Published in final edited form as:

Annu Rev Physiol. 2018 February 10; 80: 283–307. doi:10.1146/annurev-physiol-021317-121134.

Salt, Hypertension, and Immunity

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Abstract

The link between inappropriate salt retention in the kidney and hypertension is well recognized. However, growing evidence suggests that the immune system can play surprising roles in sodium homeostasis, such that the study of inflammatory cells and their secreted effectors has provided important insights into salt sensitivity. As part of the innate immune system, myeloid cells have diverse roles in blood pressure regulation, ranging from prohypertensive actions in the kidney, vasculature, and brain, to effects in the skin that attenuate blood pressure elevation. In parallel, T lymphocyte subsets, as key constituents of the adaptive immune compartment, have variable effects on renal sodium handling and the hypertensive response, accruing from the functions of the cytokines that they produce. Conversely, salt can directly modulate the phenotypes of myeloid and T cells, illustrating bidirectional regulatory mechanisms through which sodium and the immune system coordinately impact blood pressure. This review details the complex interplay between myeloid cells, T cells, and salt in the pathogenesis of essential hypertension.

Keywords

sodium; macrophage; monocyte; T cells; dendritic cells; cytokines

INTRODUCTION

Hypertension afflicts more than 1 billion people worldwide. Despite hypertension's prevalence, complete blood pressure control remains elusive in the majority of hypertensive patients (1). Because chronic hypertension is a key risk factor for stroke, myocardial infarction, heart failure, and kidney failure, the improvement of medical therapies for hypertension is critical to the reduction of preventable mortality and morbidity (2, 3). Whereas the need is clearly defined, an incomplete understanding of the pathogenesis of essential hypertension has complicated attempts to develop more efficacious medications. The study of the effects of key cardiovascular control centers, including the kidney, vasculature, central nervous system (CNS), and more recently, the skin, has yielded key insights into the mechanisms responsible for the generation of hypertension (4, 5). However,

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

elucidating the interplay between cardiovascular control tissues in the determination of blood pressure will be critical for translational advances to mitigate the global burden of this disease.

Though many factors contribute to blood pressure regulation, the importance of sodium retention in the pathogenesis of hypertension is a consistent and recurring theme (5–7). Dahl (8, 9) first reported the correlation between dietary salt ingestion and blood pressure in humans. This group found that lowering dietary sodium could reduce blood pressure. Guyton (10, 11) later hypothesized that the kidney was crucial in mediating this relationship between salt and hypertension. He argued that, through its functions to regulate volume homeostasis and sodium reabsorption, the kidney could preserve normal blood pressure via pressure natriuresis. Consequently, interference with this process could permit sustained blood pressure elevation. Nevertheless, salt sensitivity is not ubiquitous in hypertension, and specific populations have enhanced susceptibility to salt-sensitive hypertension (12–15). The processes that render some populations more salt sensitive than others are not completely clear but involve impaired renal excretion of sodium just as Guyton predicted (16). More recently, the immune system has also emerged as an important mediator of salt-sensitive hypertension (17–19). As a result, several laboratories including our own have attempted to describe mechanisms through which immune responses may contribute to hypertension and salt sensitivity.

The immune system can be considered in two functional compartments. In a simplified paradigm, the innate immune system mounts rapid, but nonspecific, responses to a wide array of pathogens, after which the adaptive immune system initiates slower, but antigen-specific, responses. Both arms have been implicated as contributors to the development of hypertension (20–22). Early suggestions of a connection between inflammation and hypertension arose from studies on kidney biopsy specimens, which demonstrated the accumulation of immune cells in the kidney in hypertension (23, 24). Subsequent studies in rodents found that the transfer of these immune cells from hypertensive animals could lead to the development of hypertension in previously normotensive animals (25). Since this early work, immune suppression has been found to impede the development of salt-sensitive hypertension and resultant target organ damage in the setting of renin-angiotensin system (RAS) activation (26, 27). The goal of this review is to outline the actions of key cells in the innate and adaptive immune systems—myeloid and T cells, respectively—in mediating hypertension and salt sensitivity.

REGULATION OF BLOOD PRESSURE BY MYELOID CELLS

Overview

Cells of myeloid lineage, including monocytes, macrophages, dendritic cells (DCs), and granulocytes, are critical to the function of the innate immune system, and numerous studies have demonstrated their involvement in hypertension (28). Pathologic assessment of rat kidneys illustrates that myeloid cells accumulate in the kidney during hypertension (29). Circulating monocytes in hypertensive humans have an enhanced proinflammatory phenotype compared to normotensive controls (30), leading to increased serum concentrations of inflammatory cytokines (31–33). In response to angiotensin II (Ang II),

the key effector of RAS-induced hypertension, hematopoietic stem cells (HSCs) increase proliferation and differentiation into proinflammatory monocytes in the bone marrow (34, 35). Furthermore, activation of type I Ang II (AT₁) receptors produces hemodynamic injury (36) that leads to the recruitment of circulating monocytes into key effector tissues in hypertension, including the heart, vasculature, and kidney (27, 37, 38). Inflammatory cytokines and reactive oxygen species (ROS) produced by these cells may induce vascular endothelial dysfunction and impair renal sodium excretion, resulting in blood pressure elevation (21).

In the classical paradigm, myeloid precursor cells in the bone marrow differentiate into promonocytes, which then enter the peripheral circulation to become monocytes. During inflammation, blood monocytes may then extravasate into injured tissues where they may further differentiate into macrophages (39). Macrophages are resident tissue phagocytes that have traditionally been described as having one of least two phenotypes: M1 (classically activated) and M2 (alternatively activated) (40). M1 macrophages exacerbate inflammation by producing ROS and proinflammatory cytokines, notably tumor necrosis factor- α (TNF- α) and interleukin-1 beta (IL-1 β). Conversely, M2 macrophages are largely anti-inflammatory and mediate tissue repair by secreting IL-10 and transforming growth factor-beta (TGF- β) (41, 42). Once polarized, macrophages remain plastic, retaining their ability to differentiate into other phenotypes following appropriate stimulation (43). More recent work has established that the M1–M2 dichotomy in macrophage phenotype does not adequately describe the full range of macrophage functions and that macrophages can exhibit a broad spectrum of phenotypes that depend on the specific activating stimulus (44). The following sections discuss the tissue-specific role of myeloid cells in hypertension.

In the Kidney

Ang II is a vasoactive peptide that promotes sodium reabsorption in the kidney nephron. As such, chronic Ang II infusion is commonly utilized as a rodent model of RAS-induced hypertension and consequent end-organ damage (45). Employing this approach in rats, Ozawa et al. (37) found that, after 12 days of Ang II infusion, rats had increased macrophage infiltration in the renal interstitium along with elevated blood pressure, interstitial fibrosis, and preglomerular fibrosis compared to sham controls. They further noted that macrophage infiltration persisted several days after cessation of Ang II infusion. Hypertension could be reestablished with a high-salt diet (HSD) after discontinuing Ang II, and the administration of mycophenolate mofetil with Ang II prevented this response, suggesting that macrophages play a key role in salt-sensitive hypertension (26). In mice, deficiency of a critical receptor for monocyte recruitment into injured tissue, CC chemokine receptor 2 (CCR2) (46, 47), during Ang II-dependent hypertension limits the accumulation of macrophages in the kidney, resulting in attenuated local oxidative stress and fibrosis (48). Thus, macrophages mediate both salt sensitivity and consequent hypertensive nephropathy.

Global RAS activation clearly induces renal inflammation. However, immune cells express the AT₁ receptor (49, 50), and several studies demonstrate that activation of the AT₁ receptor directly on macrophages may dampen the RAS-induced inflammatory response. Unlike humans, rodents have two AT₁ receptor isoforms, AT_{1a} and AT_{1b}. As AT_{1a} predominates in

most tissues, it is considered most homologous to the human AT₁ receptor (51, 52). Peritoneal macrophages from animals lacking the AT_{1a} receptor have enhanced expression of proinflammatory phenotypic markers (monocyte chemoattractant protein, TNF- α , IL-1 β) and reduced expression of anti-inflammatory phenotypic markers [mannose receptor (CD206), Ym-1, TGF- β , IL-10, decoy IL-1R], suggesting that AT₁ receptor activation on macrophages suppresses proinflammatory polarization (53). These effects on macrophage polarization may lead to the protective actions of immune cell AT₁ receptor activation. For example, bone marrow chimeras selectively deficient in the AT₁ receptor (*Agtr1a*^{-/-}) have worsened kidney fibrosis following unilateral ureteral obstruction, and AT₁ receptor deficiency or blockade on bone marrow-derived macrophages (BMDMs) drastically impairs their phagocytic capacity (54).

In our hands, using chronic Ang II infusion, we found that *Agtr1a*^{-/-} bone marrow chimeras had exacerbated blood pressure elevation, albuminuria, and accumulation of T cells and macrophages in the kidney compared to wild-type (WT) transplant controls (55). In subsequent experiments, we have utilized Cre-*lox* conditional gene targeting to selectively deplete the AT_{1a} receptor from lysozyme M-expressing (LysM⁺) myeloid cells [“macro knockout (KO)”]. LysM is expressed by activated monocytes/macrophages, allowing the study of activated macrophage functions in pathologic states such as hypertension (56). Macro KO animals had enhanced expression of macrophage proinflammatory cytokines TNF- α and IL-1 β . Furthermore, mice with AT_{1a}-deficient macrophages developed more severe kidney tubular damage and fibrosis in response to either 28 days of Ang II-induced hypertension or ureteral obstruction (57). These findings bolster the notion that AT₁ receptor activation on macrophages blunts kidney damage and fibrosis during RAS activation by dampening proinflammatory macrophage differentiation.

Both Dahl salt-sensitive rats and a subset of hypertensive humans experience increased blood pressure, albuminuria, and infiltration of macrophages and T cells in the kidneys in response to increased dietary sodium (58). Furthermore, canonical proinflammatory macrophage cytokines, TNF- α and IL-1 β , both independently influence renal sodium handling in response to RAS activation. Experiments with TNF-deficient animals have shown that TNF- α potentiates renal sodium reabsorption in the kidney's thick ascending limb via nitric oxide synthase 3 (NOS3) suppression (59). In concordance with this, our group found that selective TNF deficiency in the kidney through murine cross-transplantation attenuated the chronic hypertensive response (60). Similarly, mice deficient in the IL-1 receptor are partially protected from RAS-dependent hypertension. Our group determined that IL-1 receptor activation decreases the accumulation of NO-expressing macrophages in the kidney and consequently reduces inhibition of the NKCC2 sodium cotransporter by NO, leading to increased renal salt retention (61).

We have previously reported that selective AT₁ receptor deficiency in the kidney can attenuate RAS-induced hypertension, cardiac hypertrophy, and kidney injury and inflammation (62, 63). In aggregate, the preclinical data indicate that global RAS activation is largely inflammatory through activation of AT₁ receptors in the kidney and other target organs. We posit that the resultant target organ damage invokes secondary immune activation, which leads to the production of proinflammatory cytokines TNF- α and IL-1 β

from infiltrating mononuclear cells. In turn, these cytokines mediate hypertension and salt sensitivity, in part through impairment of renal sodium handling. By contrast, AT₁ receptor stimulation directly on macrophages may provide a feedback mechanism to temper pathogenic effects of inappropriate RAS activation in the target organ (Figure 1*a*).

In the Vasculature

The arterial network regulates blood pressure primarily via contraction and relaxation, which determines the pressure against the vessel walls. Several preclinical studies have outlined the actions of myeloid cells in the vasculature during hypertension, similar to those found in the kidney. For example, mice lacking the monocyte/macrophage chemotactic factor, macrophage colony-stimulating factor (m-CSF) (64, 65), have a deficiency in monocytes and macrophages secondary to the osteopetrotic mutation in the *m-CSF* gene (*op/op*) (66–68). These animals are partially protected from vascular endothelial dysfunction, remodeling, and oxidative stress during Ang II-dependent hypertension (69). Similar effects in the vasculature were noted in *op/op* mice in response to the deoxycorticosterone acetone (DOCA)-salt model of hypertension (70). Finally, selective ablation of LysM⁺ macrophages and monocytes with a diphtheria toxin (DTX) strategy blunts the hypertensive response, limits vascular endothelial and smooth muscle dysfunction, and diminishes vascular formation of ROS. Granulocytes also express LysM; however, only transfer of WT CD11b⁺ monocytes and not WT Gr1⁺ neutrophils into LysM⁺ mice restores Ang-II induced hypertension, vascular dysfunction, and ROS generation (38). Mechanistically, LysM⁺ monocytes can amplify production of ROS by uncoupling NOS3, triggering further increases in vascular oxidative stress and hypertension (71). Thus, the very functions of monocytes that provide innate immunity against invading microorganisms can inappropriately elevate blood pressure in the sterile condition, which is consistent with an evolutionary incentive for these cells to protect against circulatory collapse during infection.

Considerable information is now emerging to elucidate the sources of myeloid cells and their downstream effectors involved in the hypertensive response. For example, fate mapping of HSCs has challenged the previously held notion that all resident tissue macrophages are derived from circulating blood monocytes (72). Systemic RAS-activation stimulates monocytes to migrate from the spleen to vascular subendothelium, a necessary step in mediating vascular injury (73, 74). Among the myeloid cell effectors, TNF- α , a key mediator of monocyte/macrophage-induced inflammation, plays an important role in hypertensive vascular pathology. TNF-dependent activation of nuclear factor-kappa B (NF- κ B) proinflammatory signaling and NADPH oxidase stimulates ROS generation and impairs NO production in the vasculature, resulting in deterioration of vascular endothelial function and increased susceptibility to hypertensive stimuli (75–78). Global RAS-activation also drives generation of ROS through enhanced expression of NOS1 and NOS2 from vascular smooth muscle and endothelial cells, respectively (79, 80). Moreover, myeloid-specific deletion of NOS2 has highlighted a function of myeloid NOS2 to regulate basal blood pressure by limiting the bioavailability of endothelial-derived NO (81). Thus, myeloid cells derived from multiple cellular compartments engage in blood pressure homeostasis via actions in the vasculature, producing both ROS and inflammatory cytokines that contribute to vascular dysfunction and consequent blood pressure elevation (Figure 1*b*).

In the Nervous System

Myeloid cells and their canonical inflammatory cytokines acting within the nervous system contribute to the pathogenesis of hypertension. Increased inflammation in cardioregulatory centers in the brain has been associated with enhanced activation of the sympathetic nervous system, resulting in an increase in blood pressure, whereas inhibition of this inflammation ameliorates hypertension (82). Conversely, the sympathetic nervous system innervates the bone marrow (83), releasing neurotransmitters that impact the mobilization and release of HSCs into the peripheral circulation (84–87). In mature innate immune cells, sympathetic activation favors enhanced proinflammatory responses (88). For example, renal denervation inhibits myeloid cell activation and mitigates renal inflammation in Ang II-induced hypertension (89). Finally, in some human hypertensive patients, renal denervation similarly leads to diminished blood pressure, inhibited monocyte activation, and reduced serum proinflammatory markers (90). However, these clinical studies cannot discriminate an indirect effect of blood pressure reduction after renal nerve ablation to secondarily attenuate innate immunity invoked by hemodynamic injury in target organs from a direct effect of denervation to favorably alter myeloid cell function.

Microglia are derived from primitive macrophages originating from the embryonic yolk sac (91) and function as the primary innate immune cell in the CNS. Ablation of microglia through intracerebroventricular administration of DTX into transgenic CD11b-diphtheria toxin receptor (DTR) mice reduces neuroinflammation and blunts the increase in blood pressure in multiple hypertension models. Underpinning this physiologic effect, microglia depletion reduces glutamate receptor expression in the paraventricular nucleus (PVN), plasma vasopressin levels, and kidney norepinephrine concentrations, indicating that microglia mediate increases in systemic blood pressure through modulation of neuronal excitation (92). Work from other groups corroborated these findings. For example, inhibition of microglia activation in the PVN of the hypothalamus mitigates hypertension, sympathetic activation, and peripheral inflammation (93, 94).

Adding to the complexity through which myeloid cells influence blood pressure, signals from circulating myeloid cells can reach the CNS to modulate sympathetic outflow. For example, bone marrow transplanted from spontaneously hypertensive rats into normotensive rats enhances neuroinflammation and sympathetic nerve activation in Ang II-induced hypertension, likely via CCL2-mediated extravasation of proinflammatory mononuclear cells from the bone marrow into the PVN with consequent microglial activation (94). To permit such trafficking of circulating immune cells into the CNS, hypertension increases the permeability of the blood-brain barrier, permitting systemic Ang II to enter the cerebral circulation (95). Because of this leakiness in the blood-brain barrier, Ang II can activate the AT₁ receptor on perivascular macrophages (PVMs) in the brain (CD206⁺CD45^{hi}CD11b⁺), which, in contrast to our findings with intrarenal macrophages, promotes pathogenic actions of the PVMs to instigate neurovascular dysfunction through ROS production via NOX2 during chronic hypertension (96). Thus, myeloid cells intrinsic to the CNS or invading from systemic circulation can exacerbate hypertension by augmenting sympathetic outflow.

Rats with hypernatremia secondary to diabetes insipidus exhibit increased sympathetic nerve activity and elevated arterial pressure via activation of sodium-sensing neurons in the

forebrain (97). Similarly, in comparison with rats receiving water to drink, rats drinking 0.9% NaCl (sodium chloride) had enhanced renal sympathetic activation and blood pressure elevation in response to stimulation of sympathetic-regulatory neurons in the rostral ventrolateral medulla (98). Although it is known that increased salt intake can result in acute elevations of serum sodium that ultimately enhance sympathetic activity and raise blood pressure, the degree of hypernatremia necessary for these mechanisms to occur remains unclear. Additionally, whether these mechanisms of sympathetic activation remain relevant in chronic serum sodium elevation needs to be further studied. However, it is posited that chronic elevations in salt intake may induce neuroplastic changes that exacerbate increases in sympathetic activity and intensify the hypertensive response caused by other prohypertensive stimuli (e.g., RAS activation) (5). Whether increased tonicity exerts these central actions in part via salt's recently reported effects on macrophage polarization will require elucidation (99). Activated myeloid cells infiltrate key areas in the brain involved in sympathetic activation during the hypertensive response (92, 94), and the macrophage effector TNF- α acts in the CNS to potentiate blood pressure elevation by increasing salt appetite (100). Thus, myeloid cells exert myriad effects in the brain to instigate salt-sensitive hypertension. Future studies are needed to further describe how cytokines secreted from myeloid cells might serve as interlocutors in the CNS between elevated salt intake and hypertension (Figure 1c).

In the Skin

As a large interstitial reservoir for sodium storage, the skin may play a previously overlooked role in blood pressure homeostasis and salt sensitivity. In rodents fed a HSD, sodium accumulates in the skin, creating a local microenvironment that is hypertonic relative to plasma (101). Similarly, ^{23}Na -magnetic resonance imaging has revealed significant stores of sodium in the skin and skeletal muscle in humans (102, 103). Furthermore, hypertensive patients have elevated skin sodium content compared to normotensive controls, suggesting that increased skin sodium storage is associated with blood pressure elevation (102). Interestingly, much of this sodium appears to be osmotically inactive and bound to negatively charged glycosaminoglycans in the skin interstitium (104). Accordingly, recent studies by Nikpey et al. (102) comparing rats given either a low-salt, high-salt, or DOCA-salt diet suggest that interstitial and lymphatic fluid adjacent to the skin remains isotonic despite increased sodium intake and associated expansion in skin sodium stores. However, the authors found that increased dietary sodium was associated with enhancement of an osmotic gradient from the epidermis to the dermis in skin formed, in part, by alterations in urea concentration (105). These findings suggest hypertonicity in the skin may be maintained in a mechanism similar to the countercurrent multiplication seen in the kidney.

Higher stores of sodium in the skin and muscle are associated with decreased circulating levels of vascular endothelial growth factor-C (VEGF-C). VEGF-C may protect against salt sensitivity by stimulating angiogenesis of dermal lymphatic vessels to mobilize nonvascular sodium reserves back into the circulation for possible excretion by the kidney (106). Macrophages are known to stimulate lymph vessel formation (107, 108), and in landmark studies from Titze and colleagues (109, 110), macrophages augmented susceptibility to salt-sensitive hypertension by provoking VEGF-C-dependent lymphangiogenesis. In response to

osmotic stress, enhanced expression of the transcription factor tonicity-responsive enhancer-binding protein (TONEBP/NFAT5) increases expression of VEGF-C by myeloid cells (111). Depletion of these VEGF-C-producing mononuclear phagocytes via clodronate administration prior to the ingestion of a HSD provokes salt sensitivity by preventing the hyperplasia of the lymph capillary network that would otherwise limit interstitial salt accumulation in the skin (112). Moreover, TONEBP/NFAT5 deletion and VEGF-C receptor blockade induces salt-sensitive hypertension in mice, substantiating the important role of skin lymphatic electrolyte homeostasis as mediated by these macrophage-derived proteins in blood pressure regulation (101, 113).

Experiments with other rodent models corroborate that the skin participates in sodium homeostasis and blood pressure regulation. For example, deficiency of the inflammatory chemokine-scavenging receptor atypical chemokine receptor 2 increases numbers of VEGF-C⁺ macrophages near lymph vessels, the density of lymphatic vessels in the skin, and the drainage of skin interstitial fluid with consequent protection from salt-sensitive hypertension (114). Similarly, macrophage-specific deletion of cyclooxygenase-2, a key enzyme catalyzing prostaglandin synthesis, impairs VEGF-C-dependent lymphangiogenesis in the skin and exacerbates hypertension in response to a HSD (115). As TONEBP/NFAT5 in macrophages also augments production of NO via NOS2, and NO drives vasodilation and sodium excretion in the kidney, the mechanisms elucidated in the previously described studies may also be relevant to myeloid homeostatic functioning in the kidney to temper salt sensitivity (61, 99) (Figure 1*d*). For instance, enhanced skin sodium stores are associated with increased contractility of skin vessels in response to Ang II, which may potentially enhance peripheral resistance and lead to blood pressure elevation (116). However, further research is needed to clarify the exact mechanisms by which skin sodium accumulation induces blood pressure elevation and how mobilization of these sodium stores mitigates salt-sensitive hypertension.

Effects of Salt On Myeloid Cell Differentiation

Although the previous sections have detailed mechanisms through which myeloid cells in several cardiovascular control centers modulate salt sensitivity, an emerging literature now highlights a converse paradigm in which high salt concentrations influence the polarization of myeloid cells. In humans, short-term increases in dietary salt have been found to increase circulating proinflammatory CD14⁺⁺CD16⁻ monocytes (117). As discussed below, elegant rodent experiments have characterized mechanisms through which changes in tonicity impact myeloid cell differentiation.

BMDMs cultured in lipopolysaccharide (LPS) undergo polarization into a proinflammatory phenotype, M(LPS). M(LPS) incubated in high-salt media, with a tonicity approximating that found in the dermal interstitium of HSD-fed rodents (101, 118), have an enhanced proinflammatory response with exaggerated NOS2-dependent NO production that accrues from increased p38 mitogen-activated protein kinase (p38/MAPK)-dependent TONEBP/NFAT5 activation (99). NaCl-induced hyperosmotic stress also activates the NLRP3 and NLRC4 inflammasomes in BMDMs, resulting in cleavage of IL-1 β and caspase-1 to their active forms (119). In addition to driving proinflammatory differentiation of macrophages,

high salt also suppresses the IL-4- and IL-13-dependent activation of macrophages toward an anti-inflammatory phenotype (118). On a transcriptional level, high salt can increase and decrease expression of proinflammatory and anti-inflammatory genes, respectively, in BMDMs, producing the unique M(Na) phenotype (120) (Figure 2). Rodent experiments suggest that HSD-induced skin sodium storage improves host defenses against cutaneous leishmaniasis (99). Thus, accumulation of salt in the dermal interstitium may improve innate immunity but with adverse effects on the capacity for local wound healing.

A Note On Dendritic Cells

Although much of the work studying myeloid cells in hypertension has been focused on monocytes and macrophages, DCs also contribute to the pathogenesis of hypertension. DCs link the actions of the innate and adaptive immune systems, as they are innate immune cells of myeloid cell lineage that serve as potent activators of T lymphocytes via antigen presentation (121, 122). Initial development of DCs takes place in the bone marrow. DCs then migrate to other tissues to act as sentinels by scanning their surroundings for evidence of tissue damage and antigens. Upon encountering antigen, DCs mature into immune stimulatory effector cells. They then capture, process, and present antigens on major histocompatibility complexes class I and II to T cell receptors (TCRs) (123). This interaction between DCs and T lymphocytes serves as a first signal for T cell activation. However, full T cell activation requires costimulatory signals. Most commonly, this second signal involves the interaction of B7 ligands CD80 or CD86 on DCs and CD28 on T cells. However, interaction between CD70 on DCs and CD27 on T cells has been shown to be important in the formation of memory T cells (21, 124).

Human DCs have been categorized into three main subtypes. Derived from bone marrow CD34⁺ HSCs are CD11c⁻CD123⁺ plasmacytoid (p)DCs and CD11c⁺CD123⁻ conventional (c)DCs [myeloid (m)DCs]. Additionally, monocyte-derived DCs differentiate from peripheral blood monocytes in response to inflammation (125–129). Of these subtypes, mDCs and pDCs have been specifically shown to play a role in cardiovascular disease (128, 130). In multiple models of hypertension, TCR ligation and costimulation by DCs is necessary for T cell activation (131). DCs in the kidney activate memory T cells to produce inflammatory cytokines IL-17A and interferon-gamma (IFN- γ) through increased CD70 expression (132). Accordingly, the transfer of DCs from hypertensive mice can induce memory T cell proliferation and prime naive mice to develop hypertension in response to low-dose Ang II infusion (133).

Collectively, these studies suggest that essential hypertension may be an antigen-specific autoimmune disease, mediated by the actions of DCs. Regarding the specific “neoantigens” that may be responsible for initiating hypertension, Kirabo et al. (133) have reported that, during hypertension, DCs increase generation of ROS leading to lipid peroxidation and consequent formation of isoketals (isolevuglandins or γ -ketoaldehydes). Once bound to lysines in the DCs, these isoketals are loaded and presented to T cells as nonself antigens. During antigen presentation, the isoketals also stimulate the production of IL-1 β , IL-6, and IL-23 in DCs, further promoting release of effector cytokines by the activated T cells.

By contrast, the converse effects of salt on DC phenotypic differentiation would seem to dampen DC-mediated activation of adaptive immune responses, possibly as a feedback mechanism to temper DC-induced blood pressure elevation. For example, NaCl-enriched media act on mouse bone marrow–derived DCs to increase their expression of traditional macrophage cell markers, including CD11b and F4/80, mannose receptor, and arginase 1, enhancing their production of IL-10, as seen in M2 macrophages (134, 135). Consistent with this shift away from DCs toward an M2 phenotype, a hyperosmolar environment can impair DC activation of T cells despite improving antigen uptake and processing (136). Thus, the effect of salt on DC function may be to impair the initiation of adaptive immunity through the inhibition of antigen-specific cytotoxic T cell stimulation (Figure 2).

In summary, DCs stimulate T lymphocytes via antigen-specific mechanisms to promote salt retention and hypertension, whereas the retained salt then mollifies the severity of proinflammatory DC activation to provide a ceiling against unchecked adaptive immune activation in the hypertensive animal. Thus, the interactions between salt and innate and adaptive immunity are complex and tridirectional. Below, we focus on T lymphocytes, key executors of adaptive immunity in the pathogenesis of hypertension and salt sensitivity.

REGULATION OF BLOOD PRESSURE BY ACTIVATED T CELLS

Overview

T lymphocytes are cells of the adaptive immune system that help to eradicate invading bacteria, viruses, and other harmful microbes by homing to insulted tissues and releasing cytokines and/or cytotoxic factors to combat specific pathogens. However, in the absence of infection, T cells can become inappropriately activated and contribute to a variety of autoimmune pathologies. In the case of essential hypertension, T cell activation exacerbates blood pressure elevation in a variety of rodent models, from pharmacologically induced (Ang II infusion, DOCA-salt, and L-NAME) to genetic (Dahl salt-sensitive and spontaneously hypertensive rats) forms of hypertension. The events leading to T cell activation in hypertension remain elusive. The prevailing hypothesis is that T cells are activated via classical antigen presentation, whereby T cells recognize and are stimulated by scavenged antigenic peptides on the surface of antigen-presenting cells (APCs; e.g., macrophages, dendritic cells). As mentioned above, Harrison and colleagues (131, 132) have provided much of the data supporting this hypothesis, showing that inhibition of T cell/APC interaction blunts hypertension. They showed further that DCs accumulate modified proteins that may serve as neoantigens, and adoptive transfer of DCs from hypertensive mice into naive mice enhanced susceptibility to hypertension (133). An alternative hypothesis is that heat shock proteins serve as the neoantigen in essential hypertension (137). Although strong experimental evidence supports a role for T cells in hypertension, the data in humans are less robust. However, correlative studies and a few small pilot studies suggest that T lymphocytes may also serve as a therapeutic target to limit blood pressure elevation and target organ damage in hypertensive patients (138, 139). Further analysis will be needed to substantiate a causal role for activated T cells in human hypertension. In most experimental models, T cells aggregate primarily in the kidney and around the peripheral vasculature. Accordingly, putative mechanisms by which T cells promote blood pressure elevation include instigating

sodium retention in the kidney and driving vascular and kidney dysfunction caused by injurious inflammation and ROS. In addition, the CNS, a key regulator of vascular tone and even sodium handling by the kidney, appears to enhance proinflammatory T cell signaling during hypertension.

In the Kidney

The kidney is the principal controller of blood volume via complex regulation of multiple ion and water channels throughout the nephron. A clinical study from the 1950s reported “lymphocytic aggregates” present in the kidneys of hypertensive patients in postmortem histological analysis (24). In preclinical experiments, the infiltration of T cells into the kidney during hypertension was described in renovascular hypertension (140), which was followed by reports from Rodríguez-Iturbe’s group in multiple experimental models (26, 141, 142). During experimental hypertension, T cells infiltrate the kidney, disrupting the nephron’s capacity to properly excrete sodium and water, which ultimately culminates in elevated blood pressure. Depending on the model, T cells are found throughout the medullary interstitium and surrounding glomeruli and vasculature in the cortex. In some organisms, enhanced accumulation of T cells in the kidney provokes renal damage. Preventing T cell infiltration during hypertension typically correlates with lower blood pressure and/or attenuated kidney injury. For instance, treatment with a lymphocyte-specific inhibitor, mycophenolate mofetil, blunts renal T cell infiltration and abrogates hypertension and kidney damage (17, 143), pointing to T cell-specific actions within the kidney to worsen hypertension. This notion has been further validated using genetic models of T cell deficiency, in which rodents lacking T cells are protected to varying degrees from severe hypertension and retain a robust natriuretic response (18, 19, 144, 145).

The inflammatory milieu propagated by infiltrating T cells in the hypertensive kidney can alter sodium handling and promote kidney injury. Three cytokines in particular—IL-17A, IFN- γ , and TNF- α —have been implicated in hypertensive kidney dysfunction. IL-17A is produced largely by Th17 cells. IFN- γ and TNF- α are produced by CD4⁺ and CD8⁺ T cells, although not exclusively. IL-17A or IFN- γ deficiency can limit expression of sodium transporters in the proximal tubule, facilitate excretion of a saline load, and blunt the chronic hypertensive response (146, 147). Thus, these cytokines can modulate luminal surface expression of transporters in the nephron to enhance sodium reabsorption and exacerbate hypertension. In addition, IL-17A, IFN- γ , and TNF- α promote tissue injury during experimental hypertension. For example, DOCA-salt upregulates IL-17A in the kidney, which correlates with enhanced renal collagen deposition (148). Inversely, a neutralizing IL-17A antibody mitigates DOCA-salt-induced hypertension and kidney fibrosis. Similarly, mice lacking the IFN- γ receptor have reduced Ang II-dependent hypertension and renal damage (149). CD8⁺ T cells can release cytokines but also engage in direct cell-to-cell communication. Direct interaction of CD8⁺ T cells with medullary distal convoluted tubular cells (mDCTs) causes the mDCTs to upregulate the Na⁺-Cl⁻ cotransporter (NCC) sodium transporter in vitro (150). Furthermore, adoptive transfer of splenic CD8⁺ T cells isolated from hypertensive DOCA-salt mice increases renal NCC phosphorylation and causes salt-sensitive hypertension in naive recipients.

Additionally, splenic T cells can produce Ang II in vitro (151), and infiltration of T cells into the kidney during hypertension is associated with elevated formation of intrarenal Ang II in salt-sensitive hypertension (143). T cells isolated from Dahl salt-sensitive hypertensive rat kidneys have detectable renin and angiotensin converting enzyme activity. Thus, renal T cells have the capacity to synthesize Ang II. Inversely, treatment with mycophenolate mofetil blunts T cell accumulation in the kidney during hypertension and significantly reduces renal Ang II levels, indicating that infiltrating T cells may contribute to the production of intrarenal Ang II.

Regardless of the source of intrarenal Ang II, T cells can be affected by its presence because they express the AT₁ receptor. Splenocytes from AT₁ receptor–null mice show blunted proliferative and cytokine responses following T cell receptor stimulation in vitro (50, 151). These in vitro studies indicate that AT₁ activation might enhance T cell–mediated inflammation and thus amplify their deleterious effects on kidney function. However, in our experiments, targeted deletion of the AT₁ receptor selectively from T cells in vivo (T cell KO) enhanced perivascular accumulation of T cells in the kidney, upregulated mRNA expression of neutrophil gelatinase–associated lipocalin, a marker of kidney injury, and exaggerated glomerular podocyte loss during Ang II-induced hypertension (152). T cells isolated from the hypertensive kidneys of T cell KO mice were biased toward the Th1 phenotype, with exaggerated expression of mRNA for IFN- γ and TNF- α . Chronic in vitro stimulation studies confirmed that AT₁ receptor activation on T cells in this model suppressed their generation of Th1 cytokines, possibly by regulating expression of the Th1 transcription factor, T-bet. These protective actions of the T cell AT₁ receptor are directionally consistent with the results from our earlier bone marrow chimera studies and experiments exploring the functions of the macrophage AT₁ receptor (55, 57), as discussed above, but they are difficult to reconcile with the aforementioned in vitro studies from the global AT₁ KO. One possibility is that the absence of AT₁ receptors on the nonhematopoietic cells of the global KO alters the differentiation and maturation of immune cells, an effect that would be circumvented by conditional deletion of AT₁ receptors in immune cells or even transfer of bone marrow cells from an AT₁ receptor–null animal into a WT recipient. In our view, the weight of the murine data points to beneficial effects of the T cell AT₁ receptor to limit kidney damage during hypertension from injury, in contradistinction to the pathogenic actions of renal AT₁ receptors in hypertension (53, 62). To date, human studies have not confirmed a direct effect of Ang II on T cell function (153).

T cells may also drive the production of ROS that promote sodium retention and injury in the kidney. Renal oxidative stress is prevalent in hypertensive models. Adoptive transfer of T cells with an incomplete NADPH oxidase enzyme, a major source of free radicals, does not recapitulate Ang II-induced hypertension to similar levels of WT T cells in *Rag1*^{−/−} lymphocyte–deficient mice (154). In Dahl salt-sensitive rat hypertension, administration of tacrolimus, which inhibits T cell proliferation, reduces T cell infiltration into the kidneys and blunts renal oxidative stress as measured by urinary thiobarbituric acid-reactive substances (TBARS) and renal p67^{phox} expression (155). Thus, T cells propagate hypertension at least in part through the generation of ROS.

In the Vasculature

In hypertension, proinflammatory T cells infiltrate the perivascular tissue and establish a pathogenic milieu that disrupts the proper maintenance of vessel tone. *Rag1*^{-/-} mice, which lack lymphocytes, retain proper vascular relaxation during hypertension unlike their WT counterparts (154). *Rag1*^{-/-} mice also have lower vascular superoxide production. Thus, lymphocytes exacerbate systemic vasoconstriction at least in part through the generation of ROS. Similar to their actions in the kidney, inflammatory cytokines produced by T cells drive dysfunction and injury in the vasculature. For example, TNF- α potentiates Ang II-induced hypertension and aortic superoxide production. Therefore, infiltrating Th1 cells in the aorta could contribute to local TNF production, although vascular cells and many other leukocyte populations present in the hypertensive aorta also produce this cytokine. Mice lacking IL-17A have preserved vascular relaxation during Ang II-induced hypertension (146). Moreover, the accumulation of Th17 cells around the vasculature may contribute to oxidative stress, as IL-17A induces inhibitory phosphorylation of eNOS via Rho-kinase activity (156). IL-17A may also enhance leukocyte adhesion to endothelial cells in hypertension. Treatment of human and mouse primary endothelial cells with IL-17A enhances monocyte adhesion and induces endothelial expression of several proinflammatory cytokines (157). Thus, proinflammatory T cells may aggravate vascular dysfunction in hypertension via the generation of ROS, TNF- α , and IL-17A. Although most of these pathogenic actions have been ascribed to conventional T lymphocytes expressing the alpha-beta T cell receptor, the rare population of gamma-delta T cells has similar injurious effects in the vasculature during hypertension (158). On the other hand, T regulatory cells (Tregs), identified as CD4⁺CD25⁺FOXP3⁺ cells, temper hypertensive vascular injury. In multiple models, adoptive transfers of Tregs have attenuated hypertension, blunted vascular dysfunction, oxidative stress, and aortic T cell infiltration (159, 160). A single adoptive transfer of Tregs is sufficient to protect the heart in hypertension via blood pressure-independent mechanisms (161). Inversely, deletion of a principal anti-inflammatory molecule secreted by Tregs, IL-10, exacerbates hypertension and vascular dysfunction (162). Tregs, therefore, perform beneficial functions in hypertension that could be harnessed for therapy. A novel subset of CD4⁺ T cells that comprise less than 10% of splenic and approximately 1% of circulating T cells can produce acetylcholine (163). They harbor the rate-limiting enzyme in acetylcholine production, choline acetyltransferase, and have been labeled TChAT cells. Deletion of TChAT cells increases baseline blood pressure, indicating that T cell-derived acetylcholine contributes to normal blood pressure homeostasis (164). Absolute deficiency of CD4⁺ T cells does not limit hypertension or associated tissue injury, suggesting that the imbalance between the pro- and anti-inflammatory CD4⁺ subsets, not their presence, drives hypertensive pathology (165). By contrast, CD8⁺ T cells drive vascular dysfunction in hypertension. Accordingly, CD8⁺ T cell deficiency blunts Ang II-mediated hypertension and preserves endothelium-dependent relaxation. Thus, on balance, several T cell subsets have prominent effects in the vasculature to modulate blood pressure and vessel wall architecture. These vascular effects may, in turn, influence renal sodium handling by altering renal blood flow.

In the Nervous System

Sympathetic nerve stimulation from the CNS prompts constriction of peripheral vessels and re-absorption of sodium in the kidney. Moreover, sympathetic nerves also innervate the spleen and lymph nodes, allowing the CNS to directly regulate T cell reservoirs. On balance, signals from the CNS favor T cell hyperactivity during hypertension, thus rendering T cells more likely to heighten vascular tone, upregulate sodium transport in the nephron, and instigate autoimmune injury in the cardiovascular control tissues. For example, centrally administered Ang II increases splenic sympathetic nerve activity and causes upregulation of splenic expression of proinflammatory cytokines, illustrating that central prohypertensive stimuli may lower the activation threshold for peripheral T cells. Disrupting signals in key cardiovascular regions of the brain such as the PVN or rostral ventrolateral medulla via lesion or adenoviral-mediated gene transfer reduces hypertension, which was initially attributed to changes in vascular or kidney function (166). However, T cell function is also suppressed in these models, which may contribute to mitigation of hypertension. For example, ablation of the circumventricular organs responsible for central Ang II sensitivity—collectively, the AV3V—blunts Ang II-dependent hypertension as expected, but it also decreases the proportions of activated circulating T cells and the total numbers of T cells infiltrating the wall of the aorta (167). Hypertension induced by norepinephrine, the principal neurotransmitter of the sympathetic nervous system, has a similar effect on peripheral T cell activation, thus excluding direct effects of Ang II on T cell activation in this system. Whether the T cells are directly activated by the CNS or secondarily activated by changes in systemic blood pressure cannot be ascertained from this experimental design. However, sophisticated preclinical studies utilizing celiac or splenic nerve disruption have demonstrated that splenic T cell activation and egress from the spleen during hypertension requires splenic sympathetic nerve stimulation, that in turn depends on cholinergic transmission upstream at the celiac ganglion (168). Thus, splenic nerve activation contributes to hypertension by directly potentiating systemic adaptive immunity.

Oxidative stress in the CNS drives hypertension (169, 170). Superoxide dismutase (SOD3) enzymes convert superoxide into less damaging species, thus limiting local oxidative stress. Deletion of extracellular SOD3 in the circumventricular organs, primarily the subfornical organ, increases baseline blood pressures and renders mice susceptible to elevations in blood pressure during RAS activation (171). Moreover, SOD3 ablation in the circumventricular organs upregulates expression of the activation/memory T cell marker CD69 on circulating CD4⁺ T cells at baseline and augments accumulation of T cells in the aorta during hypertension. Inversely, targeted inhibition of NADPH oxidase in the subfornical organ reduces local superoxide production, mitigates Ang II-induced hypertension, and blunts the infiltration of T cells into the aorta (172). Thus, ROS generated in the CNS enhance systemic T cell activation even in the absence of hypertension. Whether the effects of oxidant stress in the CNS to drive vascular migration of T cells depend on blood pressure elevation or the converse is less clear. Sympathetic outflow reaches directly to the kidney via the renal nerve. In this regard, bilateral renal denervation blunts the chronic hypertensive response to Ang II, ameliorates hypertensive kidney injury, and limits renal T cell activation. The effects of the renal nerve to stimulate T cells are apparently independent of blood pressure as unilateral denervation allows the hypertensive response to persist and reduces T

cell infiltration only in the denervated kidney (89). Thus, sympathetic outflow from the CNS acts at the level of the vasculature and directly in the kidney to modulate T lymphocyte functions during hypertension. Collectively, the preclinical data support a paradigm in which the effects of the CNS to modulate blood pressure have both T cell–dependent and –independent components. In turn, sympathetic outflow likely primes T cells for activation via blood pressure–dependent and –independent mechanisms (Figure 3).

Salt and T Cells

Most major health organizations champion limits on salt consumption due to correlations between salt intake and cardiovascular disease, including hypertension. One adverse result of high salt consumption may be inappropriate excitation of T lymphocytes. Culturing naive T cells in the presence of high salt (40 nM NaCl) enhances their polarization toward a proinflammatory Th17 phenotype (173, 174). Accordingly, a HSD enhances the development of Th17-driven autoimmune disease in preclinical studies. As discussed above, these Th17 cells also promote hypertension by favoring sodium reabsorption at several points along the nephron (19). Serum/glucocorticoid-regulated kinase 1 (SGK1) appears to be a pivotal checkpoint in salt-mediated Th17 polarization, as inhibition of SGK1 function abrogates the effects of salt on Th17 polarization. Tonicity also influences the polarization of Tregs. Tregs suppress adaptive immunity and have been shown to ameliorate hypertension and consequent target organ damage (159, 160). High concentrations of salt, however, interfere with the immunosuppressive function of Tregs (175). Thus, because chronically high levels of salt consumption appear to raise sodium concentrations in interstitial compartments, where T cells exert pleiotropic effects on blood pressure through enhanced binding of sodium to interstitial glycosaminoglycans, a HSD may promote hypertension by both directly expanding intravascular volume and shifting the T cell repertoire toward the Th17 phenotype and away from the Treg lineage (Figure 2).

CONCLUSION

Here, we have reviewed the rapidly accumulating science describing the actions of innate and adaptive immunity in the pathogenesis of hypertension. Proinflammatory monocytes and macrophages respond to unidentified danger signals to promote vasoconstriction and sodium retention. By contrast, protective mononuclear phagocytic cells in the dermis alleviate salt sensitivity by facilitating removal of salt from the interstitium via lymphatics. DCs carrying neoantigens exposed by injury or oxidant stress engage adaptive immune responses in blood pressure regulation by stimulating T lymphocytes in the brain, vasculature, and kidney. T cell subsets can have a variety of effects on blood pressure, ranging from the prohypertensive actions of Th17 cells to stimulate sodium transport in the kidney to the protective effects of Tregs to blunt vascular reactivity. Myeloid cells and T lymphocytes modulate blood pressure through the elaboration of cytokines and through the generation of ROS, both of which are active in multiple cardiovascular control tissues. Once retained, salt can alter the phenotype of monocytes and T cells to drive them toward more proinflammatory phenotypes in a positive feedback loop that should exacerbate hypertension. On the other hand, exposure of dendritic cells to high salt concentrations may limit hypertension by mitigating their capacity to activate prohypertensive T cells.

Because of space considerations, we have omitted discussion of the important role of B lymphocytes in hypertension, a topic that is now receiving considerable attention. It was initially thought that B cells did not play a prominent role in blood pressure regulation, as adoptive transfer of B cells into lymphocyte-deficient animals could not restore the hypertensive response (154). However, subsequent studies have revealed that B cell deficiency or blockade is protective in pre-clinical models of hypertension (176, 177). Thus, B cells likely play a critical role in hypertension by directing the involvement of other constituents of the adaptive immune compartment.

On balance, myeloid cells, T cells, and salt all collude to favor increases in blood pressure. Given that a critical known function of innate and adaptive immunity is to provide protection against infection, it seems plausible that the prohypertensive effects of the immune system may have evolved to prevent the circulatory collapse that can threaten a septic organism. We have previously put forth a similar hypothesis to explain why vascular angiotensin receptors outside the kidney are enlisted to prevent hypotension (i.e., in a state of sepsis) but contribute less than renal vascular and epithelial angiotensin receptors do to sustaining hypertension, a condition in which salt is aberrantly retained by the kidney (62, 178, 179). Thus, even though inappropriate activation of the RAS is among the most potent drivers of salt-sensitive hypertension, two inhibitory feedback mechanisms involving the RAS-immune axis limit hypertension and consequent target organ damage. First, systemic vascular AT₁ receptors contribute less to blood pressure homeostasis when blood pressure is elevated, thereby limiting the retention of salt that seems to accentuate the prohypertensive actions of myeloid cells and T cells. Second, activation of AT₁ receptors directly on immune cells, as illustrated in our bone marrow chimera and conditional gene targeting studies (55, 57, 152), suppresses inflammation and thereby limits damage to the kidney, whose appropriate function can alleviate indiscriminate salt retention.

Several important questions regarding the interactions between immunity, salt, and blood pressure remain. First, relative to other key cardiovascular control centers such as the brain, the vasculature, and kidney, what proportions of susceptibility to hypertension accrue from innate and/or adaptive immune activation? In preclinical studies, genetically deleting individual constituents of the innate or adaptive immune compartment has profound effects on the hypertensive response, such that these effects cannot be additive or truly reflect the proportional contribution of these components to hypertension. Ultimately, only translational studies will reveal the relative importance of each of the immune system's components to hypertension. Second, to the extent that essential hypertension is an antigen-specific autoimmune disease, what are the neoantigens that engage adaptive immunity in the pathogenesis of hypertension? The data for the importance of isolevuglandins as neoantigens are compelling. Yet, given that hypertension exerts hemodynamic injury in several cardiovascular control tissues throughout the body, one might posit that a broad set of antigens underpin the T cell-mediated component of hypertension. In this regard, reverse engineering of the TCRs expressed on the cell membranes of the T lymphocytes most activated within the brain, vasculature, kidneys, and their draining lymph nodes during hypertension may eventually decipher the most dominant antigens involved in triggering blood pressure elevation and thereby permit specific targeting to limit the adaptive immune system's contribution to hypertension.

Most importantly, future studies need to interrogate the role of immunity in human hypertension. The preclinical data addressing the participation of immune cells and salt in blood pressure homeostasis have accumulated at an astounding pace. Careful translational studies in nonhuman primates and/or small pilot studies in humans now must determine which of the paradigms of immune-mediated hypertension will yield novel therapeutic strategies to aid the large human populations with persistently uncontrolled hypertension. When considering immunomodulatory agents for hypertension, the risk of off-target immunosuppressive effects must be weighed against the risk of catastrophic cardiovascular complications accruing from persistent and/or severe hypertension. Thus, in the human pilot studies, examining footprints of innate or adaptive immune activation may allow targeting of immunomodulatory agents toward those patients most likely to benefit from the intervention. Given that immune-mediated damage to the kidney does not always provoke salt retention in the early phases of disease, it is conceivable that some immunomodulatory agents for hypertension may help to protect target organs from progressive injury even without improvements in blood pressure control. Separating the blood pressure-dependent and – independent benefits of novel immunomodulatory agents for hypertension will thus demand both careful phenotyping of our patients and human studies of sufficient duration to calculate the long-term effects of immunomodulation on hypertension and consequent end-organ injury.

Acknowledgments

The authors acknowledge funding from the US National Institutes of Health (grants DK087893, HL128355), US Veterans Health Administration, Office of Research and Development, Biomedical Laboratory Research and Development (grant BX000893), the Duke O'Brien Center for Kidney Research (NIDDK P30DK096493).

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Figure 1.

Illustration of the diverse roles for macrophages in salt-sensitive hypertension. Through generation of inflammatory cytokines and ROS, macrophages act in cardiovascular control centers to induce hypertension. (a) In the kidney, proinflammatory macrophage canonical cytokines TNF- α and IL-1 reduce NO generation and NO-dependent inhibition of renal sodium transporters, leading to impaired sodium excretion. (b) In the vasculature, TNF augments oxidative stress and impairs NO synthesis, leading to vascular dysfunction and vasoconstriction. (c) In the brain, macrophages secrete ROS that instigate neurovascular dysfunction. They also activate microglia that subsequently increase hypertensive neuroinflammation and sympathetic neuron activation. (d) Dermal macrophages increase expression of VEGF-C in response to osmotic stress, resulting in increased lymphangiogenesis and lymphatic flow. Through this mechanism, the macrophages drive mobilization of sodium stored in the dermis and may thereby serve as an important extra-renal regulator of sodium homeostasis. Abbreviations: IL-1, interleukin-1; NF- κ B, nuclear factor-kappa B; NO, nitric oxide; NOS3, nitric oxide synthase 3; NOX2, NADPH oxidase 2; ROS, reactive oxygen species; TNF, tumor necrosis factor; VEGF-C, vascular endothelial growth factor-C.

Figure 2.

Effects of salt on the immune cell phenotype. Proinflammatory M(LPS) macrophages cultured in NaCl have enhanced production of inflammatory cytokines and reactive oxygen species. Conversely, salt impairs activation of anti-inflammatory M(IL-4, IL-13) macrophages. Similarly, naive T cells cultured in the presence of high salt have enhanced polarization toward a proinflammatory Th17 phenotype. Salt also impairs the immunosuppressive function of Tregs. Mouse bone marrow-derived DCs cultured in a hyperosmolar environment have increased expression of canonical M2 macrophage markers, including mannose receptor and arginase 1, in addition to enhanced production of IL-10. Salt also impairs DC-mediated activation of T cells despite improved DC antigen uptake and cleavage. Abbreviations: DC, dendritic cell; IL, interleukin; LPS, lipopolysaccharide; NaCl, sodium chloride; Treg, T regulatory cell.

Figure 3.

Proposed roles of T lymphocytes in hypertension and salt sensitivity. Sympathetic nervous system activation and oxidative stress in the central nervous system enhance antigen-dependent T cell activation and accumulation in the kidney and vasculature. Upon extravasation into the kidney, T cells secrete cytokines, including IFN- γ , IL-17A, and TNF in addition to ROS that impair renal sodium excretion and exacerbate blood pressure elevation. In the vasculature, generation of inflammatory cytokines and ROS promote vascular dysfunction and impaired vasorelaxation, potentiating the chronic hypertensive response. Abbreviations: IFN- γ , interferon-gamma; IL-17A, interleukin-17A; ROS, reactive oxygen species; TNF, tumor necrosis factor.