Published in final edited form as:

Curr Opin Nephrol Hypertens. 2015 September ; 24(5): 470–474. doi:10.1097/MNH.0000000000000146.

Mechanisms of T Cell Activation and Pathways of Hypertension

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Summary

Significant advancements have been made in the search for antigens and pathways responsible for activation of the adaptive immune response, furthering our understanding of the factors contributing to hypertension and potentially leading to the development of new and more effective therapies.

Keywords

T lymphocytes; hypertension; renal disease; immunity

Introduction

A role for the immune system in hypertension was demonstrated half a century ago; though intensive investigation of this relationship is a recent occurrence. Evidence of the protective influence of immunosuppression to attenuate hypertension has been demonstrated in both humans and experimental animal models; however, the obvious importance of a functional immune system for host survival drastically limits total immune suppression as having therapeutic potential. It is therefore critical to identify and understand specific components of the immune system and the precise immunological mechanisms that pathogenically contribute to hypertension, potentially resulting in a more targeted and fruitful therapeutic approach. This review will primarily focus on the various T lymphocyte subtypes and recent studies that have demonstrated the mechanisms leading to hypertension and associated renal damage.

T lymphocytes in hypertension

Although there are likely many players in the inflammatory contribution to hypertensive pathology, T lymphocytes have been a focus of many laboratories investigating this

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Purpose of review

The role of immune mechanisms to amplify hypertension in patients and animal models has been appreciated for decades. This review briefly summarizes recent studies exploring the mechanistic pathways whereby the immune system participates in hypertension and renal disease.

Recent Findings

Emphasis in this review is placed upon recent studies exploring the role of T cell subtypes, newly-described mechanisms of T cell activation, the identification of potential neoantigens, and environmental influences on immune cell activation.

Conflicts of interest None.

relationship. Contemporary interest in T cells in hypertension and cardiovascular disease can be traced to a study performed by Guzik et al. in 2007 showing the necessity of the presence of T cells for the full development of angiotensin (Ang) II-induced hypertension in mice (1). Since then, a major push to determine T cell-mediated mechanisms of blood pressure modulation has taken place. To determine the role of T cells in hypertension, investigators attempted to delineate the pathogenic T cell subtypes present in relevant tissues (mostly kidney and vasculature) and determine the pathways by which those subtypes caused disease. The understanding of T cell differentiation and subtype function is a dynamic immunological field of investigation unto itself, and novel findings in T cell immunology will continue to aide in our understanding of their role in hypertension. Recent studies have established roles for both cytotoxic (CD8+) T cells and T helper (Th, CD4+) cells in hypertension. Th cells are further subdivided into 4 main subtypes: Th1, Th2, Th17, and Tregs. Each of these subtypes has a distinct function in immune regulation and the investigation of these subtypes in hypertension is underway.

Recent studies suggest a deleterious role for CD8+ T cells in hypertension. Circulating CD8+ T cells in newly diagnosed hypertensive patients expressed significantly higher levels of apoptotic effector molecules, perforin and granzyme B, and proinflammatory cytokines, IFN γ and TNF α , compared to normotensive controls, indicating a heightened proinflammatory state (2). Renal biopsies from patients with hypertensive nephrosclerosis reveal a significant accumulation of CD8+ and CD4+ T cells in the tubulointerstitium compared to normotensive controls – a finding substantiated in experimental models of hypertension. Although the infiltration of T cells (CD4+ and CD8+) in the vasculature and kidneys of hypertensive models is well documented, a recent study by Trott et al. began to delineate their importance. Mice lacking CD8+ T cells (CD8^{-/-}) were protected from Ang II-induced hypertension and vascular dysfunction, whereas mice lacking CD4+ T cells (CD4^{-/-}) were not (3*). Furthermore, CD8^{-/-}, but not CD4^{-/-}, mice were resistant to the antinatriuretic and antidiuretic effects of Ang II and did not exhibit renovascular volume reduction as did the CD4^{-/-} mice.

Although these studies suggest a dominant role for CD8+ T cells in the disturbed renal hemodynamics and vascular dysfunction contributing to the development of hypertension, many studies implicate CD4+ T cells in the modulation of blood pressure. Transfer of CD4+ T cells from placental ischemic rats increased oxidative stress and blood pressure in normal pregnant recipients (4*). Upon stimulation, circulating CD4+ T cells from patients with pulmonary hypertension expressed higher levels of IL-17 than controls, suggesting a polarization of T cells to the pathogenic Th17 phenotype (5*). T regulatory cells (Tregs) suppress immune responses, and alteration of the Th17/Treg ratio has been implicated in many immune-mediated diseases. Experimentally, mineralocorticoid-dependent hypertension alters the Th17/Treg ratio by increasing IL-17 expression and decreasing Foxp3 (Treg-specific transcription factor) expression in the PBMCs, spleen, heart, and kidneys. Specific inhibition of IL-17 reduced arterial hypertension and mineralocorticoid-salt-induced renal and cardiac remodeling (6*).

Sex differences in the development of hypertension may be attributable to differences in T cell function. Male mice have higher blood pressure than females in Ang II-dependent

hypertension; however, this difference is abolished in Rag1^{-/-} mice. Adoptive transfer of WT male, but not WT female, CD3+ cells into male Rag1^{-/-} mice recapitulated Ang II-induced hypertension (7*). Interestingly, in vitro stimulation of WT lymph node mononuclear cells in Th0 (no cytokines) or Th17 polarizing conditions with Ang II resulted in decreased production of IFN γ , TNF α , and IL-17 in female cells but not male cells. These data suggest that Ang II may have anti-inflammatory effects on female T cells, which could mitigate hypertension.

Activation of T lymphocytes

As emphasized previously, the important contribution of T lymphocytes in the pathogenesis of hypertension has been well documented; however, the mechanisms leading to T cell activation remains unclear. Many novel concepts have emerged in an attempt to explain how various hypertensive stimuli result in such activation, including the involvement of the sympathetic nervous system, T cell receptors, humoral immunity, and the production of neoantigens.

Sympathetic Drive/CNS

The central nervous system and sympathetic tone contribute to the development and maintenance of hypertension in both humans and experimental models (8, 9). Recent studies have exposed a potentially important contribution of sympathetic drive in the activation of T lymphocytes during hypertension. The anteroventral third ventricle (AV3V) region of the circumventricular organs (CVO) in the brain processes hormonal signals that influence cardiovascular functions and body fluid regulation. By lesion of the AV3V in mice, Harrison and colleagues have demonstrated that central signals and sympathetic drive are required for Ang II-induced hypertension as well as expression of the early T cell activation marker CD69 (10). Increased dietary salt intake significantly increased sympathetic nerve activity in Sprague-Dawley rats (11). This may arise from elevated cerebrospinal fluid [Na⁺], that when detected by the CVO, results in increased sympathetic drive, potentially via endogenous ouabain (12). Very recent evidence has shown the 'angiogenic cytokine', placental growth factor (PIGF), to be necessary for Ang II-induced hypertension by serving as a neuro-immune link connecting the sympathetic nervous system and the splenic immune system (13**). Activation of PIGF in the spleen is furthermore required for the costimulation of T cells, which were determined to be the major causative players in target organ damage related to hypertension.

Costimulation

Classically, the major histocompatibility complex on antigen-presenting cells (APCs) presents peptides to the T cell receptor (TCR). Following that interaction, a second signal known as costimulation occurs, whereby CD28 on T cells interacts with B7 ligands CD80 and CD86 on APCs. Both signals are required for the activation of T cells. Preventing the interaction between T cells and APCs through inhibition of B7-dependent costimulation by fusion protein CTLA4-Ig blocked either Ang II-induced or deoxycorticosterone acetate (DOCA)-salt-induced models of experimental hypertension (14). Importantly, inhibition of B7/CD28 interaction, either pharmacologically or genetically, blocked T cell activation, T

cell cytokine production, and the migration of T cells to the vascular wall. More recently our laboratory has demonstrated that a functional T cell receptor is necessary for salt-sensitive induced hypertension (15**). Through the use of zinc-finger nuclease technology, the CD3 zeta chain of the TCR was deleted in the Dahl salt-sensitive (SS) rat, and resulted in blunted hypertension and renal damage typically associated with increased salt intake. These studies demonstrate the necessary role of the T cell receptor as well as B7/CD28 interaction in the activation of T cells that ultimately contribute to the pathology associated with hypertension.

Autoimmunity and neoantigens

Recent efforts revealed a significant involvement of B cells and the production of autoantibodies in the development of hypertension. Autoantibodies against the α_1 -adrenergic and β_1 -adrenergic receptor have been shown to pathogenically contribute to various cardiovascular diseases (16, 17). Additionally, there is an increased presence of angiotensin II type 1 receptor agonistic autoantibodies (AT1-AA) in both patients and rodent models of hypertension and pre-eclampsia (18). Mathis et al. showed that depletion of the B cell population by anti-CD20 antibody administration decreased cytokine production and blocked systemic lupus erythematosus (SLE)-induced hypertension and renal damage (19*). It remains to be seen if this pathogenic effect of B cells is limited to this particular model of SLE. Guzik et al. first showed that adoptive transfer of T cells and not B cells recapitulated Ang II-induced hypertension, originally suggesting the dispensability of B cells (1). However, T cells produce cytokines to modulate the function of other immune cells and vice versa, so interplay among immune cells during the development of hypertension is highly plausible. La Marca and colleagues highlighted this interplay in the reduced uterine perfusion pressure (RUPP) model of pre-eclampsia (20). Adoptive transfer of CD4+ T cells isolated from RUPP rats increased MAP of normal pregnant rats; however, simultaneous depletion of B cells with rituximab inhibits the ability of CD4+ RUPP cells to elevate blood pressure. Thus, there appears to be interdependency between T and B cell functionality.

What is the initiating mechanism that triggers this adaptive immune response? The activation of the adaptive immune system implies the presence of an antigen; in the context of chronic diseases such as hypertension, this activation may occur through the loss of self-tolerance by mechanisms involving both humoral and cell-mediated immunity, suggesting hypertension may be an autoimmune disease. Tremendous efforts have gone into the search of a self-antigen, or neoantigen, responsible for the initiation of this immune cascade. It is hypothesized that oxidation, nitrosylation, adduct formation, or posttranslational modifications of proteins create endogenous molecules that are no longer distinguished as self (21).

Initial studies published by Rodriguez-Iturbe's group proposed an autoimmune reaction to a stress-induced molecule, heat shock protein 70 (HSP70), as cause for salt-sensitive hypertension characterized by T cell activation and the generation of regulatory T cells (22). Tolerization experiments and overexpression studies elegantly demonstrated a central and necessary role for HSP70 as a potential antigen in the activation of T cells, modulation of IL-6 and IL-10 production, and development of hypertension. More recently, Kirabo et al. showed that Ang II-induced or DOCA-salt-induced ROS formation in dendritic cells (DCs)

were responsible for the production of isoketal adducts via lipid peroxidation. These isoketal-modified proteins, no longer recognized as self, activated DCs. Moreover scavenging of isoketals by 2-hydroxybenzylamine prevented the immunoreactivity leading to Ang II-induced hypertension and renal damage (23**). Importantly, activated DCs from Ang II-treated mice were sufficient to induce activation, survival, proliferation, and cytokine production of T cells, and were required to elicit hypertension in adoptive transfer studies. Together, these cutting-edge studies unveiled a new pathway explaining some of the potential mechanisms leading to autoimmunity and the development of hypertension and renal damage.

Dietary contributions to T lymphocyte activation in hypertension: Sodium-dependent effects

Since the 1940s, a tremendous amount of studies have been dedicated to understanding the role of salt in hypertension. Some of the first experiments connecting the pathogenesis of hypertension to abnormalities in the immune system were performed in the 1960s (24), and about a decade later, studies first published a role for the immune system in salt-driven hypertension (25). Remarkable technological advances within the past few years have allowed for the dissection of specific immune cell types and molecules contributing to sodium-dependent immune activation. Two recent studies demonstrated a dramatic induction of Th17 polarization in naïve T cells of either murine or human origin when exposed to an elevated sodium concentration (26, 27). In both studies, inhibition of serum- and glucocorticoid-inducible kinase-1 (SGK-1), an enzyme induced by sodium and known to mediate sodium homeostasis, prevented the differentiation to the Th17 phenotype, suggesting a mechanistic pathway that could be therapeutically targeted to prevent salt-induced autoimmunity. Readers are directed to a recently published review discussing the link between increased salt, SGK-1, and Th17 polarization in more depth (28*). Recent data from a human longitudinal study that investigated the effects of long-term salt-intake reduction on immune status demonstrated a decrease in total monocyte numbers that correlated significantly with salt reduction. Although no significant differences were observed in lymphocyte numbers, IL-6 and IL-23 correspondingly decreased with reduced salt intake while IL-10 increased (29*), indicating an association between dietary salt changes, cytokine production, and overall immune status.

Sodium-independent effects

Although evidence clearly shows that salt can drive hypertension and autoimmunity, the contributions of other dietary components cannot be ignored. Our laboratory has shown that isocaloric modification of the sources of dietary protein, sucrose, and fat can affect the degree of pressure elevation in experimental hypertension (30). In particular, substituting casein for wheat gluten as the protein source significantly reduced mean arterial pressure and albumin excretion, while changing the fat source of corn oil to soybean oil exacerbated MAP and albumin excretion in Dahl SS rats. Moreover, increasing the percentage of protein in the diet from 18% to 30% significantly exacerbated salt-induced increases in MAP and albumin/creatinine excretion ratio (31). Correspondingly, the high protein diet resulted in greater T lymphocyte infiltration in the kidney, which together with the increased pressure

and renal damage, was ameliorated upon administration of the immunosuppressant MMF. These studies provided evidence that dietary components independent of salt can greatly impact the hypertensive phenotype in a salt-sensitive model. Further emphasizing this point, Geurts et al. found that Dahl SS rats maintained on a grain-based diet for many generations were less susceptible to high-salt diet-induced hypertension and renal injury compared to Dahl SS maintained on a casein-based diet (32**). Interestingly, subsequent embryo-transfer experiments revealed that the maternal diet during the gestational-lactational period, and not the diet after weaning, substantially contributed to the hypertensive outcome in adult SS rats. Studies exploring the potential differences in immune cell infiltration between Dahl SS rats maintained on both diets are ongoing.

Conclusion

Great advancements have been made in the search for antigens and pathways responsible for activation of the adaptive immune response, including the discovery of HSP70 or modified proteins via isoketal adducts in DCs; however, a specific antigen recognized by the T cell receptor still remains unknown. With important dietary contributions to the complex etiology of hypertension and associated renal damage, deeper understanding of the interplay between the environment and immune system activation will be essential for the development of new and more effective therapies.

Acknowledgments

Funding Sources: DK96859, HL116264, T32HL007792

None.

Financial support and sponsorship

This work was supported by the National Institutes of Health.

References

1. 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):2449–60. [PubMed: 17875676]
2. Youn JC, Yu HT, Lim BJ, Koh MJ, Lee J, Chang DY, et al. Immunosenescent CD8+ T cells and C-X-C chemokine receptor type 3 chemokines are increased in human hypertension. *Hypertension*. 2013; 62(1):126–33. [PubMed: 23716586]
- 3*. Trott DW, Thabet SR, Kirabo A, Saleh MA, Itani H, Norlander AE, et al. Oligoclonal CD8+ T cells play a critical role in the development of hypertension. *Hypertension*. 2014; 64(5):1108–15. This study demonstrated that CD8+, and not CD4+ T cells, are required for Ang II-induced hypertension. Furthermore, CD8^{-/-} mice were resistant to the antinatriuretic and antidiuretic effects of Ang II. [PubMed: 25259750]
- 4*. Wallace K, Cornelius DC, Scott J, Heath J, Moseley J, Chatman K, et al. CD4+ T cells are important mediators of oxidative stress that cause hypertension in response to placental ischemia. *Hypertension*. 2014; 64(5):1151–8. Through adoptive transfer studies, this article highlighted the importance of CD4+ T cells in the development of oxidative stress and high blood pressure during pre-eclampsia. [PubMed: 25259742]
- 5*. Hautefort A, Girerd B, Montani D, Cohen Kaminsky S, Price L, Lambrecht BN, et al. Th17 polarization in pulmonary arterial hypertension. *Chest*. 2014 This is the first study to demonstrate

polarization of T cells to the pathogenic Th17 phenotype in patients with pulmonary arterial hypertension.

- 6*. Amador CA, Barrientos V, Pena J, Herrada AA, Gonzalez M, Valdes S, et al. Spironolactone decreases DOCA-salt-induced organ damage by blocking the activation of T helper 17 and the downregulation of regulatory T lymphocytes. *Hypertension*. 2014; 63(4):797–803. This study showed that the DOCA-salt model of hypertension alters the Th17/Treg ratio, and inhibition of IL-17 reduced arterial hypertension and prevented cardiac remodeling. [PubMed: 24420551]
- 7*. Pollow DP, Uhrlaub J, Romero-Aleshire MJ, Sandberg K, Nikolich-Zugich J, Brooks HL, et al. Sex differences in T-lymphocyte tissue infiltration and development of angiotensin II hypertension. *Hypertension*. 2014; 64(2):384–90. This article highlights that the sex differences observed in hypertension may be due to difference in T cell function, since transfer of male, but not female, T cells recapitulated Ang II-induced hypertension in Rag1^{-/-} mice. [PubMed: 24890822]
8. Guyenet PG. The sympathetic control of blood pressure. *Nature Reviews Neuroscience*. 2006; 7(5):335–46. [PubMed: 16760914]
9. Maranon RO, Lima R, Spradley FT, do Carmo JM, Zhang H, Smith A, et al. Roles for the sympathetic nervous system, renal nerves, and CNS melanocortin-4 receptor in the elevated blood pressure in hyperandrogenemic female rats. *American Journal of Physiology Regulatory, Integrative and Comparative Physiology*. 2015 ajpregu 00411 2014.
10. Marvar PJ, Thabet SR, Guzik TJ, Lob HE, McCann LA, Weyand C, et al. Central and peripheral mechanisms of T-lymphocyte activation and vascular inflammation produced by angiotensin II-induced hypertension. *Circulation Research*. 2010; 107(2):263–70. [PubMed: 20558826]
11. Fujita M, Ando K, Kawarazaki H, Kawarasaki C, Muraoka K, Ohtsu H, et al. Sympathoexcitation by brain oxidative stress mediates arterial pressure elevation in salt-induced chronic kidney disease. *Hypertension*. 2012; 59(1):105–12. [PubMed: 22083162]
12. Blaustein MP, Leenen FH, Chen L, Golovina VA, Hamlyn JM, Pallone TL, et al. How NaCl raises blood pressure: a new paradigm for the pathogenesis of salt-dependent hypertension. *American Journal of Physiology Heart and Circulatory Physiology*. 2012; 302(5):H1031–49. [PubMed: 22058154]
- 13*. Carnevale D, Pallante F, Fardella V, Fardella S, Iacobucci R, Federici M, et al. The angiogenic factor PIGF mediates a neuroimmune interaction in the spleen to allow the onset of hypertension. *Immunity*. 2014; 41(5):737–52. This study revealed that the ‘angiogenic cytokine’ placental growth factor serves as a link connecting the sympathetic nervous system and the splenic immune system. [PubMed: 25517614]
14. Vinh A, Chen W, Blinder Y, Weiss D, Taylor WR, Goronzy JJ, et al. Inhibition and genetic ablation of the B7/CD28 T-cell costimulation axis prevents experimental hypertension. *Circulation*. 2010; 122(24):2529–37. [PubMed: 21126972]
- 15*. Rudemiller N, Lund H, Jacob HJ, Geurts AM, Mattson DL. PhysGen Knockout P. CD247 modulates blood pressure by altering T-lymphocyte infiltration in the kidney. *Hypertension*. 2014; 63(3):559–64. Through zinc finger nuclease technology, this is the first study to demonstrate genetic manipulation of the T cell receptor in rats, resulting in blunted amplification of salt-induced hypertension and renal damage. [PubMed: 24343121]
16. Jahns R, Boivin V, Lohse MJ. beta(1)-Adrenergic receptor function, autoimmunity, and pathogenesis of dilated cardiomyopathy. *Trends in Cardiovascular Medicine*. 2006; 16(1):20–4. [PubMed: 16387626]
17. Luther HP, Homuth V, Wallukat G. Alpha 1-adrenergic receptor antibodies in patients with primary hypertension. *Hypertension*. 1997; 29(2):678–82. [PubMed: 9040456]
18. Xia Y, Kellems RE. Angiotensin receptor agonistic autoantibodies and hypertension: preeclampsia and beyond. *Circulation Research*. 2013; 113(1):78–87. [PubMed: 23788505]
- 19*. Mathis KW, Wallace K, Flynn ER, Maric-Bilkan C, LaMarca B, Ryan MJ. Preventing autoimmunity protects against the development of hypertension and renal injury. *Hypertension*. 2014; 64(4):792–800. This study observed decreased cytokine production and attenuation of systemic lupus erythematosus-induced hypertension by preventing autoimmunity through B cell depletion. [PubMed: 25024282]

20. Novotny SR, Wallace K, Heath J, Moseley J, Dhillon P, Weimer A, et al. Activating autoantibodies to the angiotensin II type I receptor play an important role in mediating hypertension in response to adoptive transfer of CD4⁺ T lymphocytes from placental ischemic rats. *American Journal of Physiology Regulatory, Integrative and Comparative Physiology*. 2012; 302(10):R1197–201.
21. Harrison DG, Guzik TJ, Lob HE, Madhur MS, Marvar PJ, Thabet SR, et al. Inflammation, immunity, and hypertension. *Hypertension*. 2011; 57(2):132–40. [PubMed: 21149826]
22. Pons H, Ferrebuz A, Quiroz Y, Romero-Vasquez F, Parra G, Johnson RJ, 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(3):F289–99. [PubMed: 23097471]
- 23*. Kirabo A, Fontana V, de Faria AP, Loperena R, Galindo CL, Wu J, et al. DC isoketal-modified proteins activate T cells and promote hypertension. *The Journal of Clinical Investigation*. 2014; 124(10):4642–56. This article suggests that isoketals modified in dendritic cells via ROS production are no longer recognized as self, and thereby act as a neoantigen inducing cytokine production and activation of T cells. [PubMed: 25244096]
24. White FN, Grollman A. Autoimmune Factors Associated with Infarction of the Kidney. *Nephron*. 1964; 1:93–102. [PubMed: 14248727]
25. Svendsen UG. Evidence for an initial, thymus independent and a chronic, thymus dependent phase of DOCA and salt hypertension in mice. *Acta Pathologica et Microbiologica Scandinavica Section A, Pathology*. 1976; 84(6):523–8.
26. Kleinewietfeld M, Manzel A, Titze J, Kvakana H, Yosef N, Linker RA, et al. Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells. *Nature*. 2013; 496(7446): 518–22. [PubMed: 23467095]
27. Wu C, Yosef N, Thalhimer T, Zhu C, Xiao S, Kishi Y, et al. Induction of pathogenic TH17 cells by inducible salt-sensing kinase SGK1. *Nature*. 2013; 496(7446):513–7. [PubMed: 23467085]
- 28*. Binger KJ, Linker RA, Muller DN, Kleinewietfeld M. Sodium chloride, SGK1, and Th17 activation. *Pflugers Archiv : European Journal of Physiology*. 2015; 467(3):543–50. In-depth review discussing elevated salt, serum- and glucocorticoid-inducible kinase-1 (SGK-1), and the differentiation and aberrant activation of Th17 cells. [PubMed: 25471348]
- 29*. Yi B, Titze J, Rykova M, Feurecker M, Vassilieva G, Nichiporuk I, et al. Effects of dietary salt levels on monocytic cells and immune responses in healthy human subjects: a longitudinal study. *Translational Research : the Journal of Laboratory and Clinical Medicine*. 2014 This recent human longitudinal study examined the effects of long-term salt-intake reduction and changes in the immune system. A reduction in total monocyte number as well as cytokine production was observed in subjects maintained on a lower-salt diet.
30. Mattson DL, Meister CJ, Marcelle ML. Dietary protein source determines the degree of hypertension and renal disease in the Dahl salt-sensitive rat. *Hypertension*. 2005; 45(4):736–41. [PubMed: 15699463]
31. De Miguel C, Lund H, Mattson DL. High dietary protein exacerbates hypertension and renal damage in Dahl SS rats by increasing infiltrating immune cells in the kidney. *Hypertension*. 2011; 57(2):269–74. [PubMed: 21173345]
- 32*. Geurts AM, Mattson DL, Liu P, Cabacungan E, Skelton MM, Kurth TM, et al. Maternal diet during gestation and lactation modifies the severity of salt-induced hypertension and renal injury in Dahl salt-sensitive rats. *Hypertension*. 2015; 65(2):447–55. This study highlighted the important sodium-independent dietary contributions to hypertension, where Dahl SS rats maintained on a grain-based diet were less susceptible to salt-induced hypertension and renal damage compared to Dahl SS rats maintained on a casein-based diet. [PubMed: 25452472]

Key Points

- A link between hypertension and the immune system has been well defined throughout the literature.
- There is specific interest in uncovering mechanisms implicated in the activation of the adaptive immune response, including pathways involving the sympathetic nervous system, the T cell receptor, autoimmunity, and neoantigens.
- Recent experimental data suggests a potential role for diet-related environmental factors on immune cell activation and the progression of hypertension.