitive enough to monitor therapeutic interventions and the degree of cellular recovery [40].

On the other hand, the pharmacological induction of HSP expression is an emerging pre-conditioning strategy aimed at reducing ischemia-reperfusion injury (IRI) following renal transplantation. Heat shock protein 90 (Hsp90) inhibition up-regulates protective HSP (especially Hsp70) and potentially down-regulates NF-κB by disruption of the IκB kinase (IKK) complex. TLR4 is a further regulator of NF-κB and recent studies suggest that TLR4 is determinant in mediating kidney damage following IRI [15]. Also, inflammatory events cause renal lesions during diabetic nephropathy. TLRs regulate these events [16], but their complete role is actually not well understood [17]. However, decreased expression of renal Hsp70 may contribute to activate the TLR4-initiating inflammatory signal pathway [18]. TLRs have been studied since the late 90s, becoming more evidence about his relationship with the renal inflammatory disease [19]. TLRs are expressed in various cell types, including renal cells where they contribute to inflammatory response [20].

Hsp70 acts as a ligand for TLR4, and together they could participate regulating innate immunity. Of particular interest to our knowledge, a lower expression of Hsp70 is correlated with several kidney diseases [41].

The cytokine function of Hsp70 are also evaluated in some studies, and discusses its interaction with TLR4/CD14 complexes as well as to TLR2 [42]. Thus, tumor cells that express higher Hsp70 are killed by natural-killer (NK) [43-45]. The aforementioned studies provide a solid evidence of immune system activation by Hsp70 [46].

Finally, changes in Hsp70 expression occur in the kidney under pathophysiologic conditions, understanding the role of Hsp70 in the immune/inflammatory response may aid in understanding the response of the organism (Fig. **1**).

HSP70/ANGIOTENSIN II INTERACTIONS IN THE INFLAMMATORY RENAL DISEASE

Experimental and clinical evidence indicate that the activation of the RAS predisposes to cardiovascular and renal diseases, and that Ang II has major pro-inflammatory activity inducing the expression of multiples factors such as ROS [21]. Interestingly, Hsp70 is involved in the regulation of Ang II-induced NF-κB. In agreement, HSP were related with the pro-inflammatory transcription factor NF-κB [22]. NF-κB modulates several genes that participate in the inflammation during kidney injury [47]. More specifically, experimental data suggest that Angiotensin II receptor, type 2 (AT_2) through activation of NF-κB, participates in the recruitment of renal inflammatory cells [48].

Previously, Ishizaka *et al*. demonstrated that Ang II infusion induces renal Hsp70 [23]. Subsequently, reduced oxidative stress in response to the expression of Hsp70 was involved in the preservation of renal fibrosis by losartan, an angiotensin receptor of angiotensin II [24]. Moreover, it is

believed that Hsp70 in proximal tubule membranes would exert cellular protection by modulation of NADPH oxidase subunits Nox4 [25]. Activation of the NADPH oxidase is a fundamental step in the pro-inflammatory mechanism [26]. The NADPH oxidase family of enzymes has a major role catalyzing the production of superoxides and other ROS. In turn, they play an important role for cellular signal transduction, however, an excess may cause oxidative stress, currently known as a major cause of renal inflammation and subsequent damage [49]. The proinflammatory state that culminates in the cellular oxidative, would be amplified by changes in renal antioxidants and ROS levels [50]. In this context, both the oxidative stress and the induction of the mitochondrial apoptosis, could be prevented by Hsp70 expression [51]. Also, NADPH oxidase activity was reverted in mitochondrial fractions from vitamin D inducer-treated animals [27]. Even more, vitamin D receptor (VDR)-modulated Hsp70/AT_1 expression may protect the kidneys of SHR at the structural and functional levels. Here, we propose that low AT_1 expression through VDR induction could be a consequence of the HSR Hsp70-mediated cell protection [28]. Previously, vitamin D treatment increased Hsp70 expression which was localized to renal tubular cells in the outer medulla [52]. Moreover, Hsp70 plays a role in controlling concentrations of the VDR within the cell [53]. Adams *et al*. [54] suggested that Hsp70-related intracellular vitamin D-binding proteins act as regulators of vitamin D metabolism. Hsp70 may interact with VDR prior to the activation of the latter by vitamin D [55]. In addition, Hsp70/caveolin-1 interaction has been shown to protect against Ang II-induced hypertension and exert a cytoprotective effect by downregulating NADPH [25]. In fact, caveolin 1 (a 21-kDa cytoskeletal protein) is required for normal renal AT_1 expression [56]. An interesting avenue of future research would be an assessment of the degree of interaction between the Hsp70, caveolin 1, and AT_1 proteins associated with VDR expression in SHR. In conclusion, a relationship between inflammation, RAS and vitamin D deficiency is proposed. There seems to be a predisposition to left ventricular hypertrophy, hypertension, heart failure, chronic vascular inflammation, and metabolic syndrome because of vitamin D insufficiency [57]. The pathogenesis of these diseases have been linked to inadequate stimulation of the RAS. An interesting link between VDR and RAS is possible since it is known that VDR and RAS receptors are distributed almost in the same tissues. Finally, both systems were developed simultaneously and participate in the complex inflammatory mechanisms [57].

Collectively, current data provide evidence that Hsp70 family affords protection *via* modulation of the inflammatory pathway in the inflammatory response. Further clarification of the protective mechanism of HSP could facilitate new treatment of inflammatory renal disease (Fig. **1**).

ABBREVIATIONS

ADP = Adenosine diphosphate

AKI = Acute kidney injury

Ang II = Angiotensin II

AT_1 = Angiotensin II receptor, type 1

AT_2 = Angiotensin II receptor, type 2

ATP = Adenosine triphosphate

ATPase = Adenosine triphosphatase

BAG = Anti-apoptotic protein 1

CD14 = Helper T-cell (cluster of differentiation 14)

CD25 = Helper T-cell (cluster of differentiation 25)

CD4 = Helper T-cell (cluster of differentiation 4)

Foxp3 = Forkhead box P3

Hip = Hsp70-interacting protein

HSF = Heat shock factor

Hsf1 = Heat shock factor-1

HSP = Heat shock proteins

Hsp40 = Heat shock protein 40

Hsp70 = Heat shock protein 70

Hsp72 = 70-kDa heat shock cognate protein (72-kDa)

Hsp73 = 70-kDa heat shock cognate protein (73-kDa)

Hsp90 = Heat shock protein 90

IKK = IκB kinase

IL-18 = Interleukin-18

IRI = Ischemia-reperfusion injury

IκB = Inhibitor of kappa B protein

KIM-1 = Kidney injury molecule-1

L-FABP = Liver fatty-acid-binding protein

NADPH = Nicotinamide adenine dinucleotide phosphate oxidase

NAG = N-acetyl-β-D-glucosaminidase

NF-κB = Nuclear factor kappa-light-chain-enhancer of activated B cells

NGAL = Neutrophil gelatinase-associated lipocalin

NK = Natural-killer

Nox4 = Nicotinamide adenine dinucleotide phosphate oxidase subunits 4

RAS = Renin-angiotensin system

ROS = Reactive oxygen species

SHR = Spontaneously hypertensive rats

TLR2 = Toll-like receptor 2

TLR4 = Toll-like receptor 4

TLRs = Toll-like receptors

VDR = Vitamin D receptor

CONFLICT OF INTEREST

No conflicts of interest, financial or otherwise, are declared by the author.

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