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Involvement of Stress Proteins in Renal Diseases

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Abstract

Heat shock proteins (HSPs) are a distinctive class of proteins that have evolved to cope with stress to provide cellular defence against a wide range of cell injuries. HSPs play an important role in the assembly and folding of intracellular polypeptides, and help in restoring the biological activities of abnormal proteins. Cellular stress responses include a transient rearrangement of functional activities, in order to protect and maintain essential cellular functions, possibly by inducing HSPs. HSPs help in restoring protein homeostasis and assist in cellular recovery from stress, either by repairing damaged proteins through refolding or by degrading them. Recent studies have documented the important roles of stress proteins in renal cell survival and matrix remodeling in a number of acute and chronic renal diseases. This brief review summarizes some of the important aspects of HSPs and their relevance to various renal diseases.

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Introduction

The heat shock response, first observed by Ritossa in *Drosophila* in 1962 [1], is now widely accepted as one of the universally conserved cellular defence systems. In early 1970s, the heat shock response was found to coincide with synthesis of a number of new proteins [2]. The genes and protein products quickly gained much attention and a number of heat shock proteins (HSPs) have since been identified and characterized. Subsequent research work found that in addition to heat stress, a wide range of other stressful conditions could induce the heat shock responses. The heat shock response is mediated by a

group of HSPs, a response that has been observed both in eukaryotic and prokaryotic cells. Some HSPs are strictly stress induced, whereas others could be constitutively expressed, developmentally regulated or induced by stress. In addition to heat shock, a variety of other stresses, including metabolic, toxic, and oxidative injuries can elicit similar stress responses. The primary structure of the stress proteins is highly conserved [3, 4], and the expression of HSP is not always limited to cells undergoing acute stress; a number of HSPs are constitutively expressed and actively involved in maintaining cellular homeostasis, by acting as molecular chaperones [5–7]. The HSPs regulate folding and assembly of nascent and unfolded peptides, help in transporting proteins to a particular subcellular compartment and assist in the degradation of misfolded proteins [8]. As molecular chaperones, HSPs do not only assist in the folding of nascent polypeptide chains but also help in preventing aggregation of surface-exposed hydrophobic portions of proteins, and ultimately enhance their folding. Certain HSPs exert anti-inflammatory effects by modulating the transcriptional activation of proinflammatory cytokines and adhesion molecules [9], while others including HSP-60 and -70 can induce proinflammatory cytokines, including interleukin (IL)-1 β , IL-6, IL-12, IL-15 and tumor necrosis factor- α from human monocytes [10]. Several HSPs are involved in antigen presentation, steroid receptor function, nuclear receptor binding, and apoptosis [11, 12]. HSPs also exert important roles in signal transduction by maintaining and stabilizing intracellular microenvironments.

Regulation of HSPs

The stress responses in mammalian cells are thought to be transcriptionally regulated by the heat shock transcription factor (HSF), which specifically binds to the heat shock promoter element (HSE) that contains palindromic sequences rich in repetitive purine and pyrimidine motifs [13]. The HSF family consists of four members (HSF1, HSF2, HSF3, and HSF4) in higher eukaryotes [14–18]. HSF is present in normal, unstressed cells as a monomer in the cytoplasm, but exposure of such cells to stress conditions results in conversion of HSF from an inactive monomeric form to an active trimeric DNA-binding form, which then translocates to the nucleus and interacts with HSE to induce transcription of HSP genes (fig. 1) [19, 20]. Oligomerization of the HSF and its interaction with the HSE are the hallmark of active transcriptional response to a variety of stresses that include physical and chemical stresses. All members of the HSF family share common structural features, including a conserved DNA-binding domain, an extended hydrophobic repeat involved in trimerization, and a transactivation domain [21, 22]. With the exception of those from

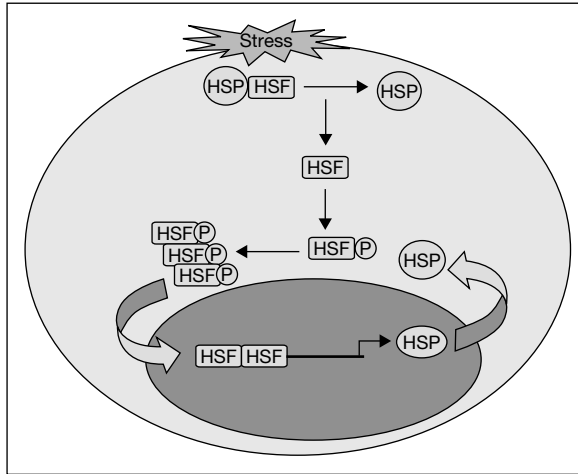


Fig. 1. Simplified schematic diagram showing the transcriptional regulation of heat shock proteins (HSPs). Heat shock transcription factor (HSF) is normally bound to HSPs and present as an inactive molecule in the cytosol. Upon exposure to stressors, HSFs are phosphorylated (P) by protein kinases, rapidly form trimers, and translocate to the nucleus where HSFs interact with heat shock promoter element (HSE) to induce the transcription of HSPs, which are then transcribed and relocated to the cytosol.

budding yeasts, HSFs also have a carboxyl-terminal hydrophobic repeat, which is thought to suppress trimer formation by interaction with the amino-terminal hydrophobic repeats [14, 23].

Most of our understanding of protein folding is based on *in vitro* studies, which needs careful interpretation for their relevance to the complex *in vivo* system, because the *in vitro* experimental solvents do not always mimic the *in vivo* complex microenvironments. One of the major differences is that most of the *in vitro* experiments deal with a single unfolded protein, which usually does not interact with other components, while in the *in vivo* situation, complex interactions among various proteins occur during protein folding. In the native *in vivo* microenvironment, chaperone-assisted folding of certain proteins is an essential phenomenon. Moreover, *in vitro* studies provide the opportunity to examine the properties of proteins, by chemical or physical denaturing, which may not always replicate the *in vivo* circumstances of protein folding.

Despite experimental limitations, both *in vivo* and *in vitro* studies have documented the important roles of HSPs in the pathogenesis of various diseases, ranging from autoimmune diseases (arthritis and diabetes) to tumors and renal diseases.

HSPs in Renal Diseases

In the accompanying chapters, the authors have elaborated on the important roles of several stress proteins in various renal pathophysiological conditions, ranging from hypoxic injury to renal fibrotic diseases and malignancies. These chapters provide comprehensive information on the involvement of HSPs in the pathophysiology of a wide range of renal injuries, including acute and chronic progressive renal diseases. Neuhofer and Beck [24] summarize the effects of osmotic stress on renal medullary cells, and how these cells adapt to high salt and urea-rich microenvironments, not only to survive, but also to achieve their organ-specific functions. It appears likely that the high expression of HSP70 in the hyperosmotic renal medulla is cytoprotective for medullary cells. Similarly, Bijian and Cybulsky [25], in their chapter, discuss the protective role of HSP27 in glomerular epithelial cells injury, and postulate that the manipulation of HSP27 expression could be potentially beneficial by modulating glomerular epithelial cell injury and subsequent proteinuria. In a separate chapter, Kelly [26] describes the diverse effects of various stress proteins in renal ischemia and reperfusion injury. HSP32, also known as heme oxygenase, oxidizes the heme portion of hemoglobin to bilirubin. The generated bilirubin regulates the NADPH concentration in the cell, and provides an antioxidant defence system to the cell. In another chapter, Akagi et al. [27] provide details on the cytoprotective roles of HSP32 and its function in acute renal failure. The relevance of HSPs in the pathomechanisms of renal cell carcinoma is outlined by Atkins et al. [28]; the differential expression of certain HSPs, including HSP27, HSP70 and HSP72 in renal cell carcinoma and in cell lines generated from renal tumors suggests the involvement of HSPs in tumor progression, possibly by regulating the rate of tumor cell proliferation and apoptosis.

The synthesis and post-translational modifications of collagens are rather complex processes and require the help of numerous enzymes and chaperones for correct conformation. HSP47, found in the endoplasmic reticulum of collagen-producing cells, helps in the correct formation of quaternary structure of collagen [29]. In many fibroproliferative diseases, the expression of HSP47 mostly parallels the extent of collagen accumulation [30–34]. In the accompanying chapter, we explain the fibrogenic role of HSP47 in chronic renal diseases, and discuss its potential as a target for the development of novel antifibrotic therapeutic agents [35]. Pockley and Muthana [36] discuss the potential role of HSPs during allograft rejection. Although direct relevance of HSPs in transplant rejection needs further studies, selective induction of HSPs during allograft rejection suggests their possible involvement in the complex process of rejection. There are still inconsistencies in human and experimental studies, which needed to be resolved. Furthermore, some of the HSPs might

exert dual effects in allograft rejection process, both as protective and aggravating factors. In view of the fact that some of the immunoinflammatory features of allograft rejection appear to be similar irrespective of the organ involved, our knowledge of transplant rejection, and exact role of HSPs in such complex process, in general, will enhance our understanding of transplant rejection responses involving kidney.

The balance between the activities of the pro- and antioxidant enzymes tightly regulates oxidative homeostasis, and this delicate balance seems to be disrupted in various renal diseases [37]. Since oxidative stress-induced renal injuries are involved in a wide range of acute and chronic renal diseases, we also included a chapter that briefly summarizes the involvement of oxidative stress in renal diseases [38].

Conclusion

Extensive research work in the last couple of years has significantly improved our understanding of the crucial roles of stress proteins in various acute and chronic renal diseases. It has been convincingly demonstrated that constitutively expressed HSPs, by acting as molecular chaperones, help in folding and conformation of nascent polypeptides through binding to their C-terminal domain, while inducible HSPs are mostly responsible for inhibiting denaturation and incorrect or abnormal aggregation of proteins following cell injury, and may have determinant effect on overall cell survival. However, the transcriptional and translational regulation of the involved stress proteins, and their signaling events in various renal diseases, need further studies to elucidate their molecular and cellular interactions, and most importantly to determine their exact role in various disease processes. The availability of such large-scale gene expression studies such as microarray and proteomics may yield useful information that will not only help in determining novel pathways but also help in focusing studies of relevant molecules. Such focused research studies will help in developing disease-specific therapeutic strategies for the treatment of various acute and chronic renal diseases.

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