The Immunological Basis of Hypertension

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A large number of investigations have demonstrated the participation of the immune system in the pathogenesis of hypertension. Studies focusing on macrophages and Toll-like receptors have documented involvement of the innate immunity. The requirements of antigen presentation and co-stimulation, the critical importance of T cell–driven inflammation, and the demonstration, in specific conditions, of agonistic antibodies directed to angiotensin II type 1 receptors and adrenergic receptors support the role of acquired immunity. Experimental findings support the concept that the balance between T cell–induced inflammation and T cell suppressor responses is critical for the regulation of blood pressure levels. Expression of neoantigens in response to inflammation, as well as surfacing of intracellular immunogenic proteins, such as heat shock proteins, could be responsible for autoimmune reactivity in the kidney, arteries, and central nervous system. Persisting, low-grade inflammation in these target organs may lead to impaired pressure natriuresis, an increase in sympathetic activity, and vascular endothelial dysfunction that may be the cause of chronic elevation of blood pressure in essential hypertension.

Keywords: autoimmunity; blood pressure; hypertension; immunity; lymphocytes, macrophages.

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“Immunity maybe inborn or acquired. The former is always natural, that is to say, independent of direct intervention of human art. Acquired immunity (may be) spontaneous or maybe the result of human intervention.”

Immune reactivity in experimental and human hypertension has been reported in occasional investigations for more than half a century, but in most cases it has been considered epiphenomena associated with the increase in blood pressure. In early studies, the observation that most strongly suggested a pathogenic role for the immune system in hypertension was the demonstration that a functional thymus was a requirement for the maintenance of hypertension in various animal models. Renewed interest in the immune pathogenesis of hypertension has followed the findings that patients with essential hypertension have markers of systemic inflammation, the discovery of agonistic antibodies directed to angiotensin II and adrenergic receptors in specific conditions associated with high blood pressure, and the demonstration that the suppression of T cell–driven inflammation in target organs corrects, ameliorates or prevents experimental hypertension.

The innate immune system is responsible for the immediate inflammatory response recruited as a defense mechanism against infections or in response to tissue injury. Dendritic cells, macrophages, natural killer (NK) T cells, and Toll-like receptors (TLRs) of the inflammasomes represent components of the innate immune system that have been investigated in hypertension. Evidence for the participation of other components of innate immunity remains limited at the present time.

Dendritic cells

Dendritic cells are increased, infiltrating the kidney and arterial walls in hypertension models. Dendritic cells promote a differentiation of T cells toward a CD4+ IL-17 phenotype in response to aldosterone. In addition, they likely play a role as antigen-presenting cells because their number is increased in experimental models in which the hypertensive response is ameliorated by inhibition of co-stimulatory pathways (discussed in the section of adaptive immunity).

Macrophages

A consistent finding in experimental models of hypertension is the infiltration of macrophages in the kidney and periadventitial areas in the aorta and medium-sized arteries.
A reduction in macrophage infiltration is associated with improvement of hypertension in spontaneously hypertensive rats (SHRs).\textsuperscript{12} Dahl salt-sensitive rats,\textsuperscript{13} hypertension induced by angiotensin II\textsuperscript{14} and aldosterone,\textsuperscript{15} salt-dependent hypertension,\textsuperscript{16–18} and autoimmune hypertensive renal disease,\textsuperscript{19} Wenzel et al.\textsuperscript{20} studied the role of myelomonocytic cells in the pathogenesis of hypertension and vascular dysfunction by the daily administration of low doses of diphtheria toxin in the LysM\textsuperscript{21} mice with induced expression of the diphtheria toxin receptor. This strategy depleted circulating monocytes and protected the mice from developing angiotensin II–induced hypertension. This effect was reversed by the adoptive transfer of monocytes. Concordant with these results, osteopetrotic mice that have a mutation in the colony-stimulating factor gene and a generalized deficiency in macrophage populations are protected against hypertension induced with angiotensin II and aldosterone.\textsuperscript{21} In another study, treatment with a CCR2 antagonist, which blocks a chemokine receptor responsible for macrophage infiltration in the arterial wall, completely reversed the influx of macrophages and significantly reduced hypertension.\textsuperscript{22} Similar improvement was found blocking the monocyte chemoattractant protein (MCP-1) receptor in angiotensin II and desoxycorticosterone acetate (DOCA)–salt–induced hypertension.\textsuperscript{23} However, in other investigations the depletion of macrophages did not result in the improvement of blood pressure.\textsuperscript{24,25} The disagreement in these experiment may be due to the lack of discrimination between proinflammatory and protective (antihypertensive) effects of macrophages. For example, Titze and colleagues\textsuperscript{26,27} have shown that skin macrophages respond to the interstitial tonicity-responsive enhancer binding protein (TONEBP) with the production of VEGF-C, which stimulates the development of lymphatic capillaries and sequesters Na\textsuperscript{+} and Cl\textsuperscript{−} in the interstitium, ameliorating hypertension.

**NK cells**

Interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), interleukin 2 (IL-2), and interleukin 4 (IL-4) are all rapidly released by NK cells, and 2 important studies have suggested they may play a role in hypertension-related inflammation. Koomans et al.\textsuperscript{28} have shown that monocytes and NK cells present a program of reciprocal activation in hypertension. Their studies have demonstrated that the inflammation and vascular dysfunction induced by angiotensin II are associated with the accumulation of NK cells and macrophages in the aortic wall. Angiotensin-induced cellular infiltration in vascular walls is drastically reduced in the Tbx21\textsuperscript{−/−} mice. Tbx2 drives IFN-γ production, and the response to angiotensin may be restored in the Tbx21\textsuperscript{−/−} mice by the combined administration of IFN-γ–competent NK cells and monocytes, but not by the adoptive transfer of either one of them alone. The role of NK cells was also shown by the studies of Taherzadeh et al.\textsuperscript{29} who were able to induce susceptibility to L-NAME hypertension and vascular remodeling in the constitutively resistant Th2-biased BALB-C mice by the introduction of an NK gene complex of the Th1-biased C57BL/6 mice.

### Inflammasomes and Toll-like receptors

The innate immune response depends on the recognition of molecular patterns that activate the multimeric protein complexes that constitute the inflammasomes and result in the activation of caspase 1, which induces the secretion of proinflammatory cytokines and a form of cell death called pyroptosis.\textsuperscript{30} In addition, the inflammasome induces an effective antigen presentation to naive T cells and thereby plays a crucial role of shaping the subsequent adaptive immune response. Molecular patterns recognized by the inflammasome are pathogen-associated and danger-associated molecular patterns. In the pathogenesis of essential hypertension, pathogen-associated molecular patterns appear to be less relevant; nevertheless, 1 study\textsuperscript{31} reported that periodontitis is associated with a higher risk of hypertension in postmenopausal women. Among the pattern recognition receptors, the TLRs are the best studied and, up to the present time, the only group that has been shown to play a role in inflammation related to hypertension. TLRs are expressed by T and B lymphocytes, antigen-presenting cells, and somatic cells, including endothelial and vascular smooth muscle cells. In adult SHRs there is an increase in TLR4 expression, and administration of anti-TLR4 antibody reduced serum interleukin 6 levels, improved endothelial-induced vasodilatation, and corrected hypertension.\textsuperscript{32} TLR4 knockout mice fail to develop L-NAME–induced hypertension.\textsuperscript{33} Increased TLR7/8- and TLR9-mediated interleukin 6 release was observed in splenic cell cultures of SHRs (but not Wistar rats) subjected to cholinergic (nicotinic) stimulation.\textsuperscript{34}

Peripheral blood monocytes of patients with essential hypertension show increased TLR4 mRNA levels that become downregulated after 12 weeks of intense antihypertensive treatment.\textsuperscript{34} In a subgroup of patients with essential hypertension, the activation of the inflammasome has been suggested by the finding of a mutation in the gene of the sensor molecule, NPLR3.\textsuperscript{35}

A large number of danger-associated molecular patterns related to vascular inflammation and dysfunction are capable of activating TLR4 and TLR2, including angiotensin II,\textsuperscript{36} C-reactive protein,\textsuperscript{37} uric acid,\textsuperscript{38} and Heat shock proteins (HSPs) 60\textsuperscript{39} and 70.\textsuperscript{40} HSP60,\textsuperscript{41} HSP70,\textsuperscript{42,43} C-reactive protein,\textsuperscript{44} and uric acid\textsuperscript{45} have also been associated with essential hypertension. Recently, it has been theorized that fetal programming of hypertension could result from activation of the innate immune system driven by danger-associated molecular patterns originating from the placenta or fetal tissues in complicated pregnancies.\textsuperscript{46}

### ADAPTIVE IMMUNITY IN HYPERTENSION

The adaptive immune response is the reaction of the immune system to specific antigens that results in immunological memory. Evidence of its role in hypertension includes studies of antigen presentation, lymphocyte activation, and antibody production.

**Antigen presentation**

The activation of T cells by antigens is facilitated by T-cell co-stimulation via B7 (CD80) ligands. Recently Vinh et al.\textsuperscript{47} showed an increased number of activated dendritic cells in
angiotsenin II and DOCA-salt hypertension and found that the hypertensive response could be prevented by pharmacological inhibition of the CD28/B7 co-stimulatory pathway. Amelioration of angiotensin II–induced hypertension was also observed in the B7 knockout mice that lack co-stimulatory proteins CD80 and CD86. Furthermore, the hypertensive response to angiotensin was restored by engrafting wild-type bone marrow in B7 knockout mice.45

**Proinflammatory T-cell activation**

More than a decade ago, it was shown that angiotensin II infusions induced a Th1-type cell-mediated immune response characterized by increase in IFN-γ and a decrease in IL-4 in the spleen and kidney.48 Subsequently, a large number of studies have shown T lymphocytes in target organs are driving inflammation and hypertension. These studies will be discussed in the next section. In humans, indirect evidence of the role of T lymphocytes was reported by Seaberg et al.,49 who found that, after controlling for age, race, body mass index, and smoking, untreated HIV-infected patients with chronic low lymphocyte counts had a lower prevalence of systolic hypertension than HIV patients treated with antiretroviral drugs in whom the prevalence of hypertension increased over time and was similar to uninfected control subjects. Additional evidence was given in the studies of Herrera et al.,50 who examined the effects of immunosuppression in 8 patients with essential hypertension who were prescribed mycophenolate mofetil (MMF) for the treatment of rheumatoid arthritis or psoriasis. During treatment with MMF, blood pressure was significantly reduced without changes in diet or antihypertensive treatment.

TNF-α and IL-6 may be increased47,52 or unchanged53 in hypertensive patients. One cytokine of potential importance is IL-17, which is elevated in the circulation in hypertensive patients.54 Madhur et al.54 also observed an increase in IL-17 production in the angiotensin II infusion model and found that the IL-17 knockout mice had less arterial immune cell infiltration and lower blood pressure during the chronic phase of this model.

Recently, Youn et al.55 found that hypertensive patients have increased numbers of CD8+ cytotoxic T cells with immunosenescence markers: loss of CD28 and acquisition of CD57. The loss of CD28 in hypertensive patients appears contrary to the role played by the co-stimulatory CD28/B7 molecules in hypertension demonstrated in the studies of Vinh et al.47 An explanation for this apparent paradox was suggested in an editorial commentary56 that hypothesized that inflammation in target organs could be responsible for the formation of increasing numbers of neoantigens and repeated bouts of antigen stimulation would lead to long-term CD28 loss in hypertensive patients.

**Regulatory T cells**

T regulatory lymphocytes (Tregs) are a subpopulation of T cells that limit immune responses and suppress inflammatory reactivity. Tregs are generated in the thymus (natural Tregs) and in the periphery in response to stimuli that induce immune tolerance. In mice, forkhead box p3 (Foxp3) is a specific marker for Tregs. In humans, Foxp3 expression is not always associated with regulatory function, and an additional subtype of CD4 Tregs (Foxp3–IL-10+), induce suppression of the immune response. Demonstration of a role for Tregs in experimental models of hypertension suggests indirectly the involvement of the immune system in the pathogenesis of hypertension.

Barhoumi et al.59 demonstrated that the administration of CD4+CD25+ Foxp3 Tregs reduces vascular immune cell infiltration, improves endothelial vasodilatation, and reduces blood pressure in mice receiving angiotensin II infusions. Similar benefits were observed in aldosterone-induced hypertension.59 In contrast, Kavan et al.59 did not find changes in blood pressure despite improvement of cardiac hypertrophy and fibrosis. Different experimental designs may be the reason for the contrasting results in these studies. Although a direct demonstration of the participation of Tregs in the modulation of genetic models of hypertension has not been investigated, the aortic expression of Foxp3, transforming growth factor beta, and IL-10, markers of immune suppression associated with Tregs, were all increased in consomic rats in which chromosome 2, a site of genes responsible for inflammation and hypertension, was transferred from normotensive Brown Norway to Dahl salt-sensitive rats. As a result, vascular inflammation and salt-dependent hypertension were suppressed in the consomic rats.60

**Antibodies in hypertension**

The generation of antibodies is an indication of B cell–mediated adaptive immune response. Table 1 summarizes recent investigations that have reported associations between specific antibodies and hypertension. Most of these investigations have focused on antibodies that bind to receptors mimicking the natural ligands and induce a stimulatory effect (agonistic antibodies). The most comprehensively studied is the agonistic antibody directed to the second extracellular loop of the angiotensin II type 1 receptor (AA-AT1r), first described in women with preeclampsia and also found in patients with essential hypertension, transplant rejection, systemic sclerosis, aldosterone-producing adenoma, and 8%–14% of normal individuals.61–67 Hypertensive patients with circulating AA-AT1r have an enhanced response to treatment with AT1r blockers.69 Other autoantibodies have also been identified: agonistic antibodies against alpha-1 adrenergic receptor (AA-a1AR) are directed against the first or the second receptor loop and are expected to enhance peripheral vasoconstriction. They have been found in patients with essential refractory hypertension.68–70 Agonistic antibodies against the beta-1 adrenergic receptors (AA-β1AR) bind to the second receptor loop in cardiomyocytes and are capable of increasing cardiac output and blood pressure and of inducing experimental cardiomyopathy. Zhou et al.72 have found an antibody directed against the L-type voltage-gated calcium channels in 30% of patients with essential hypertension and 6.7% of healthy control subjects. It is assumed that this antibody may be agonistic and, by increasing the calcium concentration in vascular smooth muscle cells, would cause vasoconstriction and
increase peripheral resistance. The hypertension resulting from the agonistic antibodies appears to be primarily due to increased peripheral vascular resistance by vasoconstriction and increased cardiac output. There is also the possibility, unexplored at the present time, that sympathetic and angiotensin overactivity induced by agonistic antibodies could have collateral immune-mediated reactivity.

Antibodies against HSPs have also been found in hypertensive patients, and, rather than being pro-hypertensive, the antibodies are likely part of an adaptive immune response against HSP70 in which the immune cell–driven inflammation in target organs is the pivotal element for the development of salt-sensitive hypertension. Finally, circulating immunoglobulin G and immunoglobulin M antibodies with affinity for endothelial cells have been found in patients with borderline hypertension and eclampsia.

### Table 1. Serum antibodies in hypertension

<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th>Molecular targets</th>
<th>Clinical conditions</th>
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</thead>
<tbody>
<tr>
<td>Anti–angiotensin II type 1 receptors (agonistic)</td>
<td>Second extracellular loop</td>
<td>Eclampsia and pre-eclampsia, essential hypertension, transplant rejection, systemic sclerosis, adrenal adenoma</td>
</tr>
<tr>
<td>Anti–alpha adrenergic receptors (agonistic)</td>
<td>First or second extracellular loop</td>
<td>Refractory hypertension</td>
</tr>
<tr>
<td>Anti–beta-1 adrenergic receptors (agonistic)</td>
<td>Second extracellular loop (cardiomyocytes)</td>
<td>Dilated cardiomyopathy</td>
</tr>
<tr>
<td>Anti–L-type voltage-gated calcium channels (agonistic)</td>
<td>Alpha 1c-subunit of L-type Ca²⁺ channel used as antigen for detection</td>
<td>Essential hypertension</td>
</tr>
<tr>
<td>Anti–heat shock proteins</td>
<td>HSP70, HSP65</td>
<td>Increased titers in essential hypertension and atherosclerosis</td>
</tr>
<tr>
<td>Anti–endothelial cell</td>
<td>Endothelial cells</td>
<td>Borderline hypertension, eclampsia</td>
</tr>
</tbody>
</table>

The agonistic characteristic was demonstrated in anti–angiotensin type I receptors, anti–alpha adrenergic receptors, and anti–beta adrenergic receptors and assumed in the anti–L-type voltage-gated calcium channels.

Abbreviation: HSP, heat shock protein.

INFLAMMATION IN TARGET ORGANS: PATHOPHYSIOLOGY OF HYPERTENSION

Inflammation in the kidney, arteries, and CNS is central in the pathogenesis of hypertension.

Renal inflammation

Renal immune cell infiltration is a constant feature in experimental and clinical studies of hypertension. Renal biopsies taken during sympathectomies done for the treatment of hypertension more than half a century ago showed clusters of T lymphocytes in tubulointerstitial areas. Increased numbers of immune cells were also shown in autopsy studies of white and black hypertensive patients, and a recent study also reported in renal biopsies of 7 patients with hypertensive nephrosclerosis the tubulointerstitial infiltration of CD4 and CD8 lymphocytes and increased expression of the T-cell chemokine, IFN-inducible T-cell a chemottractant.

In all experimental studies shown in Table 2, a reduction in immune cell infiltration with immunosuppressive therapy or by genetic manipulations resulted in amelioration or correction of hypertension. In the SHRs, in salt-sensitive hypertension, and in hypertensive patients, the severity of hypertension is correlated with the intensity of immune cell renal infiltration. In salt-sensitive hypertension, the severity of hypertension is directly correlated with the renal angiotensin II concentration and inversely correlated with the plasma angiotensin II concentration, which, as expected, is suppressed by the high-salt diet.

How is hypertension induced by renal inflammation? The complex pathophysiology of pressure natriuresis is outside the limits of this review, but impairment in this relationship is central in the development of hypertension that represents an adaptive response to maintain sodium balance. Franco et al. found that in salt-sensitive hypertension, accumulation of tubulointerstitial immune cells is directly associated with blunting of pressure-dependent natriuresis (Figure 1). Crowley et al. gave insight to the relationship between lymphocyte activity and urinary sodium excretion, demonstrating that scid mice, which have deficient lymphocyte activity, were protected against angiotensin II–dependent hypertension by a pressure-induced natriuresis that was a consequence of renal overexpression of eNOS and COX2 and higher generation of nitric oxide and prostaglandin E2.

Renal inflammation, immune cell infiltration, and augmented angiotensin II activity may be generated in renal tubular cells and in infiltrating cells because T cells have a functional renin-angiotensin system. In the kidney, angiotensin II impairs pressure natriuresis, and this effect is counteracted by L-arginine, but the relationship between angiotensin activity and hypertension is complex and dependent on the type of cells expressing AT1Rs. Elegant studies by Crowley et al. demonstrated that bone marrow chimeras lacking AT1R have similar baseline blood pressure as wild-type controls and, surprisingly, presented an augmented hypertensive response to angiotensin II infusions, indicating a protective role of AT1R in the bone marrow–derived cells against the hypertensive actions of angiotensin II.
Table 2: Studies on the role of renal inflammation in the pathogenesis of hypertension

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Experimental models</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Athymic (nude) mice/neonatal thymectomy</td>
<td>Renal infarct,² DOCA-salt,³ NZB mice⁴</td>
<td>Acute hypertension unchanged; late (chronic) phase hypertension corrected. Reduction in renal inflammation</td>
</tr>
<tr>
<td>Adrenal steroids/6 MP</td>
<td>Renal infarct⁷⁹</td>
<td>Improvement in hypertension. Reduction in antikidney and antiartery antibodies</td>
</tr>
<tr>
<td>Transfer of splenic cells from DOCA-salt hypertensive rats</td>
<td>Normotensive rats⁸⁰</td>
<td>Induction of renal inflammation and hypertension (by immune reactivity against arterial walls)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>NZB mice,⁸¹ SHRs⁸²</td>
<td>Reduction in perivascular immune cell infiltration in the kidneys. Amelioration of hypertension</td>
</tr>
<tr>
<td>Cyclosporin A</td>
<td>dTGF rats⁸³</td>
<td>Reduced renal injury, proteinuria, and immune cell infiltration. Amelioration of hypertension</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>SHRs,¹¹ Dahl SS,¹³ post all SSHBP,¹⁶,¹⁷ post L-NAME SSHBP,¹⁸ DOCA-salt,¹⁵ chronic lead toxicity,⁴⁴ overload proteinuria,⁸⁵ cellophane wrapped kidney,⁸⁶ prenatally programmed hypertension,⁶⁷ dTGF rats ¹⁴</td>
<td>Reduction of immune cell infiltration, angiotensin II, and oxidative stress. Amelioration of hypertension and prevention of SSHBP</td>
</tr>
<tr>
<td>Ehanercept/dexamethasone</td>
<td>dTGF rats¹⁴</td>
<td>Reduction in renal inflammation and renal injury. No effect on blood pressure</td>
</tr>
<tr>
<td>Inhibition of NFkB</td>
<td>SHRs,⁸⁶ dTGF rats⁸⁹</td>
<td>Reduced renal injury, proteinuria, and immune cell infiltration. Amelioration of hypertension in SHRs, not in the dTGF rats</td>
</tr>
<tr>
<td>Mutation of Rag 1 gene</td>
<td>Dahl salt-sensitive rat⁹⁰</td>
<td>Reduction in renal immune cell infiltration and albuminuria and amelioration of salt-induced hypertension</td>
</tr>
<tr>
<td>CD247 knockout</td>
<td>Dahl salt-sensitive rat⁹¹</td>
<td>Reduction in renal T-cell infiltration and correction of hypertension</td>
</tr>
<tr>
<td>Induction of immune tolerance to HSP70</td>
<td>L-NAME–induced SSHBP⁴³</td>
<td>Reduction in renal immune cell infiltration, prevention of SSHBP</td>
</tr>
</tbody>
</table>

Studies demonstrating the role of renal inflammation in the pathogenesis of hypertension.
Abbreviations: 6MP, 6 mercaptopurine; DOCA, deoxycorticosterone acetate; dTGF, double transgenic rat harboring human renin and angiotensinogen genes; NFkB, nuclear factor kappa B; NZB, New Zealand black; SHR, spontaneously hypertensive rat; SS, salt sensitive; SSHBP, salt-sensitive hypertension.

Vascular inflammation

Vascular inflammation is a characteristic of hypertension. In experimental models of hypertension, there is infiltration of CD4 and CD8 T cells, macrophages, and dendritic cells in perivascular tissue and adventitia in large (aorta) and medium-sized (mesenteric arteries) vessels.⁵⁷-⁵⁹,¹⁰¹ In the kidney, immune cells are preferentially found surrounding renal arteries.¹³ The reasons for the perivascular accumulation of immune cells are not defined, but there are sympathetic nerve endings in these areas, and perivascular inflammation is critically dependent on the CNS.¹⁰² Suppression of vascular inflammation has been associated with the correction of hypertension in various experimental models (Table 3).²¹-²³,⁵⁷-⁶⁰,¹⁰¹-¹⁰⁶ The experiments of Guzic et al.¹⁰¹ showed, for the first time, that adoptive transfer of T cells restored the full hypertensive response to angiotensin II in mice genetically devoid of T and B lymphocytes (rag²/² mice) that were resistant to angiotensin II. Interestingly, hypertension related to life stress is also associated with vascular inflammation; maternal separation, a recognized animal model for behavioral stress in early life, results in exaggerated sensibility to angiotensin and vascular inflammation in adult life. These findings are not observed in the rag²/² mice and restored by adoptive T lymphocyte transfer.¹⁰⁵ Because oxidative stress is generated by inflammation and angiotensin II, it is somewhat surprising that deletion of extracellular superoxide dismutase (SOD3) in vascular tissue does not modify inflammation or angiotensin II–induced hypertension.¹⁰⁷

The mechanisms by which vascular inflammation favors the development of hypertension are related to increased vascular tone and impairment in arterial relaxation. The latter is a critical physiological response mediated by nitric oxide activity in normotensive humans to counteract increased sympathetic vasoconstriction.¹⁰⁸ A number of experimental studies have shown that, when vascular inflammation is present, the endothelial (acetylcholine-induced) relaxation in contracted aortic rings is incomplete and the norepinephrine-induced vasoconstriction is enhanced.⁵⁷,⁵⁸,⁶⁰,¹⁰¹ A role of inflammation in the impairment of the vascular physiology is demonstrated by the restoration of the vasodilatation capacity as a result of the adoptive transfer of Tregs.⁵⁷,⁵⁸

CNS inflammation

The CNS, the sympathetic nervous system (SNS), and the immune system are interconnected in the physiological modulation of hemodynamic and immune responses.¹⁰⁹ In
general, epinephrine and norepinephrine inhibit selectively Th1 and favor Th2 immune responses, but the preexisting state of T cells determines the ultimate responses of sympathetic SNS activation. For example, CD4 cells cultured under Th1-promoting conditions respond to norepinephrine with a robust production of IFN-α. The increases in peripheral vascular resistance, cardiac output, and sodium reabsorption resulting from activation of the SNS are well recognized, and, in addition, adrenergic stimulation increases the TLR-mediated production of proinflammatory cytokines by macrophages. In contrast with the abundance of data on the participation of the SNS in immune responses,

Table 3. Studies showing the role of vascular inflammation in the pathogenesis of hypertension

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Experimental model</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin II–induced hypertension</td>
<td>Rag−/− mice</td>
<td>Resistance to angiotensin II hypertension. Adoptive transfer of T cells induces vascular inflammation and restores sensitivity to angiotensin II</td>
</tr>
<tr>
<td></td>
<td>IL-17−/− mice</td>
<td>IL-17 needed for vascular inflammation and hypertension</td>
</tr>
<tr>
<td></td>
<td>Adoptive transfer of T regulatory cells</td>
<td>Improvement of inflammation and amelioration of hypertension</td>
</tr>
<tr>
<td></td>
<td>Deletion of vascular superoxide dismutase</td>
<td>Reduction in nitric oxide. Inflammation and hypertension unaffected</td>
</tr>
<tr>
<td></td>
<td>MK2−/− mice</td>
<td>Suppression of ICAM-1, MCP-1, and vascular inflammation. Amelioration of hypertension</td>
</tr>
<tr>
<td></td>
<td>Osteopetrotic mice (Op/Op) deficient in m-CSF</td>
<td>Reduced vascular inflammation, increased AC-induced vascular relaxation, no increase in media thickness</td>
</tr>
<tr>
<td></td>
<td>Selective ablation of myelomonocytic cells</td>
<td>Reduced number of monocytes in blood and in vessels. Reduced inflammation, increased vascular relaxation. Transfer of monocytes reversed effects</td>
</tr>
<tr>
<td>Aldosterone-induced hypertension</td>
<td>Adoptive transfer of T regulatory cells</td>
<td>Suppression of vascular inflammation and correction of hypertension</td>
</tr>
<tr>
<td>DOCA-salt</td>
<td>CCR2 antagonist</td>
<td>Suppressed vascular macrophage, correction of hypertension</td>
</tr>
<tr>
<td>Stress-induced hypertension</td>
<td>Effects of early life stress on the response to angiotensin II</td>
<td>Increased vascular inflammation, increased hypertension in response to angiotensin II</td>
</tr>
<tr>
<td>Cold-induced hypertension</td>
<td>IL-6−/− mice</td>
<td>Reduction in inflammation in arteries, heart and kidney. Amelioration of hypertension</td>
</tr>
</tbody>
</table>

Studies showing the relevance of vascular inflammation in the pathogenesis of experimental hypertension.

Abbreviations: AC, acetylcholine; CCR2, chemokine (C-C motif) receptor 2; CSF, colony stimulating factor; DOCA, deoxycorticosterone acetate; ICAM-1, intercellular adhesion molecule 1; IL-6, interleukin 6; IL-17, interleukin 17; MCP1, monocyte chemoattractant protein 1; MK2, mitogen activated protein kinase 2; Rag−/−, recombination activating gene knockout; SOD, superoxide dismutase.
Immunity in Hypertension

scarce information exists on the inhibitory effects of parasympathetic stimulation on immunity. It has been found that loss of parasympathetic downregulation of innate immune responses may favor hypertension in SHRs. Recent studies have focused on the antihypertensive potential of cholinergic activity mediated by α-7 nicotinic acetylcholine receptors. In SHRs, the α-7 nicotinic receptors in the spleen are reduced, and it has been suggested that, as a result, there is overexpression of inflammatory cytokines in several organs, including the kidney. However, further studies are needed to define the role of this pathway in the pathogenesis of hypertension.

Many of the studies examining the role inflammation within the brain in hypertension have focused on circumventricular regions because these areas lack a blood–brain barrier and have an abundance of AT1r. The importance of the integrity of this region in hypertension was shown by Marvar et al., who found that lesions in the anterointernal third ventricle impair activation of lymphocytes and their homing to the arterial walls and, thereby, ameliorate angiotensin II–induced hypertension. Induction of oxidative stress in the subfornical organ in the hypothalamus by the knockdown of superoxide dismutase increases vascular infiltration of activated lymphocytes and worsens hypertension and, conversely, reducing the superoxide generation by the knockdown of the p22 subunit of the NADPH oxidase ameliorates angiotensin II–dependent hypertension. In the same model, suppressing inflammation in the subfornical organ with minocycline or by the induction of IL-10 overexpression ameliorates hypertension. The participation of brain receptors of angiotensin II is also critical in other models of hypertension; for example, DOCA-salt hypertension is ameliorated if the AT1rs in the subfornical organ are knocked down. Recent studies by Siramula et al. have demonstrated the role of TNF in the CNS in the development of hypertension. These investigators showed that inhibition of brain TNF by intracerebroventricular infusion of etanercept protects rats against angiotensin II–induced hypertension by restoring the balance between prohypertensive (ACE and AT1R) and antihypertensive (ACE2, Mas, and AT2 receptors) axes of the renin-angiotensin system, in association with inhibition of inflammatory cytokines and oxidative stress in the paraventricular nucleus. Because hypertensive patients have circulating markers of inflammation, it is relevant that systemic inflammation may cause inflammation in the CNS: proinflammatory cytokines are
produced in the rostral ventrolateral medulla in response to 2 weeks of infusion of lipopolysaccharide.\textsuperscript{118}

Other recent investigations have centered on the nucleus tractus solitarii in the brain stem, which is a pivotal region for the regulation of arterial pressure. In SHR, the proinflammatory molecule functional adhesion molecule 1 (JAM 1) is highly overexpressed in the vascular endothelial cells in this area in association with dysregulation of the expression of several genes associated with inflammation. These findings were associated with accumulation of leukocytes within the capillaries in this region, a finding considered important in the development of hypertension.\textsuperscript{119}

In summary, the mechanisms involved in the development of hypertension resulting from inflammation in the CNS include SNS stimulation and the activation and homing of T cells for the induction of arterial inflammation.

**RECENT RESEARCH ON AUTOANTIGENS IN HYPERTENSION**

A critical aspect of study in the immune pathogenesis of hypertension is the identification of antigen(s) responsible for driving the immune response in essential hypertension. Because the antigenic antibodies are present in only a fraction of the hypertensive patients, other antigens may be playing a role in the vast majority of patients with essential hypertension. The possibility that multiple antigens play a role in the pathogenesis of hypertension is suggested by the demonstration of T-cell senescence markers compatible with repeated bouts of neoantigens generation.\textsuperscript{50} We suggested\textsuperscript{9} that autoimmune reactivity to HSPs could play a role in hypertension because these molecules, which function as chaperones of nascent proteins, are very immunogenic when accessing the extracellular compartment. We centered our studies on HSP70 because it is expressed in the kidney, arteries, and CNS by stimuli associated with hypertension, such as angiotensin II, oxidative stress, sympathetic stimulation, and stress.\textsuperscript{8} In addition, HSP70 is increased in the kidney in animal models of hypertension,\textsuperscript{32} and patients with essential hypertension have anti-HSP70 serum antibodies.\textsuperscript{42,43,73} In salt-sensitive hypertension induced by transient L-NAME administration, we found that induction of immune tolerance to HSP70 prevented renal inflammation and hypertension. Furthermore, the adoptive transfer of IL-10–producing Tregs from tolerized rats corrected the salt-dependent hypertension. Finally, salt-induced increments in blood pressure resulted from genetically induced overexpression of HSP70 in the kidney of rats previously sensitized to HSP70.\textsuperscript{41} Taken together these experiments suggest that HSP70 should be investigated as one of the potential antigens in human essential hypertension.

**CONCLUDING REMARKS**

Investigations in the last decade have provided compelling evidence that innate and adaptive immunity play a central role in hypertension (Figure 2). The role of B cells is evidenced by the generation of antigenic antibodies directed to angiotensin II and adrenergic receptors. The most definitive data supporting the role of antigenic antireceptor antibodies correspond to the AA-AT1r in eclampsia and preeclampsia. However, pregnancy-associated hypertension is an acute, self-limited condition. In salt-sensitive primary hypertension, studies to date suggest a role for T cell–mediated inflammation and T cell–suppressor responses. Inflammation-derived neoantigens and surface of intraacellular immunogenic proteins, such as HSP70, could be central in the development of autoimmunity that would drive a low-grade inflammation in target organs that underpins the increase in blood pressure. Therapeutic strategies of potential clinical use may result from the insights gained in studies on the role of immunity in hypertension.

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**DISCLOSURES**

R.J.J. is on the Scientific Board of Amway, XORT Therapeutics, and Rivermend Health and has patent and patent applications related to lowering uric acid or blocking fructose metabolism in the treatment of hypertension and metabolic disorders. B.R.-I., H.P., and Y.Q. declared no conflict of interest.

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