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Themed Section: Immune Targets in Hypertension

REVIEW ARTICLE

The role of autoimmune reactivity induced by heat shock protein 70 in the pathogenesis of essential hypertension

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Autoimmunity is increasingly recognized as having a central role in essential hypertension. Heat shock proteins (HSPs) are immunodominant molecules with high interspecies homology and autoimmune reactivity directed against HSP70 may play a role in the pathogenesis of hypertension. Autoimmunity to HSP70 may result from molecular mimicry between human HSP and bacterial HSP or, alternatively, as a response to HSP70–peptide complexes generated during cellular stress and delivered to the major histocompatibility complex by antigen-presenting cells. HSP70 is increased in the circulation and kidney of hypertensive patients, and genetic polymorphisms of HSP70 are associated with essential hypertension. Depending on the route and conditions of administration, HSP70 may induce or suppress immune-related inflammation. Renal inflammation induced by immunity to HSP70 causes hypertension in laboratory animals, and administration of specific peptide sequences of HSP70 results in a protective anti-inflammatory response that prevents and corrects salt-induced hypertension. Potential therapeutic uses of HSP70 in essential hypertension deserve to be investigated.

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Abbreviations

APC, antigen-presenting cell; DAMPs, danger-associated molecular patterns; HSF, heat shock factor; HSP, heat shock protein; isoLGs, isolevuglandins; L-NAME, N^{ω}-nitro-L-arginine methyl ester; MHC I, major histocompatibility complex class I; MHC II, major histocompatibility complex class II; PRR, pattern recognition receptor; SHR, spontaneously hypertensive rat; Treg, regulatory T-cell; TLR, toll-like receptor

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Introduction

Hypertension (defined here as BP ≥ 140/90 mmHg) is the most important contributor to the global burden of disease and causes 9.4 million deaths each year (Lim *et al.*, 2010). Despite important advances in the knowledge and treatment of hypertensive cardiovascular disease, the vast majority of patients with hypertension do not have a recognized aetiology and are grouped as patients with 'essential' or 'primary' hypertension. A large body of experimental and clinical evidence has established that autoimmune reactivity plays a central role in essential hypertension and potential antigens are being actively investigated (Rodriguez-Iturbe *et al.*, 2017). In 2004, we (Rodriguez-Iturbe *et al.*, 2004) raised the possibility that **heat shock proteins (HSPs)** drive autoimmunity in this condition.

Renal overexpression of **HSP70** and high titres of anti-HSP antibodies have been found in hypertensive cardiovascular disease; however, a causal role of HSP70 in hypertension has not been conclusively established. The aim of this article is to review the observations that support the notion that HSP70 is not an innocent bystander but instead plays a pivotal role in the pathogenesis of high BP.

HSPs are intracellular proteins that respond to cellular stress and act as chaperones of other 'client' peptides to which they bind to prevent their irreversible aggregation and promote their correct folding, physiological assembly and intracellular trafficking. The HSPs interact in a complex network of ATP-independent and ATP-dependent chaperones that are primarily cytoprotective and are critically involved in the functional preservation of many regulatory pathways. Once their function is accomplished, the HSPs dissociate from their client proteins.

HSPs were initially discovered in the larvae of *Drosophila melanogaster* exposed to heat (Ritossa, 1962). They constitute 5–10% of the total protein content of the cells and increase markedly in response to physical, metabolic (reactive oxygen and nitrogen species), hypoxic, ischaemia–reperfusion and toxic damage and represent one of the best preserved defence mechanisms in prokaryotic and eukaryotic cells (Hendrick and Hartl, 1993). Overproduction of HSPs results from the interaction of phosphorylated trimmers of heat shock factors (HSFs) with the promoter region or heat shock element of the HSP gene. There are four HSFs of which HSF1 and HSF2 are the most widely expressed, and their activation (phosphorylation) is induced by members of the MAPK subfamilies (**ERK1**, **JNK** and **p38 protein kinase**). Under normal conditions, monomeric HSFs are sequestered in the cytoplasm in complexes with HSP40, HSP70, HSP90 and cytosolic chaperonin-containing **T-complex 1 ring protein** (TCP1), but when stress-induced denatured proteins increase in the cell they bind to the HSPs, the HSP–HSF complexes are dissociated, and the free HSFs are liberated, phosphorylated and translocated to the nucleus. The intracellular content of HSPs is adjusted to an appropriate amount by transcriptional and poststranscriptional regulatory mechanisms (Kregel, 2002; Gomez-Pastor *et al.*, 2017).

Increased and decreased circulating levels of HSPs have been found in a large number of disease and non-disease conditions (Qui *et al.*, 2015) and have been implicated in cancer, transplantation rejection, atherosclerosis, Alzheimer's disease, diabetes, arthritis, multiple sclerosis, asthma, neurodegeneration (Huntington's chorea and Parkinson's disease), cerebral and myocardial ischaemia, Mesoamerican (dehydration induced) nephropathy and immunity to infectious agents. Our own studies have focused on the role that autoimmune reactivity directed against HSP70 may be playing in the pathogenesis of hypertension.

HSP70 and immune reactivity

HSPs are classified by their molecular weight and grouped in families. HSP70 and other members of the HSPA (HSP70) family have an N-terminal ATPase domain and a C-terminal domain that binds hydrophobic regions in polypeptides. Repeated binding and dissociation is required for the refolding that takes place until hydrophobic regions in the polypeptide are no longer exposed. In addition to the chaperone function, HSPs, and specifically HSP70, are immunodominant molecules capable of stimulating as well as suppressing inflammation (van Eden *et al.*, 2012; Calderwood *et al.*, 2016).

Their ability to induce self-immune reactivity may be part of natural autoimmunity and also may be associated with pathological autoimmune conditions. Anti-HSP antibodies, particularly anti-**HSP60** and anti-HSP70, have been demonstrated in umbilical cord and remain at constant levels independently of infections (Menoret *et al.*, 2000), suggestive that these anti-HSP autoantibodies may have a role in the normal immune system. Disease-related HSP autoimmunity is considered by some to be a consequence of overriding the protection of natural immunity as a result of a phenotypical change in natural autoantibodies or caused by the increment in anti-HSP reactivity induced by genetic or environmental causes (van Eden *et al.*, 2005; Cohen, 2013).

The HSPs are intracellular proteins, but they are also present in extracellular locations relevant to their capacity to induce autoimmune responses. In fact, HSP70 and low titres of anti-HSP70 antibodies are found in the peripheral circulation in normal individuals (Pockley *et al.*, 1998; Srivastava *et al.*, 2016). The mechanisms that result in the extracellular translocation of HSP70 include not only cellular damage but also extrusion in exosomes and ectosomes (Lancaster and Febbraio, 2005; Calderwood, 2007), as well as an association with secretory lysosomes (Mambula and Calderwood, 2006) and possibly an interaction with lipids in cell membranes (Nickel and Seedorf, 2008).

The predisposition of HSPs to induce autoimmunity is critically associated with their interspecies homology. Molecular mimicry means there is potential for cross-immune reactivity between the HSPs in invading microorganisms and the corresponding HSP in the host and, thereby, the generation of unintentional autoimmune responses directed to human HSP. Epitopes of *Mycobacterium leprae* and *Mycobacterium tuberculosis* HSP70 are recognized by T-cell clones (van Eden *et al.*, 1988; Janson *et al.*, 1991) that are capable of inducing inflammatory diseases (Van Eden *et al.*, 1985). In addition to molecular mimicry, autoimmunity directed to HSP70 may also be the result of epitope spreading after immune reactivity is generated by novel HSP70–peptide epitopes produced during cellular injury.

Of importance, the T-cells that are reactive to fragments of HSPs, most notably HSP60 and HSP70, are capable of inducing a protective, anti-inflammatory regulatory T-cell (Treg) response. Experimental models of arthritis, type 1 diabetes, atherosclerosis and experimental allergic encephalitis have been shown to be protected by the administration of microbial HSPs (Wendling *et al.*, 2000; van Eden *et al.*, 2005).

HSP70 in adaptive immunity

Exogenous and membrane-bound antigens are presented by major histocompatibility complex class II (MHC II) molecules in antigen-presenting cells (APCs), in association with co-stimulatory signals to $CD4^+$ lymphocytes that are activated and generate a helper pro-inflammatory immune response. Endogenous and viral antigens are presented by MHC I to $CD8^+$ lymphocytes that generate a cytotoxic immune response. However, elution studies have also demonstrated that a number of antigenic peptides in MHC II molecules are proteins from the cytoplasm, membrane and nucleus and are, therefore, delivered to this location by cross-presentation pathways that include chaperone-mediated traffic. HSP70 has been found to protect cytoplasmic autoantigens from degradation and present them to MHC II molecules (Auger *et al.*, 1996; Zhou *et al.*, 2005). HSP70 is also a participant in chaperone-mediated autophagy (Deffit and Blum, 2015) and in the internalization of receptor–ligand complexes mediated by one of its client proteins: claritin (Stricher *et al.*, 2013).

In addition to playing a role in the traffic of endogenous antigens to the MHC I and MHC II molecules, HSPs may also chaperone client exogenous antigens and facilitate their cross-presentation to the MHC I in APCs. In this manner, HSPs may be instrumental in $CD8^+$-generated responses to exogenous antigens (Ichiyanagi *et al.*, 2010; Imai *et al.*, 2011; Murshid *et al.*, 2012). Therefore, HSPs are involved in the access of antigens to both MHC I and MHC II molecules in APCs and may be responsible for simultaneous activation of both $CD4^+$ and $CD8^+$ T-cells, a phenomenon known as dendritic cell 'licensing' (Smith *et al.*, 2004).

HSP70 in innate immunity

The activation of innate immunity is the initial, non-specific response to pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) that when interacting with pattern recognition receptors (PRRs) activate transcription factors and induces the production of proinflammatory cytokines. The best studied PRRs are the toll-like receptors (TLRs). HSP70 utilizes **TLR2** and **TLR4** to transduce its pro-inflammatory signal (Asea *et al.*, 2002). However, the direct interaction between HSPs and TLRs has yet to be conclusively proven, and it is likely that the activation of innate immune mechanisms by HSP70 may involve binding to scavenger receptors in endothelial cells that cooperate with TLRs in the downstream activation of the innate immune response (Gong *et al.*, 2009; Murshid *et al.*, 2016). HSP70 may act as a DAMP using TLR4-initiated pathways to stimulate innate immunity (Asea *et al.*, 2002; Calderwood *et al.*, 2012); however, many of the HSP70-induced responses suppress inflammation (van Eden *et al.*, 2012).

While there is compelling evidence for the participation of HSPs in autoimmune reactivity, some studies have demonstrated that endotoxin contamination of the HSP preparation plays a role in the cytokine generation that HSP70 induces in macrophages (Gao and Tsan, 2003) as well as in the activation of APCs (Bausinger *et al.*, 2002) and in the stimulation of antibody responses induced by peptide–HSP70 complexes (Marincek *et al.*, 2008). Therefore, under certain conditions, HSP70 may require collaboration with endotoxin for the responses it induces in the immune system.

HSP70 overexpression and hypertension

An increasingly recognized feature in hypertension is the presence of immune cell infiltration in the kidneys and arterial walls. While early studies suggested these inflammatory changes might be occurring secondary to hypertensive damage, recent studies suggest the inflammatory response is responsible for impairing the excretion of sodium by the kidney (impaired pressure natriuresis) and contributes to the impaired vasodilator response of small blood vessels (impaired endothelial vasodilatation). Inflammation in these target organs and hypertonicity of the sympathetic nervous system are key elements in the pathophysiology of hypertension. A large body of research during the last decade has established the pivotal role of innate and adaptive immunity in the generation of the inflammatory process that underpins the elevation of BP (Rodriguez-Iturbe *et al.*, 2017). The postulated role of HSP70 in the pathogenesis of essential hypertension rests on its potential to act as an autoantigen that triggers persistent inflammation in the kidney, vasculature and the CNS. While HSP70 blood levels are not significantly related to risk factors of cardiovascular disease (including hypertension) (Dhingra *et al.*, 2006), there is ample evidence that HSP70 is overproduced in hypertension. High BP induced by a variety of experimental methods results in levels of expression of the HSP70 gene in the aorta that are directly related to the changes in BP (Xu *et al.*, 1995) In experimental hypertension, increased HSP70 protein has been identified in adventitial areas of the arteries and in the kidney (Figure 1) and interestingly in the spontaneously hypertensive rat (SHR) the expression of HSP72 predates the development of hypertension (Bravo *et al.*, 2003; Rodriguez-Iturbe *et al.*, 2017). Patients with essential hypertension have increased levels of HSP70 and HSP70 mRNA in the peripheral circulation (Srivastava *et al.*, 2016), and their lymphocytes have an augmented expression of the HSP70 gene under heat stress (Kunes *et al.*, 1992).

The association of HSP70 with other potential antigens in hypertension

The identification of antigens that play a role in hypertensive cardiovascular disease is a subject of intense investigation. Independently of its self-antigenic potential, HSP70 plays a critical role in the complex immune response induced by other antigens. Firstly, the antigenic strength of peptides is increased by their binding to HSPs; this

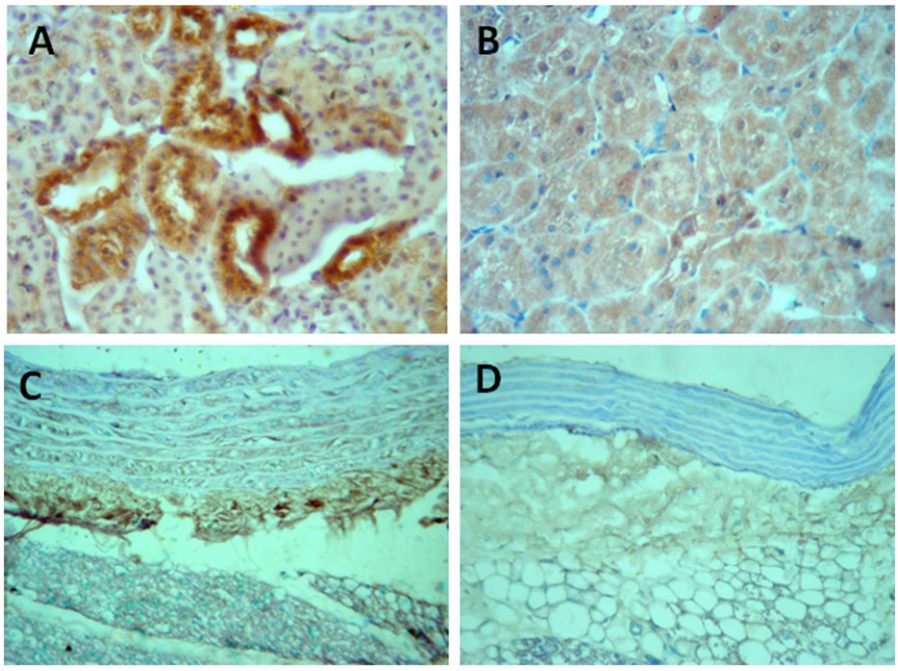

Figure 1

Immunoperoxidase staining for HSP70 in the kidney (A, B) and in adventitial areas of the aorta (C, D). Overexpression in the renal proximal tubules and in periaortic tissue and infiltrating cells of rats with hypertension induced by inhibition of NOS with L-NAME (A, C) contrasts with the negative staining in placebo-treated control normotensive rats (B, D) (original magnification ×400).

adjuvant characteristic is the basis of the administration of cancer-related peptides in association with HSP70 (Calderwood *et al.*, 2016). In addition, the activation of CD4 helper cells (Th1, Th2, T17 and Treg) and CD8 cytotoxic responses that are characteristic of hypertension (Trott *et al.*, 2014; Rodriguez-Iturbe *et al.*, 2017) suggests a correspondent relationship between extra- and intracellular antigenic peptides with HSPs (Binder, 2014).

Among the peptides of pathological relevance are the protein–protein and protein–DNA adducts formed by the binding of lysine residues to γ-ketoaldehydes (isolevuglandins and isoketals) generated *via* the isoprostane pathway of free radical-mediated lipid peroxidation (Salomon and Miller, 1985). Isolevuglandin (isoLG)–protein adducts were initially found in patients with atherosclerosis and end-stage kidney disease (Salomon *et al.*, 1997) and since then have been linked to a large number of disease conditions (Salomon and Bi, 2015) including hypertension (Kirabo *et al.*, 2014; Wu *et al.*, 2016; Dixon *et al.*, 2017). In hypertension, isoLG adducts formed in dendritic cells are presented in the context of MHC I to effector $CD8^+$ T-cells (Trott *et al.*, 2014). To our knowledge, there is at present no evidence of isoLG–protein adducts interacting with HSPs, but it appears likely that their intracellular traffic and delivery to MHC I is accomplished in association with HSPs. The reason for this assertion is that free antigenic peptides cannot be detected in cells unless they are released from chaperones by mild acid treatment (Menoret *et al.*, 1999), and disruption of the binding of peptides with HSP70, HSP60 and **HSP90** abolishes the presentation of peptides to MHC I (Binder *et al.*, 2001; Callahan *et al.*, 2008). Therefore, the evidence available indicates that peptides depend on the functional integrity of HSPs to gain access by canonical as well as by cross-presentation pathways to both MHC I and MHC II molecules in APCs. The role of HSP70 in intracellular antigenic trafficking is complemented by its participation in endocytosis, receptor-mediated binding and chaperone-mediated autophagy (Crotzer and Blum, 2008).

Pathogenic relevance of HSP70 in hypertension

While increased HSP70 is a feature of hypertension, the existence of a causal relationship needs to be established. It should be recognized that the participation of HSP in adverse biological events depends on the circumstances and timing of their overproduction. Immediate effects of HSPs in hypertension are protective, suppressing the activation of NF-κB and ameliorating the BP response to angiotensin II (Chen *et al.*, 2004). However, chronic HSP70 overexpression is likely to be pro-hypertensive because of its ability to induce autoimmune responses. The administration of exogenous HSP70 also induces different responses depending on the route of administration; for instance, delayed-type hypersensitivity results from administration of HSP70 in the footpads (Pons *et al.*, 2013), while administration of HSP70 by nasal or i.p. routes induces IL-10-mediated anti-inflammatory responses (Wendling *et al.*, 2000; van Eden *et al.*, 2005; Pons *et al.*, 2013).

Table 1

Studies suggesting the association of HSP70 with primary hypertension and high BP

Finding	Reference
HSP70 overexpression in hypertension	
Patients with essential hypertension have increased HSP70 levels and a sixfold increment in HSP70 mRNA in peripheral circulation that correlates with markers of systemic inflammation	Srivastava *et al.* (2016)
High BP induces genetic increments of HSP70 in aorta related to the changes in BP	Xu *et al.* (1995)
Lymphocytes of patients with essential hypertension have augmented HSP70 gene expression under heat stress	Kunes *et al.* (1992)
HSP70 is overexpressed in the kidney and aorta in the SHR. Expression of HSP72 predates the development of hypertension	Bravo *et al.* (2003) and Rodriguez-Iturbe *et al.* (2017)
Increased immune reactivity to HSP70 in experimental and human essential hypertension	
High titres of serum anti-HSP70 in the SHR and in patients with essential hypertension	Pockley *et al.* (2002), Rodriguez-Iturbe and Johnson (2010) and Chavez *et al.* (2006)
T lymphocytes of rats with salt-sensitive hypertension and of patients with essential hypertension proliferate strongly in response to specific peptide sequences of mycobacterial HSP70	Parra *et al.* (2008) and Pons *et al.* (2013)
Intrarenal genetic induction of HSP70 in rats immunized to HSP70 induces renal inflammation and salt-driven hypertension	Pons *et al.* (2013)
I.p. HSP70 administration induces an IL-10-driven T-cell response that prevents SSHTN. Adoptive transfer of T-cells from protected rats improves established salt-sensitive hypertension	Pons *et al.* (2013)
Genetic association of HSP70 and essential hypertension	
Increased incidence of hypertension in individuals with specific HSP70 haplotypes in a highly homogeneous ethnic minority	Li *et al.* (2009)
Single nucleotide polymorphisms in the HSP70 family group (HSP1A and HSP1B; SNP: rs805303 and locus; and BAT2–BAT5) associated with essential hypertension	International Consortium for Blood Pressure Genome-Wide Association Studies (2011)

Several observations suggest that immune responses activated by HSP70 in fact play a role in the long-term pathogenesis of hypertension. These observations are summarized in Table 1:

- Circulating HSP70, anti-HSP70 and HSP70 mRNA in essential hypertension. As noted earlier, the European Lacidipine Study on Atherosclerosis found high titres of anti-HSP70 antibodies in hypertensive individuals independently of age, smoking habits or blood lipids (Pockley *et al.*, 2002). Our own studies in selected patients with essential hypertension (Figure 2) and in the SHR (Rodriguez-Iturbe and Johnson, 2010) are concordant with these findings (Chavez *et al.*, 2006; Rodriguez-Iturbe and Johnson, 2010). Not only are the blood levels of HSP70 mRNA increased in essential hypertension but also they are directly correlated with the levels of TNF-α, IL-6 and C-reactive protein (CRP) (Srivastava *et al.*, 2016). These relationships are suggestive of an association between HSP70 overproduction and systemic inflammation.
- T-cell reactivity to HSP70 in human and experimental hypertension. T lymphocytes of rats with salt-sensitive hypertension induced by transient administration of angiotensin II and L-NAME develop a proliferative response when cultured with HSP70 derived from *M. tuberculosis*.

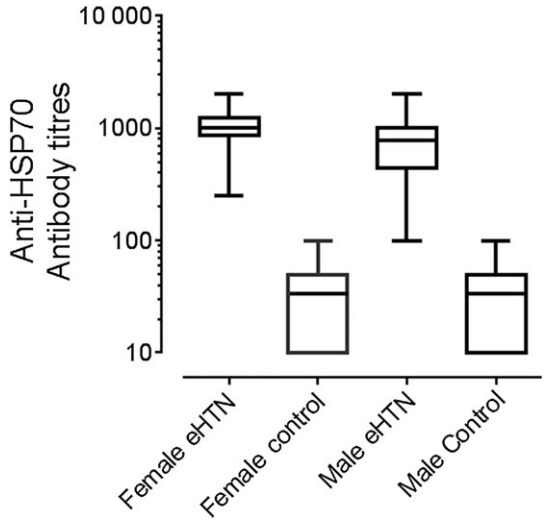

Figure 2

Plasma anti-HSP70 antibody titres in female (n = 15) and male (n = 15) patients with severe (≥160/110) essential hypertension (eHTN) and normotensive controls of both sexes (male n = 15; female n = 13). Differences between eHBP and controls, $P < 0.001$ (figure made with data from Chavez *et al.*, 2006).

More importantly, T lymphocytes of patients with essential hypertension also show reactivity to mycobacterial HSP70 (Parra *et al.*, 2008; Pons *et al.*, 2013) (Figure 3). These studies demonstrate immune recognition of specific epitopes of mycobacterial HSP70 in essential hypertension.

- HSP70 prevents and corrects hypertension in animal models. Specific amino-acid sequences of HSP70 derived

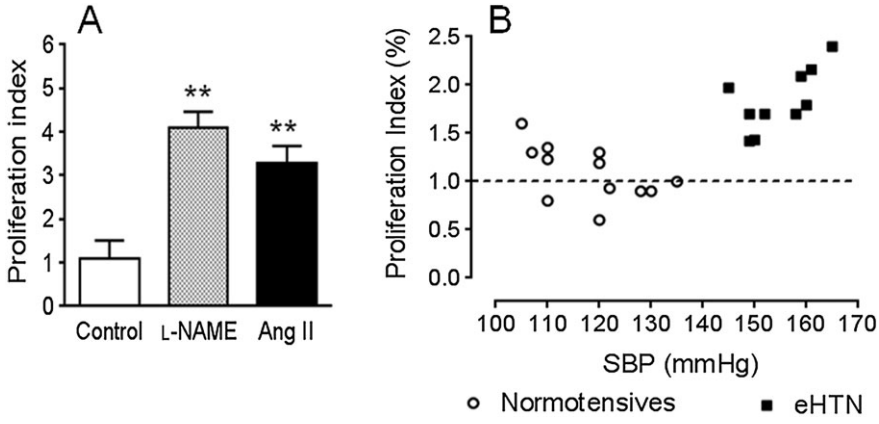

Figure 3

Proliferation of splenic T-cells from (A) rats with salt-sensitive hypertension induced by transient inhibition of NOS (L-NAME) or by transient administration of angiotensin II (Ang II), cultured for 72 h with recombinant rat HSP70. $^{**}P < 0.01$ versus control. (B) Proliferation index of peripheral blood T-cells of patients with essential hypertension (eHTN) and normotensive controls, incubated with a specific HSP70 peptide sequence (HSP70 AA 139–153 1A/1B). Difference in mean values of proliferation index in eHTN and normotensive controls, $P < 0.01$. In the patients with eHTN (B), a significant correlation exists ($P < 0.05$) between systolic BP (SBP) and proliferation index. Proliferation index = CPM of antigen-treated cells − background / CPM of untreated cells − background. Phytoheamagglutinin and ovalbumin used as positive and negative controls respectively (not shown). Figures made using data from Parra *et al.* (2008) and Pons *et al.* (2013).

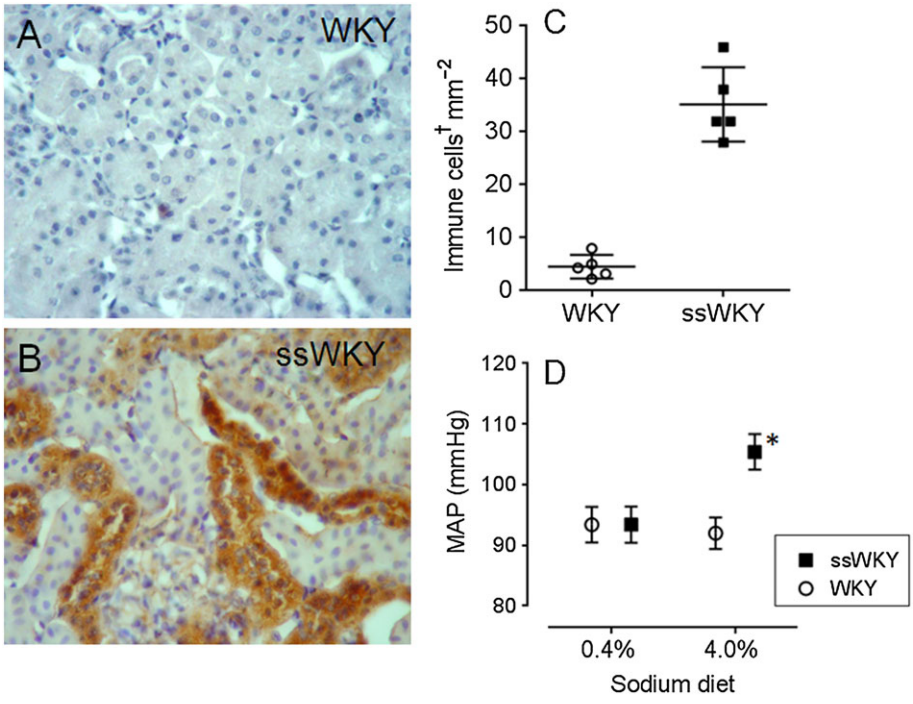

Figure 4

Induction of renal HSP70 expression in rats immunized with HSP70. Normotensive Wistar Kyoto (WKY) rats immunized with injections of HSP70 and adjuvant in foot pads (ssWKY) received HSP70 gene or empty plasmid in both renal veins. Renal sections of rats untreated (A) and 72 h after delivery of HSP70 gene (B), demonstrating HSP70-positive tubular areas. ssWKY rats developed immune cell infiltration ($P < 0.001$) in the kidneys after HSP70 gene delivery (C) and responded to a 4% sodium diet with an increase in BP ($^{*}P < 0.05$) (D). †Immune cells in (C) are the sum of CD5+ and CD68+ (lymnphocytes and macrophages) cells. Figures made using data from Pons *et al.* (2013).

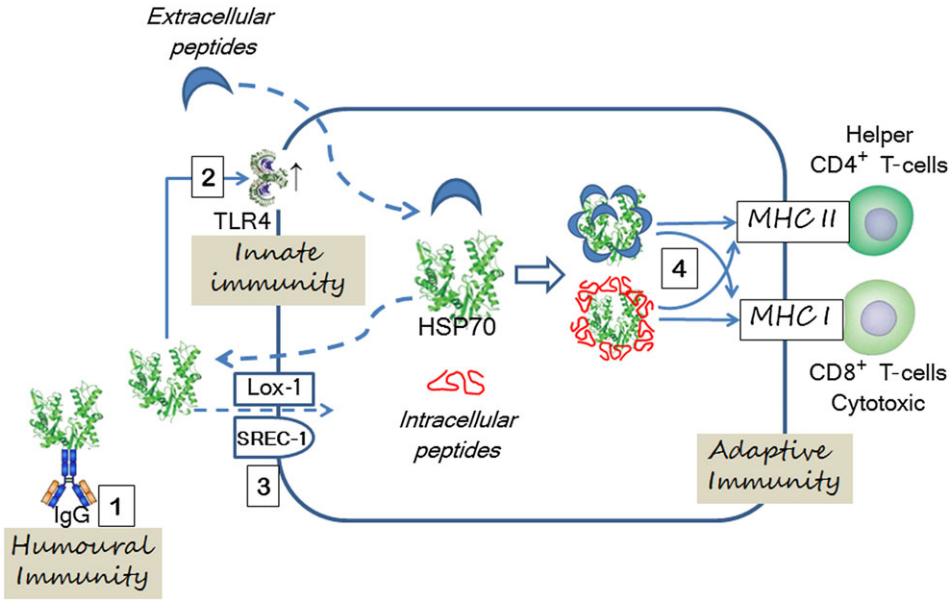

Figure 5

The role of HSP70 in essential hypertension depends on activation of adaptive autoimmune reactivity to itself or to the generation of neoantigens and, possibly, stimulation of innate immunity. Extracellular HSP70 induces the generation of anti-HSP antibodies (1) and overexpression of TLR2 and TLR4 (2). A direct interaction between HSPs and TLRs has not been demonstrated, and it is possible that stimulation of TLRs by HSPs is indirect. A lectin-type oxidized LDL receptor (Lox-1) and scavenger receptor associated with endothelial cells (SREC-1) mediate HSP70 endocytosis (3). Extracellular and intracellular peptides (isoketal–protein adducts and others) are associated with HSP70 that by repeated folding prevent their aggregation and support their traffic to MHC I and MHC II in APCs by both canonical and cross-presentation pathways (4) and augment their antigenic potential. Interrupted lines indicate transmembrane displacement.

from *Mycobacterium tuberculosis* are reactive with both human and rat T-cells (Wendling *et al.*, 2000). Intraperitoneal administration of one such peptide induced an IL10-driven anti-inflammatory response that suppressed the immune reactivity to HSP70 and prevented the development of experimental salt-dependent hypertension. Furthermore, the adoptive transfer of T-cells from rats that had been tolerized to HSP70 was found to improve established salt-sensitive hypertension (Pons *et al.*, 2013).

- Sensitization to HSP70 induces hypertension in normotensive naive rats. Experiments were also done to show that *de novo* sensitization of T-cells to HSP70 in the kidney could induce the development of salt-sensitive hypertension. Specifically, we found that immunization of rats with HSP70 followed by intrarenal induction of the HSP70 gene resulted in renal inflammation and an increase in BP in response to a high-salt diet (Pons *et al.*, 2013) (Figure 4).
- Genetic associations of HSP70 and essential hypertension. A fivefold increased risk of hypertension was found in association with specific haplotypes of HSP70 (haplotypes H5 and H8) in ethnic minorities in China (Li *et al.*, 2009). In addition, studies of the human genome have demonstrated an association between essential hypertension and single nucleotide polymorphisms in the HSP70 family (**HSPA1L**, HSPA1A and HSPB1) (International Consortium for Blood Pressure Genome-Wide Association Studies, 2011). To be noted, the expression of inducible HSPA1 and HSPB1 genes located within the MHC has been related to the generation of autoantibodies in systemic autoimmune disorders (Mišunová *et al.*, 2017).

Concluding remarks

Immune reactivity to and overexpression of HSP70 is a feature of experimental and human essential hypertension. Recent evidence suggests that HSP70 plays a role in the pathogenesis of hypertensive cardiovascular disease. HSP70 may facilitate the development of hypertension by being both a target for autoimmune responses, as well as its ability to enhance the antigenic potential of extracellular or intracellular peptides generated by cellular stress by permitting their traffic to the MHC I and II molecules in APCs (Figure 5). The therapeutic potential of anti-inflammatory Treg responses elicited by administration of HSP70 and HSP70-derived peptides to ameliorate established primary hypertension deserves to be investigated.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding *et al.*, 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander *et al.*, 2017a,b).

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Conflict of interest

B.R.-I. has no conflicts of interest. R.J.J. is on the Scientific Board of XORT Therapeutics and has patent and patent applications related to lowering uric acid or blocking fructose metabolism in the treatment of hypertension and metabolic disorders. Both R.J.J. and M.A.L. are members of Colorado Research Partners, LLC, that is developing inhibitors of fructose metabolism.

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