Heat Shock Proteins

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The heat shock proteins (HSPs), are a family of proteins that have been linked to different cellular functions, being activated under conditions of cellular stress, not only imposed by thermal variation but also toxins, radiation, infectious agents, hypoxia, etc. Regarding pathological situations as seen in cardiorenal syndrome (CRS), HSPs have been shown to be important mediators involved in the control of gene transcription and intracellular signaling, in addition to be an important connector with the immune system. Thus, HSPs have been targeted by researchers as important connectors between kidney and heart.

heat shock proteins   renal diseases   cardiac diseases   immune system

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1. Heat Shock Proteins: Definition and Function

Heat shock proteins (HSPs) are a family of proteins produced by both unicellular and pluricellular organisms in response to different categories of stress conditions and were initially described by Ferruccio Ritossa in the early 1960s in *Drosophila melanogaster* [1][2]. However, it was not until the 1980s that these proteins were studied in depth by William Currie in heart tissue [3][4][5].

HSPs are stress proteins that possess molecular sizes ranging from 10 to 150 kDa, and they are found in all principal cellular compartments. These proteins were first discovered as cell protectors that function after exposure to high temperatures [6]. Researchers subsequently observed that HSPs also act as molecular chaperones that play critical roles in protein folding, intracellular protein trafficking, and the response to unfolded and denatured proteins resulting from heat and other stressors. Therefore, the study of HSPs has undergone explosive growth; however, their role in the context of cardiorenal syndrome (CRS) remains largely unexplored.

HSPs are proteins that are strongly conserved throughout the evolution of eukaryotes, and they protect organisms against injurious stimuli [7]. Normal levels of HSPs are required for the natural mechanism of protein folding, the maintenance of transduction signals, and development [8]. During pathological conditions, HSPs have been reported to respond to injuries caused by temperature, toxins, hypoxia, infectious agents, nitric oxide (NO), radiation, and other stressors. During these stimuli, HSPs are highly expressed [7].

In general, HSPs regulate the formation and trafficking of the protein complex, the refolding of mitochondrial and denatured proteins, the prevention and/or inhibition of protein unfolding and aggregation, and apoptosis [9]. In their anti-apoptotic role, these proteins regulate the activity of caspases, the c-Jun N-terminal kinase (JNK) pathway,

and the nuclear factor kappa B (NF-kB) pathway [10]. In their anti-inflammatory role, HSPs suppress NF-kB, decrease pro-inflammatory cytokine levels, and/or stimulate damage-associated molecular patterns (DAMPs) in a manner that exacerbates them [10].

HSP families have been characterized according to their molecular weight. The most studied of these families are small HSPs (sHSPs), HSP60, HSP70, and HSP90. They can also be classified as stress-induced (when they are rapidly and highly expressed in response to stress) and those that function independent of stress (when they are constitutively expressed in cells) [11]. To perform their functions, HSP families possess singular structural domains and features.

As described above, HSPs can play double roles during pathological situations and can act as chaperones and anti-apoptotic modulators in response to pro-inflammatory and pro-oxidative stress. It has been demonstrated that intracellular and extracellular HSPs possess distinct functions during injury [12]. While the extracellular HSPs are described as agonists for TLRs and DAMPS, intracellular HSPs appear to decrease inflammation and inhibit the release of reactive oxygen species (ROS) [7]. After several years of studies focused on deciphering the active mechanisms underlying this paradox, Demeester et al. revealed that when the HSP causes inflammation, cytoprotection is being promoted, and when inflammation activates the HSP, cell death is promoted [13]. Twenty years after the proposal of this paradox, only a small number of studies have attempted to further elucidate it. The majority of the current explanations for this paradox involve the participation of NF-кB and how this nuclear factor behaves during pathological conditions [7].

Cardiorenal involvement of HSPs as its own subspecialty remains at a very early stage. In the literature, the implications of HSPs in heart and kidney pathologies have previously been separately characterized, thus reinforcing the dual role of intra-and extracellular HSPs in the emergence and aggravation of these diseases (**Table 1**).

Table 1. Correlation between different types of CRS and HSP-mediated cardiovascular diseases.

Classification	CRS Types	Pathologies	HSPs
Cardio-renal	1	Decompensated heart failure, congestion, acute coronary injury, acute kidney injury	HSP70
	2	Chronic heart failure, coronary heart disease, chronic kidney disease	HSP60 HSP90

Classification	CRS Types	Pathologies	HSPs
Reno-cardiac	3	Renal ischemia, acute renal failure, arrhythmia, acute heart failure, myocardial infarction, atrial fibrillation, cardiac hypertrophy	HSP27 HSP60 HSP90
	4	Chronic kidney disease, uremic toxins accumulation, diastolic dysfunction, myocardial remodeling	HSP70 HSP72 HSP90
Systemic	5	Sepsis, cirrhosis, diabetes	HSP60 HSP90

...tress was also able to induce higher "SP71" synthesis [14]. Furthermore, the expression of HSPs is enhanced not only by metabolic insults [15] but also by other types of stress such as ischemia at the heart level [16]. Thus, as Dillmann et al. observed in the ischemic area of dog hearts after occlusion of the left anterior descending coronary artery [17], Currie in perfused rat hearts demonstrated that HSP70 acts as an indicator of cellular stress, thus indicating that not only ischemia but also perfusion at supra-optimal temperature increases the synthesis of this protein as a typical heat-shock response [5]. In the heart, HSP70 prevents disease and protects cardiomyocytes from stress [18]. The expression of HSP70 is elevated in myocardial tissues following cardiac surgery, general surgery, or ischemia [19]. Studies have reported a diminished incidence of postoperative atrial fibrillation (AF) in patients with high levels of intracellular HSP70, and these findings are contrary to those in patients with low HSP70 who exhibit an increased risk of postoperative AF [20][21][22].

The kidneys and heart are essential organs that are required for proper functioning of the body. The function of the heart is associated with pumping blood throughout the body, while the kidneys clean the blood, remove toxins and excess metabolites, and control blood pressure. Although these appear to be easy assignments, they demand delicate and accurate processes that are dependent upon each other. Since the 1830s, the connection between the heart and kidneys has been studied. The first study examining this connection was published in 1836 by Robert Bright after he observed the prevalence of cardiovascular diseases (CVD) in patients with renal disease that were accompanied by the secretion of urinary albumin [23].

After this initial observation, studies examining the connection between the heart and kidneys revealed a specific disorder termed cardiorenal syndrome (CRS). In 2008, the Acute Dialysis Quality Initiative defined the newest description and classifications of CRS that included two major CRS groups (cardiorenal and reno-cardiac) based on the initial pathology. These are further sub-grouped into five types of CRS [24]. Based on this, CRS is defined by meaningful heart–kidney connections that divide similarities in pathophysiology, where an injury in one of the organs leads to an injury in the other.

The study of CRS is of paramount importance to develop effective clinical treatments, as heart problems represent the largest cause of death in the world at approximately 15 million deaths per year [25]. According to the World Health Organization (WHO), approximately 43% of deaths caused by CVD were in patients who exhibited some level of kidney failure, thus clinically evidencing the link between the heart and kidneys. The inflammatory process covers all CRS types as a type of starting point. Cytokine release appears to be the primary cardiorenal connector, as cytokines can interact directly with heart tissue. It is established that blood tumor necrosis factor-alpha (TNF-α), interleukin (IL-) 1, and IL-6 are all increased during CRS [26][27]. This inflammatory process can be initiated or maintained by HSPs, the essential proteins involved in the control of gene transcription and intracellular signaling in addition to acting as important modulator of the immune system [6].

HSP90 proteins critically involved in the modulation of several cell signaling pathways; however, the expression and even the functions of HSP90 may be altered under pathological conditions [28]. Indeed, HSP90 expression is affected by indoxyl sulfate, a uremic toxin that accumulates in the body during CKD progression. Milanesi et al. demonstrated that indoxyl sulfate induces HSP90 expression in kidney fibroblasts (NRK-49F cells) [29]. However, in these cells selective HSP90 inhibition reverses the inductive effect of indoxyl sulfate on monocyte chemoattractant protein-1 (MCP-1), α-smooth muscle actin, collagen I, and transforming growth factor-β (TGF-β) expression, thus indicating that HSP90 contributes to kidney inflammation and fibrosis at the cellular level [30]. In vivo, the authors also observed an increase in HSP90 expression in the kidneys of mice treated with indoxyl sulfate [29]. Furthermore, clinical studies have demonstrated that the HSP90α isoform is present at elevated serum levels in pediatric patients with CKD compared to levels in the control group [31].

According to another study, serum levels of HSP60 were associated with the risk of death and readmission in patients with acute heart failure [32]. In an experimental model, it was demonstrated that extracellular HSP60 induces apoptosis in cardiac myocytes via TLR4 [33]. A previous study from our group observed the involvement of HSP60 in cardiomyocyte hypertrophy and its association with inflammation and TLR4 activation. In this study, primary culture of cardiomyocytes treated with HSP60 showed hypertrophy, increase on complement system components, C3 and factor B as well as an increase in IL-6 and TNF-α expression [34].

It is also established that cardiac myocytes can release HSP60 in exosomes; however, the role of HSP60 in intercellular communication through extracellular vesicles remains unclear [35]. Additionally, studies have demonstrated that atherosclerotic lesions exhibit increased HSP60 expression [36]. HSP60 can also regulate

important cellular mechanisms such as VSMC migration and proliferation that could contribute to atherosclerosis and endothelial damage [37].

Despite its importance in the cardiovascular system, few studies have investigated the role of HSP60 in kidney diseases. Fang et al. demonstrated that HSP60 is a target of miR-382 that reduces its expression in renal cells and contributes, at least in part, to renal tubulointerstitial fibrosis that is related to CKD progression [38]. In diabetic nephropathy, HSP60 may also be involved in renal tubular cell dysfunction [39][40].

In general, the TLR2/4 pathway is the one that interacts with both organs and innate immune system. This conversation between heart–kidneys axis and HSPs depends on different molecular mechanisms of action. In general, HSP27, 60 or 70 couple to TLRs activating IKKγ or MAPK/p38 pathways. In the nucleus, NF-kB is responsible for the inflammatory gene expression while p38 activates the apoptotic genes [41][42]. This inflammatory response is observed in many cardiac injuries and kidney diseases, in addition of CRS itself [27]. Not only can this inflammation be induced by HSPs in CRS, but also the fibrosis observed during the syndrome [18][43]. The interaction of HSP90 with the receptor of TGF-β has been described to stimulate fibrosis by SMAD2/3 in renal tissue and can also promote fibroses in heart [44]. Last, but no less important, stress factors (free radicals, hypoxia, environmental factors, etc.) caused by CRS can directly induce an increase on HSPs expression by HSF1 phosphorylation. The activation of HSF1 has already been studied to cause cardiac dysfunction [45] and cause more apoptosis during renal injury [46].

Therefore, the cardiovascular and renal systems are strongly linked and present a complex relationship in which HSPs may be relevant in the pathological processes that affect these two systems. However, our knowledge regarding the role of HSPs in CRS is incomplete, and further studies are required. Based on the complexity of the relationship between cardiovascular and renal diseases, understanding the pathophysiological mechanisms involved in this process, including the possible role of HSPs, may be relevant for the development of new therapeutic strategies for CRS.

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