Published in final edited form as:
Curr Hypertens Rep. 2014 April ; 16(4): 424. doi:10.1007/s11906-014-0424-1.

Autoimmunity: An Underlying Factor in the Pathogenesis of Hypertension

Keisa W. Mathis, **Hanna J. Broome**, and **Michael J. Ryan**
Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS USA

Abstract

One in every three adults in the United States has hypertension, and the underlying cause of most of these cases is unknown. Therefore, it is imperative to continue the study of mechanisms involved in the pathogenesis of hypertension. Decades ago, studies speculated that elements of an autoimmune response were associated with the development of hypertension based, in part, on the presence of circulating autoantibodies in hypertensive patients. In the past decade, a growing number of studies have been published supporting the concept that self-antigens and the subsequent activation of the adaptive immune system promote the development of hypertension. This manuscript will provide a brief review of the evidence supporting a role for the immune system in the development of hypertension, studies that implicate both cell-mediated and humoral immunity, and the relevance of understanding blood pressure control in an autoimmune disease model with hypertension.

Keywords

Adaptive immunity; Autoantibodies; Autoimmunity; B cells; Blood pressure; Immune system; Inflammation; Lupus; Systemic lupus erythematosus; SLE; T cells

Introduction

Hypertension was recognized by what was termed a hardened pulse in the arteries as early as 2600 B.C., but was not classified as a treatable “cardiovascular disease” until 1913 [1, 2]. It affects 25–35% of people over the age of 18 worldwide, and for most of the greater than 77 million diagnosed adults in the United States, the cause is unknown [3, 4]. Although the reasons for this can be debated, only about half of hypertensive patients are achieving blood

Corresponding author: Michael J. Ryan, Associate Professor, University of Mississippi Medical Center, Department of Physiology and Biophysics, 2500 North State Street, Jackson, MS 39216-4505, Office: 601-984-1842, Lab: 601-815-4856, Fax: 601-984-1817, mjryan@umc.edu.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

Hanna J. Broome declares that she has no conflict of interest.

Keisa W. Mathis has received a grant from the National Institutes of Health NRSA (F32).
Michael J. Ryan has received a grant from the American Heart Association and the Veterans Affairs Merit Award.

pressure control, despite the continued development of therapies over the last century [5]. Taken together, this suggests that there is continued need to examine the underlying factors that promote the development of hypertension and limit the efficacy of treatment for these patients. Although it has been recognized for many years, the association between immune system activation and the pathogenesis and maintenance of hypertension has become a robust area of scientific inquiry over the past decade. Among the studies published in this area, many of them implicate an autoimmune phenomenon as potentially contributing to the hypertension. The purpose of this brief review is to highlight some of the key studies showing a mechanistic role for the immune system in the development of hypertension, review evidence supporting the concept that a loss of immune tolerance and the resulting autoimmunity may be an important underlying factor, and promote the idea of studying experimental models of autoimmunity as a means to better understand the link between immune system activation and hypertension.

Immune system activation and hypertension: a brief overview

A role for immune system activation has been well-documented in both human and experimental hypertension from as early as 1964, when White and Grollman reported that injection of renal particles induced a hypertensive phenotype in rats that was associated with the presence of anti-kidney antibodies [6]. In addition, they demonstrated that immunosuppressive therapy protected from increases in blood pressure in an experimental model of kidney infarction and that anti-kidney “precipitins” were elevated in the sera of hypertensive patients [6]. In 1976, Svendsen and colleagues reported that mice lacking a thymus – and therefore mature T cells – were protected from deoxycorticosterone acetate (DOCA)-salt hypertension [7]. In 1985, Norman and colleagues implanted the thymus from normal animals into spontaneously hypertensive rats and demonstrated that this transfer of normal immune cells effectively reduced blood pressure [8, 9]. These early studies suggested a role for immune cells in the pathogenesis of hypertension and also hinted at the possibility that autoimmunity may be an important contributing factor.

In subsequent years, reports on the association between the immune system and human hypertension continued. For example, circulating inflammatory cytokines (i.e., tumor necrosis factor [TNF]-α, interleukin [IL]-6) are increased in patients with essential hypertension and even directly correlate with blood pressure in individuals who are not hypertensive [10, 11]. A mechanistic role for cytokines in the development of hypertension has been confirmed in studies utilizing experimental animal models, where blockade of TNF-α reportedly attenuates or delays the development of hypertension caused by chronic angiotensin II infusion [12–14], mineralocorticoid-induced hypertension [15], and salt-sensitive hypertension [16]. A mechanistic role for IL-6 in angiotensin II-mediated hypertension was demonstrated using IL-6 knockout mice [17], and there is data pointing to a role for the proinflammatory cytokine IL-17 in angiotensin-mediated hypertension as well. For example, T cells from angiotensin II-infused mice produce and release more IL-17, and IL-17 knockout mice are protected from angiotensin II-induced hypertension [18]. In addition, data from the LaMarca laboratory indicate that infusion of IL-17 into normal pregnant rats leads to chronic increases in blood pressure [19] and that blocking IL-17 activity with the soluble receptor to the cytokine prevents pregnancy-induced increases in

blood pressure [20]. Although the mechanisms for IL-17-induced hypertension remain unclear, there is some evidence suggesting that IL-17 promotes hypertension by reducing endothelial nitric oxide synthase [21]. Interestingly, IL-17 is an important factor in the development of autoimmune-induced tissue injury.

Inflammatory cytokines are produced by a variety of different cell types, including those of the adaptive immune system, and several lines of evidence support a role for adaptive immunity in the pathogenesis of hypertension in humans. The use of mycophenolate mofetil (MMF), an immunosuppressive therapy that depletes B and T cells, has been reported to lower blood pressure in small clinical studies of patients with hypertension and chronic kidney disease [22, 23]. Mechanistic insight for the beneficial effects of MMF has been obtained in studies using experimental models of hypertension including angiotensin II [24, 25], salt-sensitive [26–30], mineralocorticoid-induced [31], spontaneously hypertensive [32, 33], and several others [34–36]. These studies generally show that MMF protects against renal and vascular infiltration of the T cells and macrophages that promote tissue injury and inflammation, and they support a role for adaptive immune system activation in the development of hypertension.

While the studies described above clearly support a role for adaptive immunity, seminal work from Guzik et al. provided definitive evidence that specifically T cells, and not B cells, are essential for the development of angiotensin II-mediated hypertension in mice [12]. In these studies, recombination activating gene (rag)-1 knockout mice lacking both T and B cells were infused with angiotensin II, and the hypertensive response was blunted. In order to determine the role of specific cell types in the development of angiotensin II hypertension, they adoptively transferred T cells into one subset of animals and B cells into another. The results demonstrated that T cells, and not B cells, restored the increases in blood pressure due to chronic infusion of angiotensin II. An important role for T cells in angiotensin II-induced and salt-sensitive hypertension has been subsequently confirmed by others using mouse and rat models of hypertension [25–28, 30, 36–40]. More recently, significant progress has been made toward understanding the role of specific T cell subsets in blood pressure regulation, including T helper 17 (Th17) cells [18], T regulatory cells [41], and cytotoxic T cells (CD8+) [42]. Based on these studies, a general model for the involvement of T cells and adaptive immunity in hypertension has emerged. This model predicts that a physiological stressor like angiotensin II or chronic high salt causes local injury, resulting in the release of neoantigens that initiate an adaptive immune response and contribute to sustained hypertension [43–45]. The involvement of self-antigens suggests the possibility that loss of tolerance and autoimmunity can be an underlying factor in the pathogenesis of hypertension.

Evidence for autoimmunity in the development of hypertension

A loss of immunological tolerance to self-antigens was initially characterized as a “horror autotoxicus” by Paul Ehrlich, the 1908 Nobel Laureate in Physiology & Medicine, and is now commonly referred to as autoimmunity. Autoimmunity is a contributing factor in over 80 different disorders that collectively impact 4–7% of the population in the United States. Importantly, cardiovascular disease and hypertension are prevalent in some of the most

common autoimmune disorders, including rheumatoid arthritis and systemic lupus erythematosus (SLE) [46–50]. T cells have a central role in the development of autoimmune disorders, in part through the production of proinflammatory and immunomodulatory cytokines and by promoting antibody production from B cells through a process called T cell help.

The work of Rodriguez-Iturbe and colleagues has significantly advanced the concept that autoimmunity can underlie the development of hypertension, particularly salt-sensitive hypertension. They hypothesize that heat shock protein (HSP) 70, a chaperone protein capable of inducing an immune response, is an important antigen that promotes salt-sensitive hypertension [51, 52]. The idea is based on evidence that HSP70 is increased in patients with essential hypertension and that renal expression of HSP70 is increased in animal models of hypertension [35, 53]. Furthermore, HSP70 is thought to contribute to the pathogenesis of hypertension because it induces proliferation of T cells from saltsensitive animals [51].

In an elegant set of studies, Pons et al. determined that HSP70 was, indeed, a contributing factor in the development of salt-sensitive hypertension [52]. Briefly, animals were made salt-sensitive by inhibiting nitric oxide synthase with L-NAME, and then hypertensive by subsequently placing the animals on a high-salt diet. They demonstrated that increasing immune tolerance to HSP70 in salt-sensitive animals prevented the development of hypertension and that adoptive transfer of T cells, but not B cells, from HSP70-tolerized rats corrected salt-sensitive hypertension. In addition, they determined that renal delivery of the HSP70 gene (via plasmid) to normal animals that were previously sensitized to HSP70 enhanced the blood pressure response to high-salt diet. Taken together, these data provide strong evidence for the role of HSP70 as a neoantigen that initiates an immune response and contributes to salt-sensitive hypertension.

It is worth noting that recent work implicates a potential role for dietary salt in the promotion of autoimmunity. This concept is supported by data showing that short-term (up to 3 weeks) increases in dietary salt exacerbate autoimmune disease progression in an animal model of multiple sclerosis (experimental autoimmune encephalitis, EAE). While there was no impact of dietary salt on blood pressure in this study, the effects to promote EAE were attributed to induction of T helper 17 cells via increased expression of serum/glucocorticoid-regulated kinase 1 (SGK1) [54, 55]. Recall that Th17 cells and IL-17 have been implicated in experimental hypertension [18–21]. Whether high-salt-induced activation of the immune system can contribute to hypertension in human and experimental hypertension has not been extensively examined. Studies from our own laboratory show that a shortterm (4-week) high-salt diet does not exacerbate autoantibody production or further increase blood pressure in a hypertensive mouse model with the autoimmune disorder systemic lupus erythematosus (SLE) [56]. However, one limitation is that the study was conducted in adult mice at an age when blood pressure is already moderately increased (≈10 mmHg) and antibodies are present. Therefore, the impact of long-term dietary salt on immune system activation and the pathogenesis of autoimmune diseases, like SLE, that are associated with hypertension remain to be tested.

Examining mechanisms of increased blood pressure that occur with autoimmunity can fill an important niche in the field of hypertension research. While published work clearly shows the importance of T cells, and not B cells, in experimental models of angiotensin II and salt-sensitive hypertension, it is important to recognize that many individuals with hypertension do not have elevated circulating angiotensin II or blood pressure that is sensitive to changes in dietary salt. In addition, a growing body of evidence suggests an association between humoral (antibody-mediated) immunity and human hypertension. Therefore, the remainder of this review will discuss evidence for B-cell involvement in human hypertension and the utility of studying an experimental model of autoimmunity to understand the link between immune system activation and hypertension.

Evidence for antibody-mediated immunity in the development of hypertension

An association between humoral immunity and hypertension has been recognized for many years through clinical studies showing increased circulating autoantibodies in patients with hypertension. For example, Kristensen and colleagues reported an increase in IgG and IgM antibodies in patients with essential hypertension [57, 58]. In addition, Gudbrandsson and colleagues showed increases in antinuclear antibodies consistent with systemic autoimmune disorders in patients with essential hypertension [59]. Whether activation of the humoral immune response contributes to the hypertension in these patients remains to be determined.

While it remains unclear whether these nonspecific antibodies are pathogenic in hypertension, a role for specific activating antibodies has been reported. There is evidence that agonistic antibodies of the α1-adrenergic receptor, β1-adrenergic receptor, and angiotensin type 1 (AT1) receptor are mechanistically involved in cardiovascular disorders, including hypertension. For example, removal of pathogenic α1-adrenergic receptor antibodies in patients with refractory hypertension was shown to reduce blood pressure [60]. Other evidence suggests that antibodies to the β1-adrenoreceptor in the heart are associated with dilated cardiomyopathy [61], and that AT1 receptor antibodies are linked with preeclampsia and renal allograft rejection [62, 63]. Taken together, these data strongly support the suggestion that humoral immune system activation can contribute to the pathogenesis of hypertension.

Systemic lupus erythematosus: an important disease model to study the link between immune system activation and hypertension

SLE is an autoimmune disease that predominantly affects women of reproductive age, with an estimated prevalence of between 20–200/100,000 people worldwide [64–66]. SLE involves multi-organ inflammation resulting from adaptive immune system activation in response to self-antigens and the subsequent production of autoantibodies (commonly antinuclear). Different T cell subsets have important roles in the development of autoimmune diseases by promoting B cell production of autoantibodies as well as by the release of inflammatory cytokines. T helper 2 cells are implicated in humoral-mediated immunity, while T helper 1 cells release IFN-γ, which activates macrophages and elicits

local inflammation and TNF-α production. T helper 17 cells also contribute to autoimmunity through the release of IL-17, which can also increase TNF-α production. A primary site of tissue injury in SLE is the kidney, where immune complexes consisting of nuclear antigens and IgG antinuclear antibodies deposit in the glomerular basement membrane, triggering macrophage infiltration and inflammatory response. The leading cause of mortality among SLE patients is cardiovascular disease, and for reasons that are not completely understood, there is a significantly higher prevalence of hypertension among these patients when compared to healthy age-matched females [49]. Interestingly, many of the elements of immune system activation that have been implicated in human and experimental hypertension (i.e., cytokines, T cells, antibodies) are known mediators of autoimmune diseases like SLE. Therefore, a deeper understanding of the pathogenesis of hypertension during SLE will likely advance the overall field of hypertension research with respect to underlying immune mechanisms of the disease.

Experimental animal models of SLE have been widely used to understand mechanisms of autoimmunity and the development of lupus nephritis. One model, in particular, that may be informative for studying the link between autoimmunity and hypertension is the female *NZBWF1* mouse, a model of SLE generated by crossing New Zealand Black (NZW) and New Zealand White (NZW) inbred strains. The resulting F1 offspring produce the double-stranded (ds) DNA autoantibodies that are characteristic of human SLE and develop immune complex-mediated glomerulonephritis. In addition, the disease progression occurs at an earlier age and is more severe in female mice, thus modeling the strong female bias that is present in human SLE. Importantly, these mice develop hypertension that coincides with the increase in autoantibody production [56, 67–70]. The hypertension in this model is also associated with low plasma renin [71], and we reported that blood pressure is not sensitive to salt, at least in response to a relatively short-term dietary salt increase in adult female mice [56]. Therefore, this is a genetic model of hypertension with a suppressed renin-angiotensin system (consistent with most essential hypertensive patients) that is strongly associated with immune system activation. Factors that contribute to the hypertension in this model include vascular endothelial dysfunction, impaired renal hemodynamics (i.e. attenuated renal blood flow and increased renal vascular resistance), and renal inflammation [56, 72–74]. To illustrate the importance of renal inflammation in SLE-associated hypertension, our laboratory showed that mice treated with the TNF-α antagonist etanercept had lower blood pressure compared with vehicle-treated animals [70]. The lower blood pressure was associated with reduced renal cortical macrophage infiltration, NFκB activation, and oxidative stress. In a subsequent study, we demonstrated that treatment with antioxidants protected against the development of hypertension and renal injury (albuminuria) in the same SLE mouse model [67]. Whether renal NFκB activation, specific immune cell subsets (i.e., T and B cells), and autoantibodies contribute mechanistically to the impaired renal function and hypertension during SLE is not clear. In order to begin to address these issues, we recently conducted preliminary studies to directly test whether humoral immunity underlies the hypertension associated with SLE. Based on the evidence linking autoantibody production with hypertension in humans, we hypothesized that preventing autoimmunity in this model would stop the development of hypertension. In order to test this, we administered a monoclonal antibody to CD20 to in order to deplete B

cells. We found that B-cell depletion prior to the onset of SLE prevented the hypertension and renal injury in mice with SLE, and thus directly supports the concept that autoimmunity and the production of antibodies is an important factor in the development of hypertension [75]. In addition to targeting B cells, we also have preliminary results suggesting that inhibition of T cells in SLE mice with established renal injury attenuates the further progression of hypertension [76]. Taken together, these data show that that the humoral immune system activation and renal inflammation that are hallmarks of SLE have an important causal role in the associated hypertension. Going forward, it will be important to investigate the importance of specific adaptive immune cell subsets and the role of specific cytokines and inflammatory signaling pathways on renal function in order to better understand the link between autoimmunity and blood pressure control.

Conclusions and perspectives

The major goal of this review was to highlight some of the key evidence, both historical and recent, that implicates immune system activation in the pathogenesis of hypertension. A summary of studies implicating a role for immune system activation in human hypertension is shown in Table 1. A significant amount of the published work has emphasized the importance of T-cell subsets and specific inflammatory cytokines in both human and experimental hypertension. However, there is a growing body of evidence that the loss of immune tolerance and the production of autoantibodies associated with autoimmunity can have a pathogenic role for hypertension as well. Autoimmune disorders, including SLE, rheumatoid arthritis, psoriasis, scleroderma, and systemic sclerosis, are associated with prevalent hypertension and many elements of immune system activation (i.e., T cells, autoantibodies, macrophage, cytokines) reported using models of angiotensin II and salt-sensitive hypertension. In future studies, it will be particularly informative to include experimental models of autoimmunity with associated hypertension when examining the link between immune system activation and blood pressure control.

References

1. Strickler C. Significance of hypertension. South Med J. 1917; 10:191–194.
2. Freis E. Hypertension, Pathophysiology Diagnosis and Management. Hypertension, Pathophysiology Diagnosis and Management (2 ed.). 1995:2741–2751.
3. Staessen J, Wang J, Bianchi G, Birkenhager W. Essential hypertension. Lancet. 2003; 361:1629–1641. [PubMed: 12747893]
4. Chobanian A. Shattuck Lecture: The hypertension paradox-more uncontrolled disease despite improved therapy. New England Journal of Medicine. 2009; 361:878–887. [PubMed: 19710486]
5. Lloyd-Jones D, Adams R, Brown T, Carnethon M, Dai S, De S, et al. Heart disease and stroke statistics--2010 update: A report from the American Heart Association. Circulation. 2010; 121(e46):e215.
6. White F, Grollman A. Autoimmune factors associated with infarction of the kidney. Nephron. 1964; 1:93–102. [PubMed: 14248727]
7. Svendsen U. Evidence for an initial, thymus independent and a chronic, thymus dependent phase of DOCA and salt hypertension in mice. Acta Pathol Microbiol Scand A. 1976; 84:523–528. [PubMed: 998251]
8. Khraibi A, Norman R, Dzielak DJ. Chronic immunosuppression attenuates hypertension in Okamoto spontaneously hypertensive rats. American Journal of Physiology: Heart and Circulatory Physiology. 1984; 247(16):722–726. This study suggested a role for autoimmunity in an

experimental model of hypertension. The major finding was that cyclophosphamide effectively reduced blood pressure in spontaneously hypertensive rats.

9. Dzielak DJ. Immune mechanisms in experimental and essential hypertension. American Journal of Physiology: Regulatory, Integrative and Comparative Physiology. 1991; 260(29):459–467. This report is an editorial review which highlights the research that had been done at that time regarding the link between hypertension and immune system activation.
10. Bautista L, Vera L, Arenas I, Gamarra G. Independent association between inflammatory markers (C-reactive protein, interleukin-6, and TNF-alpha) and essential hypertension. J Hum Hypertension. 2005; 19:149–154.
11. Chae C, Lee R, Rifai N, Ridker P. Blood pressure and inflammation in apparently healthy men. Hypertension. 2001; 38:399–403. [PubMed: 11566912]
12. Guzik TJ, Hoch NE, Brown KA, McCann LA, Rahman A, Dikalov S, et al. Role of the T cell in the genesis of angiotensin II-induced hypertension and vascular dysfunction. The Journal of Experimental Medicine. 2007; 204(10):2449–2460. [PubMed: 17875676] This paper is a seminal study demonstrating that T cells, and not B cells, are involved in the development ofangiotensin II mediated hypertension.
13. Ferreri N, Zhao Y, Takizawa H, McGiff J. Tumor necrosis factor-alpha-angiotensin interactions and regulation of blood pressure. J Hypertens. 1997; 15:1481–1484. [PubMed: 9431855]
14. Tran L, MacLeod K, McNeill J. Chronic etanercept treatment prevents the development of hypertension in fructose-fed rats. Mol Cell Biochem. 2009; 330:219–228. [PubMed: 19440659]
15. Elmarakby A, Quigley J, Imig J, Pollock J, Pollock D. TNF-alpha inhibition reduces renal injury in DOCA-salt hypertensive rats. American Journal of Physiology: Regulatory, Integrative and Comparative Physiology. 2008; 294:76–83.
16. Elmarakby A, Quigley J, Pollock D, Imig J. Tumor necrosis factor alpha blockade increases renal Cyp2c23 expression and slows the progression of renal damage in salt-sensitive hypertension. Hypertension. 2006; 47:557–562. [PubMed: 16415373]
17. Lee D, Sturgis L, Labazi H, Osborne J, Fleming C, Pollock J, et al. Angiotensin II hypertension is attenuated in interleukin-6 knockout mice. American Journal of Physiology: Heart and Circulatory Physiology. 2006; 290:935–940.
18. Madhur MS, Lob HE, McCann LA, Iwakura Y, Blinder Y, Guzik TJ, et al. Interleukin 17 promotes angiotensin II-induced hypertension and vascular dysfunction. Hypertension. 2010; 55(2):500–507. [PubMed: 20038749] This studywas one of the first to establish a role of IL-17 in the development of hypertension.
19. Dhillion P, Wallace K, Herse F, Scott J, Wallukat G, Heath J, et al. IL-17-mediated oxidative stress is an important stimulator of AT1-AA and hypertension during pregnancy. American Journal of Physiology: Regulatory, Integrative and Comparative Physiology. 2012; 303(4):353–358.
20. Cornelius D, Hogg J, Scott J, Wallace K, Herse F, Moseley J, et al. Administration of interleukin-17 soluble receptor C suppresses Th17 cells, oxidative stress, and hypertension in response to placental ischemia during pregnancy. Hypertension. 2013; 62(6):1068–1073. [PubMed: 24060899]
21. Nguyen H, Chiasson V, Chatterjee P, Kopriva S, Young K, Mitchell B. Interleukin-17 causes rhokinase- mediated endothelial dysfunction and hypertension. Cardiovascular Research. 2013; 97(4):696–704. [PubMed: 23263331]
22. Herrera J, Ferrebuz A, MacGregor EG, Rodriguez-Iturbe B. Mycophenolate mofetil treatment improves hypertension in patients with psoriasis and rheumatoid arthritis. Journal of American Society of Nephrology. 2006; 17:218–225. This is an important study demonstrating that immunosuppressive therapy can reduce blood pressure in hypertensive patients with underlying autoimmune disorders.
23. Ferro C, Edwards N, Hutchison C, Cockwell P, Steeds R, Savage C, et al. Does immunosuppressant medication lower blood pressure and arterial stiffness in patients with chronic kidney disease? An observational study. Hypertension Research. 2011; 34(1):113–119. [PubMed: 20962786]

24. Muller DN, Shagdarsuren E, Park J-K, Dechend R, Mervaala E, Hampich F, et al. Immunosuppressive treatment protects against angiotensin II-induced renal damage. American Journal of Pathology. 2002; 161(5):1679–1693. [PubMed: 12414515]
25. Rodriguez-Iturbe B, Quiroz Y, Gordon K, Rincon J, Chavez M, Parra G, et al. Mycophenolate mofetil prevents salt-sensitive hypertension resulting from angiotensin II exposure. Kidney International. 2001; 59:2222–2232. [PubMed: 11380825]
26. Mattson DL, James L, Berdan EA, Meister CJ. Immune suppression attenuates hypertension and renal disease in the Dahl salt-sensitive rat. Hypertension. 2006; 48:149–156. [PubMed: 16754791]
27. Miguel C, Das S, Lund H, Mattson DL. T lymphocytes mediate hypertension and kidney damage in Dahl salt-sensitive rats. American Journal of Physiology: Regulatory, Integrative and Comparative Physiology. 2010; 298:1136–1142.
28. Quiroz Y, Pons H, Gordon K, Rincon J, Chavez M, Parra G, et al. Mycophenolate mofetil prevents salt-sensitive hypertension resulting from nitric oxide synthesis inhibition. American Journal of Physiology: Renal Physiology. 2001; 281:38–47.
29. Tian N, Gu J, Jordan S, Rose R, Hughson M, Manning R. Immune suppresion prevents renal damage and dysfunction and reduces arterial pressure in salt-sensitive hypertension. American Journal of Physiology: Heart and Circulatory Physiology. 2007; 292:1018–1025.
30. De M, Das S, Lund H, Mattson D. T lymphocytes mediate hypertension and kidney damage in Dahl salt-sensitive rast. American Journal of Physiology: Regulatory, Integrative and Comparative Physiology. 2010; 298:1136–1142.
31. Boesen E, Williams D, Pollock J, Pollock D. Immunosuppression with mycophenolate mofetil attenuates the development of hypertension and albuminuria in deoxy-corticosterone acetatesalt hypertensive rats. Clin Exp Pharmacol Physiol. 2010; 37:1016–1022. [PubMed: 20626757]
32. Rodriguez-Iturbe B, Quiroz Y, Nava M, Bonet L, Chavez M, Herrera0Acosta J, et al. Reduction of renal immune cell infiltration results in blood pressure control in genetically hypertensive rats. American Journal of Physiology: Renal Physiology. 2002; 282:191–201.
33. Rodriguez-Iturbe B, Quiroz Y, Ferrebuz A, Parra G, Vaziri N. Evolution of renal interstitial inflammation and NF-kappaB activation in spontaneously hypertensive rats. Am J Nephrology. 2004; 24:587–594.
34. Ardiles L, Ehrenfeld P, Quiroz Y, Rodriguez-Iturbe, Herrera-Acosta J, Mezzano S, et al. Effect of mycophenolate mofetil on kallikrein expression in the kidney of 5/6 nephrectomized rats. Kidney Blood Press Res. 2002; 25:289–295. [PubMed: 12435874]
35. Bravo J, Quiroz Y, Pons H, Parra G, Herrera-Acosta J, Johnson RJ, et al. Vimentin and heat shock protein expression are induced in the kidney by angiotensin and by nitric oxide inhibition. Kidney International Supplement. 2003:S46–S51. [PubMed: 12969127]
36. Pechman K, Basile D, Lund H, Mattson DL. Immune suppression blocks sodium-sensitive hypertension following recovery from ischemic acute renal failure. American Journal of Physiology: Regulatory, Integrative and Comparative Physiology. 2008; 294:1234–1239.
37. Crowley S, Song Y-S, Lin EE, Griffiths R, Kim H-S, Ruiz P. Lymphocyte responses exacerbate angiotensin II-dependent hypertension. American Journal of Physiology: Regulatory, Integrative and Comparative Physiology. 2010; 298:1089–1097.
38. Crowley SD, Vasievich MP, Ruiz P, Gould SK, Parsons KK, Pazmino AK, et al. Glomerular type 1 angiotensin receptors augment kidney injury and inflammation in murine autoimmune nephritis. The Journal of Clinical Investigation. 2009; 119(4):943–953. [PubMed: 19287096]
39. Crowley SD, Frey CW, Gould SK, Griffiths R, Ruiz P, Burchette JL, et al. Stimulation of lymphocyte responses by angiotensin II promotes kidney injury in hypertension. American Journal of Physiology: Renal Physiology. 2008; 295:515–524.
40. Hoch NE, Guzik TJ, Chen W, Deans T, Maalouf SA, Gratze P, et al. Regulation of T-cell function by endogenously produced angiotensin II. American Journal of Physiology: Regulatory, Integrative and Comparative Physiology. 2009; 296:208–216.
41. Barhoumi T, Kasal D, Li M, Shbat L, Laurant P, Neves M, et al. T regulatory lymphocytes prevent angiotensin II-induced hypertension and vascular injury. Hypertension. 2011; 57:469–476. [PubMed: 21263125]

42. Youn J, Yu H, Lim B, Koh M, Lee J, Chang D, et al. Immunosenescent CD8+ T cells and C-X-C chemokine receptor type 3 chemokines are increased in human hypertension. Hypertension. 2013; 62(1):126–133. [PubMed: 23716586]
43. Harrison D, Guzik T, Lob HE, Madhur MS, Marvar P, Thabet S, et al. Inflammation, immunity, and hypertension. Hypertension. 2011; 57:132–140. [PubMed: 21149826]
44. Rodriguez-Iturbe B, Franco M, Tapia E, Quiroz Y, Johnson R. Renal inflammation, autoimmunity and salt-sensitive hypertension. Clinical and Experimental Pharmacology and Physiology. 2012; 39:96–103. [PubMed: 21251049]
45. Quiroz Y, Johnson R, Rodiguez-Iturbe B. The role of T cells in the pathogenesis of primary hypertension. Nephology Dialysis Transplantation. 2012; 27(S4):iv2–iv5.
46. Panoulas V, Metsios G, Pace A, John H, Treharne G, Banks M, et al. Hypertension in rheumatoid arthritis. Rheumatology. 2008; 47:1286–1298. [PubMed: 18467370]
47. Al-Herz A, Ensworth S, Shojania K, Esdaile J. Cardiovascular risk factor screening in systemic lupus erythematosus. Journal of Rheumatology. 2003; 30:493–496. [PubMed: 12610807]
48. Budman D, Steinberg A. Hypertension and renal disease in systemic lupus erythematosus. Archives of Internal Medicine. 1976; 136:1003–1007. [PubMed: 962443]
49. Sabio J, Vargas-Hitos J, Navarrete-Navarrete N, Mediavilla J, Jimenez-Jaimez J, Diaz-Chamarro A, et al. Prevalence of and factors associated with hypertension in young and old women with systemic lupus erythematosus. Journal of Rheumatology. 2011; 38(6):1026–1032. [PubMed: 21406497] This study directly assessed the prevalence of hypertension in female SLE patients and demonstrated that it is 2–4 times greater in age-matched healthy females.
50. Selzer F, Sutton-Tyrrell K, Fitzgerald S, Tracy R, Kuller L, Manzi S. Vascular stiffness in women with systemic lupus erythematosus. Hypertension. 2001; 37:1075–1082. [PubMed: 11304506]
51. Parra G, Quiroz Y, Salazar J, Bravo Y, Pons H, Chavez M, et al. Experimental induction of saltsensitive hypertension is associated iwth lymphocyte proliferative response to HSP70. Kidney International Supplement. 2008:S55–S59. [PubMed: 19034328]
52. Pons H, Ferrebuz A, Quiroz Y, Romero-Vasquez F, Parra G, Johnson R, et al. Immune reactivity to heat shock protein 70 expressed in the kidney is cause of salt-sensitive hypertension. American Journal of Physiology: Renal Physiology. 2013; 304:289–299. This study provides convincing evidence for HSP70 as a self-antigen that could contibute to the autoimmunity and immune system activation in hypertension.
53. Ishizaka N, Aizawa T, Ohno M, Usui S, Mori I, Tang S, et al. Regulation and localization of HSP70 and HSP25 in the kidney of rats undergoing long-term administration of angiotensin II. Hypertension. 2002; 39:122–128. [PubMed: 11799090]
54. Kleinewietfeld M, Manzel A, Titze J, Kvakan H, Yosef N, Linker R, et al. Sodium chloride drives autoimmune disease by the induction of pathogenic Th17 cells. Nature. 2013; 496:513–517. [PubMed: 23467085]
55. Wu C, Yosef N, Thalhamer T, Zhu C, Xiao S, Kishi Y, et al. Induction of pathogenic TH17 cells by inducible salt-sensing kinase SGK1. Nature. 2013; 496(7446):513–517. [PubMed: 23467085]
56. Mathis KW, Venegas-Pont M, Masterson C, Wasson K, Ryan MJ. Blood pressure in a hypertensive mouse model of SLE is not salt-sensitive. American Journal of Physiology: Regulatory, Integrative and Comparative Physiology. 2011; 301:1281–1285. This study shows that salt sensitivity does not contribute to the hypertension in SLE mice.
57. Kristensen B, Andersen P. Autoantibodies in untreated and treated essential hypertension. Acta Med Scand. 1978; 203:55–59. [PubMed: 305193]
58. Kristensen B, Andersen P, Wiik A. Autoantibodies and vascular events in essential hypertension: a five-year longitudinal study. J Hypertension. 1984; 2:19–24.
59. Gudbrandsson T, Hansson L, Herlitz H, Lindholm L, Nilsson LA. Immunological changes in patients with previous malignant essential hypertension. Lancet. 1981; 1:406–408. [PubMed: 6110039]
60. Wenzel K, Haase H, Wallukat G, Derer W, Bartel S, Homuth V, et al. Potential relevance of alpha (1)-adrenergic receptor autoantibodies in refractory hypertension. PLoS ONE. 2008; 3:e3742. [PubMed: 19011682]

61. Jahns R, Boivin V, Lohse M. Beta(1)-Adrenergic receptor function, autoimmunity, and pathogenesis of dilated cardiomyopathy. Trends in Cardiovascular Medicine. 2006; 16:20–24. [PubMed: 16387626] This describes an important role for autoantibodies in cardiovascular disorders.
62. Xia Y, Kellems R. Angiotensin receptor agonistic autoantibodies and hypertension: Preeclampsia and beyond. Circulation Research. 2013; 113:78–87. [PubMed: 23788505]
63. Dragun D, Muller D, Brasen J, Fritsche L, Nieminen-Kelha M, Dechend R, et al. Angiotensin II type 1-receptor activating antibodies in renal-allograft rejection. New England Journal of Medicine. 2005; 352(6):558–569. [PubMed: 15703421]
64. Pons-Estel G, Alarcon G, Scofield L, Reinlib L, Cooper G. Understanding the epidemiology and progression of systemic lupus erythematosus. Seminar in Arthritis and Rheumatism. 2010; 39(4): 257. This paper describes the current statistics on patients with SLE.
65. Lawrence R, Helmick C, Arnett F, Deyo R, Felson D, Giannini E, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis and Rheumatism. 2013; 41(5):778. [PubMed: 9588729]
66. Chakravarty E, Bush T, Manzi S, Clarke A, Ward M. Prevalence of adult systemic lupus erythematosus in California and Pennsylvania in 2000: estimates obtained using hospitalization data. Arthritis and Rheumatism. 2007; 56(6):2092. [PubMed: 17530651]
67. Mathis KW, Venegas-Pont M, Masterson C, Stewart N, Wasson K, Ryan MJ. Oxidative stress promotes hypertension and albuminuria during the autoimmune disease systemic lupus erythematosus. Hypertension. 2012; 59:673–679. [PubMed: 22291449] This study shows that renal oxidative stress has a causal role in the development of hypertension during SLE.
68. Mathis KW, Venegas-Pont M, Flynn E, Williams J, Maric-Bilkan C, Dwyer T, et al. Hypertension in an experimental model of systemic lupus erythematosus occures independently of the renal nerves. American Journal of Physiology: Regulatory, Integrative and Comparative Physiology. 2013; 301:1286–1292.
69. Ryan MJ, McLemore GR. Hypertension and impaired vascular function in a female mouse model of systemic lupus erythematosus. American Journal of Physiology: Regulatory, Integrative and Comparative Physiology. 2007; 292:736–742.
70. Venegas-Pont M, Manigrasso MB, Grifoni SC, LaMarca BB, Maric C, Racusen LC, et al. Tumor necrosis factor-alpha antagonist etanercept decreases blood pressure and protects the kidney in a mouse model of systemic lupus erythematosus. Hypertension. 2010; 56:643–649. [PubMed: 20696988] This work illustrates the important role of renal cytokines in the pathogensesis of hypertension during SLE.
71. Rudofsky UH, Dilwith RL, Roths JB, Lawrence DA, Kelley VE, Magro AM. Differenses in the occurence of hypertension among (NZB × NZW)F1, MRL-lpr, and BXSB mice with lupus nephritis. American Journal of Pathology. 1984; 116:107–114. [PubMed: 6377906] This study demonstrates that mice with SLE have increased systolic pressure and low plasma renin.
72. Venegas-Pont M, Mathis KW, Iliescu R, Ray WH, Glover P, Ryan M. Blood pressure and renal hemodynamic responses to acute angiotensin II infusion are enhanced in a female mouse model of systemic lupus erythematosus. American Journal of Physiology: Regulatory, Integrative and Comparative Physiology. 2011 Jul; 301(5):1286–1292.
73. Laragh J. Laragh's lessons in pathophysiology and clinical pearls for treating hypertension. American Journal of Hypertension. 2013; 14(9):837–854. [PubMed: 11587148]
74. Obarzanek E, Proschan M, Vollmer W, Moore T, Sacks F, Appel L, et al. Individual blood pressure responses to changes in salt intake: results from the DASH-Sodium trial. Hypertension. 2003; 42(4):459–467. [PubMed: 12953018]
75. Mathis KW, Wallace K, Wasson K, Masterson C, Ryan M. T cells promote the progression of hypertension and renal injury during systemic lupus erythematosus. Hypertension. 2012; 60:A174.
76. Mathis KW, Wallace K, LaMarca B, Ryan M. Humoral immune system activation promotes the development of hypertension. FASEB Journal. 2013; 27:906.4.
77. Seaberg EC, Muñoz A, Lu M, Detels R, Margolick JB, Riddler SA, Williams CM, Phair JP. Association between highly active antiretroviral therapy and hypertension in a large cohort of men followed from 1984 to 2003. AIDS. 2005; 19(9):953–960. [PubMed: 15905677]

78. Stumpf C, Auer C, Yilmaz A, Lewczuk P, Klinghammer L, Schneider M, Daniel WG, Schmieder RE, Garlichs CD. Serum levels of the Th1 chemoattractant interferon-gamma-inducible protein (IP) 10 are elevated in patients with essential hypertension. Hypertens Res. 2011; 34:484–488. [PubMed: 21228779]

79. Jong-Chan Y*, Hee Tae Y*, Beom JL, Myoung JK, Jino L, Dong-Yeop C, Yoon SC, Sang-Hak L, Seok MK, Yangsoo J, Ook JY, Eui-Cheol S, Sungha P. Immunosenescent CD8+ T cells and C-X-C chemokine receptor type 3 chemokines are increased in human hypertension. Hypertension. 2013; 62:126–133. [PubMed: 23716586]

80. Hughson MD, Gobe GC, Hoy WE, Manning RD, Douglas-Denton R, Bertram JF. Associations of glomerular number and birth weight with clinicopathological features of African Americans and whites. Am. J. Kidney Dis. 2008; 52:18–28. [PubMed: 18514988]

81. Heptinstall RH. Renal biopsies in hypertension. Br. Heart J. 1954; 16:133–141. [PubMed: 13160264]

82. Pockley AG, De Faire U, Kiessling R, Lemne C, Thulin T, Frostegard J. Circulating heat shock protein and heat shock protein antibody levels in established hypertension. J. Hypertens. 2002; 20:1815–1829. [PubMed: 12195124]

83. Kunes J, Poirier M, Tremblay J, Hamet P. Expression of HSP70 gene in lymphocytes from normotensive and hypertensive humans. Acta Physiol. Scand. 1992; 146:307–311. [PubMed: 1481687]

84. Lefkos N, Boura P, Boudonas G, Zacharioudaki E, Efthimiadis A, Tsougas M, Epivatianos P. Immunopathogenic mechanisms in hypertension. Am. J. Hypertens. 1995; 8:1141–1145. [PubMed: 8554739]

85. Kronbichler A, Mayer G. Renal involvement in autoimmune connective tissue diseases. BMC Med. 2013; 11:95. [PubMed: 23557013]

86. Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and hypertension: a systematic review and meta-analysis of observational studies. J. Hypertens. 2013; 31(3):433–442. [PubMed: 23249828]

Table 1

Evidence supporting a role for immune system activation in human hypertension	Reference(s)
Restoration of T cell counts in patients with HIV increases the prevalence of hypertension	77
Anti-kidney antibodies are present in the sera of hypertensive patients	6
Immunosuppressive therapy lowers blood pressure in hypertensive patients	22, 23
Proinflammatory cytokines/mediators positively correlate with blood pressure	10, 11, 18, 78, 79
Circulating CD8+ T cells are increased in hypertensive patients	79
Renal lymphocyte infiltration is increased in patients with hypertension	80, 81
Circulating heat shock proteins, known immune modulators, are increased in hypertensive patients	82, 83
Circulating autoantibodies are increased in patients with essential hypertension, refractory hypertension, and preeclampsia	57–60, 63, 84
Immunoadsorption of pathogenic autoantibodies lowers blood pressure in hypertensive patients	60
The prevalence of hypertension is increased in patients with immune-mediated diseases (i.e., systemic lupus, rheumatoid arthritis, psoriasis, scleroderma).	46, 49, 85, 86