Inflammation, Immunity, and Oxidative Stress in Hypertension—Partners in Crime?

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Hypertension is considered as the most common risk factor for cardiovascular disease. Inflammatory processes link hypertension and cardiovascular disease, and participate in their pathophysiology. In recent years, there has been an increase in research focused on unraveling the role of inflammation and immune activation in development and maintenance of hypertension. Although inflammation is known to be associated with hypertension, whether inflammation is a cause or effect of hypertension remains to be elucidated. This review describes the recent studies that link inflammation and hypertension and demonstrate the involvement of oxidative stress and endothelial dysfunction—two of the key processes in the development of hypertension. Etiology of hypertension, including novel immune cell subtypes, cytokines, toll-like receptors, inflammasomes, and gut microbiome, found to be associated with inflammation and hypertension are summarized and discussed. Most recent findings in this field are presented with special emphasis on potential of anti-inflammatory drugs and statins for treatment of hypertension.

Key Words: Inflammation, Immune activation, Oxidative stress, Hypertension, Anti-inflammatory drugs

Hypertension (HTN) is a global health problem. Analysis of the data from 135 population-based studies involving 968,419 adults from 90 countries showed that about 31% have HTN.[1] HTN remains an important public health problem in the United States with 874 million adults having systolic blood pressure (BP) ≥140 mm Hg.[2] The prevalence of HTN among adults is 29.0%, with an increased prevalence in non-Hispanic Black and older individuals.[3] Data from the National Vital Statistics System noted that there were 78,862 deaths primarily attributable to high BP in 2015.[4] Despite advances in therapy, the death rate attributable to high BP increased by 10.5% from 2005 to 2015.[2] A number of factors contribute to the pathogenesis of HTN. Accumulating evidence suggests that altered immunity and inflammation is important in the genesis of HTN and also a mediator of its complications. In this review, we will discuss how disturbed innate and adaptive immune responses mediate neuroendocrine disturbance and vascular inflammation leading to systemic HTN.

IMMUNITY AND INFLAMMATION

Innate and adaptive immunity are 2 important components of the immune system. Innate immunity provides a rapid antigen-independent nonspecific first line of defense against exogenous and endogenous pathogens or injury (Fig 1). In this, pattern recognition receptors present on the cells of the innate immune system detect the pathogen-associated molecular patterns and initiate the host responses,[5] which include (1) generation of cytokines, chemokines, complements, and interferons through activation of transcriptional machinery, (2) induction of immune processes such as phagocytosis, autophagy, and apoptosis,[6] and (3) initiation of a highly specific long lasting adaptive immune response. Antigen-presenting cells (APCs) such as dendritic cells (DCs) take up the antigens, process them into short peptides, and present them in the context of a major histocompatibility complex leading to activation of T helper cells ($CD4^+$) and cytotoxic ($CD8^+$) T cells. Type 1 T helper (Th1) cells produce interferon-gamma, interleukin (IL)-2, and tumor necrosis factor (TNF)-β, which activate the macrophages. Type 2 T helper cells (Th2) generate IL-4, IL-5, IL-10, and IL-13, which facilitate antibody production. Depending on the microenvironment, macrophages may evolve into proinflammatory M1 or anti-inflammatory M2 subtypes. M1 macrophages release proinflammatory cytokines that induce $CD4^+$ cell activation.[7] On the other hand, M2 macrophages generate anti-inflammatory cytokines such as IL-10 and promote activation of regulatory T cells (Tregs). Cytokines can recruit polymorphonuclear neutrophils and monocytes to sites of injury and induce expression of adhesion molecules, integrin ligands, intercellular adhesion molecules, and vascular cell adhesion molecules on vascular endothelial cells. The resulting vascular inflammation has been shown to cause endothelial dysfunction and HTN.[8]

PATHOGENESIS OF ESSENTIAL HYPERTENSION

The central mechanism of essential HTN is an increase in peripheral resistance to blood flow, especially in the small resistant arteries.

$$BP = \text{Cardiac Output} \times \text{Systemic Vascular Resistance}$$

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BP is a heritable trait with 30% to 70% of the phenotypic variation attributable to genetic variation.[9,10] Initial "single gene locus theory"[11] was replaced by "polygenic theory"[12] that evolved into the "mosaic hypothesis"[13] that emphasized on 5 gene–environmental interaction. The key determinants of BP are the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone system (RAAS), and the plasma volume (Fig 2). Other contributing factors include excess production of hormones promoting sodium retention and vasoconstriction such as activation of RAAS. Their effect is further enhanced by excess sodium intake and reduced potassium intake, deficiencies of vasodilators, such as prostacyclin and nitric oxide (NO), disturbed kallikrein-kinin system, alteration in vascular growth factors, exposure to adverse environmental factors such as excess atmospheric particulate matter and stress. Increasing age, obesity, and insulin resistance are well known risk factors for HTN. Guyton and colleagues[14] proposed a central role for kidney in the pathogenesis of HTN (Fig 3). They observed that most systems that would increase BP, such as activation of the SNS, could only have a transient effect, and a sustained increase in BP would require a resetting of the pressure natriuresis curve. They further postulated that both salt-resistant and salt-sensitive HTN were renal dependent, but that they exhibited different types of pressure natriuresis curves.

CLINICAL SUMMARY

- Experimental studies show that immune activation and inflammation are involved in the pathogenesis of hypertension.
- T cells express angiotensinogen, angiotensin converting enzyme and produce angiotensin II.
- Increased generation of reactive oxygen species and the associated decrease in nitric oxide (NO) cause endothelial dysfunction leading to hypertension.
- Laboratory research and association studies in humans support the role of anti-inflammatory therapy for hypertension.

HISTORICAL PERSPECTIVE OF IMMUNITY AND HYPERTENSION

In the 1960s, investigators showed that immunosuppression attenuates HTN in rats with partial renal infarction,[15] and transfer of lymph node cells from rats with renal infarction causes HTN in normal rats.[16] However, the enthusiasm for the immune mechanism for HTN was lost when depressed T-cell function was reported in spontaneously hypertensive rats (SHRs),[17,18] and restoration of T-cell function by engraftment with normal thymus reduced BP.[17] In 1980s, Olson showed that injection of splenic cells from deoxycorticosterone acetate (DOCA)-salt hypertensive and renal hypertensive rats to normotensive rats renders them hypertensive.[19] Advances in molecular methods have enabled our understanding of the immune mechanisms underpinning the pathogenesis of HTN. Recently, investigators have shown that T cells in the renal interstitium contribute to HTN through augmented angiotensin II (Ang II) and oxidant generation and reduction in local NO.[20,21] Rodriguez-Iturbe and colleagues[22] showed that the reduction in intrarenal T cells and macrophages could also block salt-sensitive HTN in the Ang II model.

IMMUNE CELLS IN HYPERTENSION

Here we will discuss the cell type that are involved in immune regulation and play an important role in hypertensive response.

Monocyte and Macrophages

Cells of the monocyte/macrophage lineage are important in vascular remodeling. Ang II was incapable of inducing endothelial dysfunction, vascular remodeling, or HTN in homozygous osteopetrotic mice (Op/Op), which is deficient in macrophage colony–stimulating factor.[23] Similar finding was noted in DOCA-salt challenge in the same mouse model.[24] Wenzel and colleagues[25] showed that infiltrating monocytes with a proinflammatory phenotype and macrophages are essential for Ang II–induced vascular dysfunction and HTN. Mice with severe combined immunodeficiency (lacking both T and B lymphocytes) exhibit a blunted BP response and reduced sodium retention in response to Ang II.[26] Guzik and colleagues[27] reported that RAG-1$^{-/-}$ mice, also lacking T and B cells, have blunted BP response and do not develop vascular dysfunction during Ang II infusion or DOCA-salt exposure. They further showed that adoptive transfer of T cells, but not of B cells, restored the hypertensive effect of Ang II in these mice.[27]

Lymphocytes

Increased proportion of immunosenescent, proinflammatory, cytotoxic CD8^{+} T cells that are CD28 null and positive for CD57 is seen in patients with HTN.[28] T cells express angiotensinogen, angiotensin-converting enzyme, and renin and produce Ang II.[29,30] Infiltrating lymphocytes in renal sections of experimental models of salt-sensitive HTN stained positive for Ang II.[31] Th17 cells are a subset of T cells characterized by the expression of retinoic acid–related orphan receptor γt and by the production of IL-17. Madhur and colleagues[32] showed that Ang II increased IL-17 production from T lymphocytes and that Ang II-induced increases in BP were not sustained in IL-17$^{-/-}$ mice. Once thought to be generated only by Th17 cells, IL-17 is now known to be secreted by macrophages, DCs, natural killer T cells, and γδ T cells in response to immune system activation.[33] Administration of recombinant IL-17 in C57BL/6 mice decreased NO-dependent vascular relaxation via Rho-kinase signaling and caused HTN.[34] Ang II–mediated HTN associated vascular dysfunction, vascular inflammation, oxidative stress, and aortic stiffening were reduced in IL-17A null mice (IL-17A$^{-/-}$).[32] Similarly, IL-17 has been demonstrated to have deleterious cardiovascular effects in rodent models of DOCA-salt–dependent HTN.[35] Interaction of the T-cell receptor with the processed peptide presented by the APC and

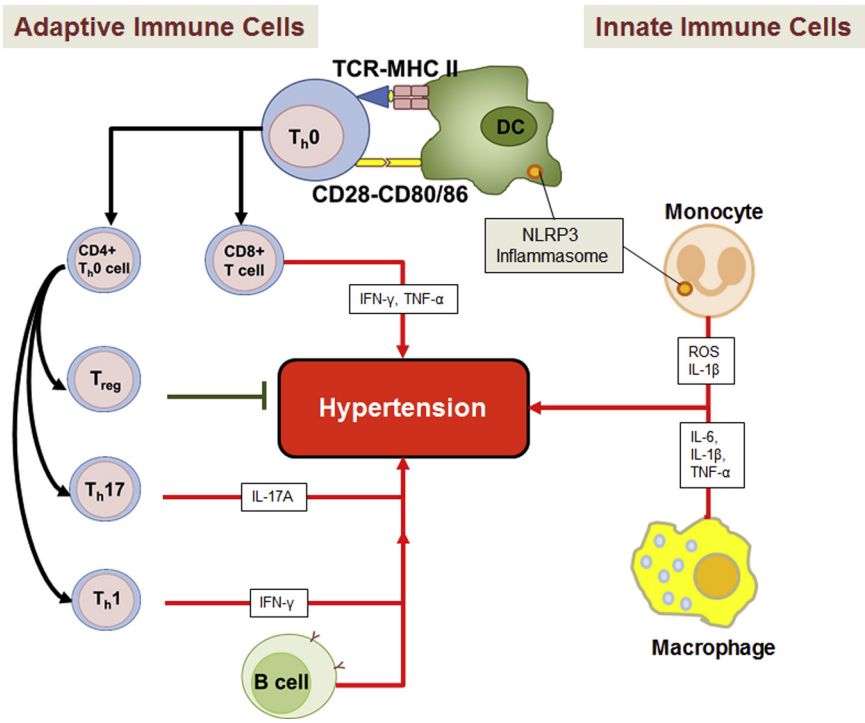

Figure 1. Innate and adaptive immune cells that play a role in hypertension. Innate immune cells such as monocytes, macrophages, and DCs inhibit or promote hypertension by producing various cytokines and ROS. Monocytes and DCs also contain the NLRP3 inflammasome, which also plays an important role in hypertension. Adaptive immune cells such as the B cells, $CD4^+$ T cells (Treg, Th17, and Th1 cells), and $CD8^+$ T cells also produce cytokines that inhibit or promote hypertension. Abbreviations: Ang II, angiotensin II; BP, blood pressure, CNS, central nervous system; DAMP, damage-associated molecular pattern; DC, dendritic cell; IFN, interferon; IL, interleukin; ROS, reactive oxygen species; TCR-MHC, T-cell receptor-major histocompatibility complex; TNF, tumor necrosis factor.

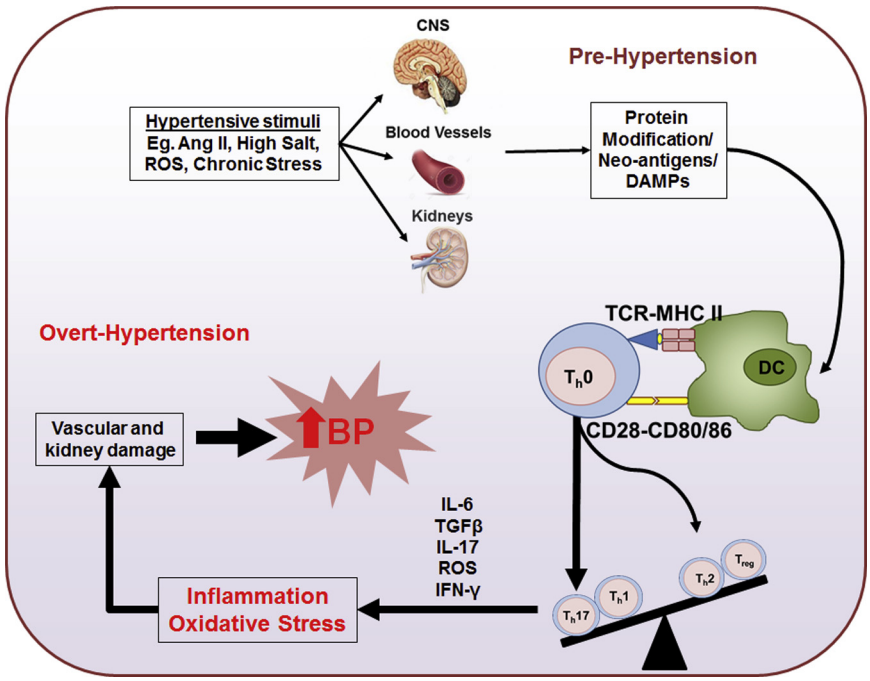

Figure 2. Immune cell activation and inflammation as critical mediators of hypertension. Activation of central nervous system by hypertensive stimuli such as angiotensin II, high salt intake, ROS, and chronic stress will lead to an increase in sympathetic

simultaneous interaction of receptors on the T-cell surface with B7 ligands on the APC surface are required for T-cell activation. Vinh and colleagues[36] demonstrated that in an experimental model of HTN, blockade of B7-dependent costimulation by cytotoxic T-lymphocyte antigen-4-Ig reduces the development of HTN in response to Ang II and DOCA, opening a new promising avenue for the development of therapies against the disease.

Dendritic Cells

DCs are bone marrow-derived APCs. A complex pattern of interlinked DCs is present in most human and animal tissues, such as arteries, kidneys, and brain, which are involved in BP regulation. An amiloride-inhibitable sodium channel regulates sodium entry in DCs, leading to intracellular calcium influx and activation of protein kinase C.[37] This results in increased superoxide production and accumulation of immunogenic isolevuglandins (IsoLGs) in DCs.[37] IsoLGs can cross-link lysine residues on proteins, rendering them immunogenic, which are presented by DCs to T lymphocytes, triggering T-cell activation and HTN.[38] Furthermore, IsoLGs-containing DCs generate excess IL-6, IL-1β, and IL-23, which promote differentiation of T cells into proinflammatory IL-17–producing cells.[32] Importantly, the use of IsoLG scavengers prevented DC activation and ameliorated HTN, presenting a therapeutic potential.[38]

Regulatory T Cells

Tregs are characterized by the expression of $CD4^+CD25^+$ and the transcription factor Foxp3. These cells play a crucial role in maintaining immunologic self-tolerance and protection from autoimmune diseases. Tregs release soluble factors such IL-10, IL-35, and transforming growth factor-β (TGF-β), which have an anti-inflammatory effect.[39] Adoptive transfer of Tregs prevented Ang II–induced HTN, endothelial dysfunction, vascular stiffness, and vascular inflammation.[40] Similarly, aldosterone induced increase in BP, endothelial dysfunction, oxidative stress, and infiltration of aorta and kidney with immune cells were attenuated by adoptive transfer of Treg cells.[41] Transfer of Tregs isolated from normotensive mice to hypertensive mice significantly reduced BP and improved endothelium-dependent relaxation in coronary arterioles.[42]

INFLAMMASOMES

The inflammasomes are multiprotein intracellular innate immune system receptors that induce inflammation in response to pathogen-associated molecular pattern and damage-associated molecular patterns. The nucleotide-binding oligomerization domain (Nod)-like receptor containing pyrin domain 3 (NLRP3) inflammasome is the most characterized member of the pattern recognition receptors. Activation of the NLRP3 inflammasome involves triggering of caspases that facilitate the maturation of inactive proinflammatory cytokine precursors. Murine adenosine triphosphate (ATP)-induced HTN is accompanied by increased caspase-1 activity, IL-1β production, and $CD43^+$ T-cell infiltration in the renal medulla.[43] An intronic 42 base pair variable number of tandem repeat polymorphism in the *CIAS1* gene that encodes for NLRP3 has been linked to essential HTN in humans.[44] Interestingly, the *CIAS1* gene is part of the CATERPILLER gene family, which also contains PYRIN-containing Apaf-1-like protein 5 (PYPAF5) that encodes the Ang II/vasopressin receptor implicated in salt-sensitive HTN in the Dahl SS model.[45] Pharmacologic inhibition and genetic modulation of NLRP3 activation results in potent therapeutic effects in a wide variety of experimental inflammatory diseases.[46] Caspase-1 inhibitor WEHD (Trp-Glu-His-Asp motif) attenuated inflammasome activation and blocked ATP-induced HTN.[43]

TOLL-LIKE RECEPTORS IN HYPERTENSION

Toll-like receptors (TLRs) are major components of the innate immune system that recognize damage-associated molecular pattern to initiate inflammatory signaling. About 12 TLRs have been identified in mammals, which are expressed in immune and nonimmune cells in specific combinations.[47,48] All TLRs contain a cytoplasmic Toll/IL-1 receptor domain, which on activation recruits adaptor proteins such as myeloid differentiation factor 88 (MyD88), MyD88-adapter-like (Mal), IL-1 receptor–associated kinase-4 (IRAK4), and Toll/IL-1 receptor–containing adaptor molecule. Different signaling cascades are activated by TLRs depending on the adaptor protein binding. The cytokine cascade initiated by TLR is essential for the transition from nonspecific innate to targeted adaptive immunity. TLRs could modulate vascular function, induce low-grade vascular inflammation, and thus contribute to HTN.[49-51] Ang II upregulated TLR-4 expression and increased TNF-α in rat vascular smooth muscle cells.[52] TLR signaling from the neuroimmunosympathetic connection from the central nervous system to the immune system is altered in SHRs.[53] These rats have increased expression of TLR-4 protein in mesenteric arteries and treatment with anti–TLR-4 antibody lowers BP.[49]

OXIDATIVE STRESS IN HYPERTENSION

The reactive oxygen species (ROS) including superoxide (O_2^-), hydroxyl radical (HO•), hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^-$), nitric oxide (NO•), and hypochlorous acid (HOCl) are produced during cellular metabolism and scavenged by antioxidants. ROS are

outflow, which causes a modest increase in blood pressure (prehypertension). Increase in pressure will lead to increase in ROS production in the kidney and vasculature, and formation of neoantigens from endogenous proteins. These neoantigens are presented to T cells by DCs, causing T-cell activation and cytokine production, including IL-17. These cytokine productions will promote inflammation and oxidative stress in kidney and vascular smooth muscle leading to sodium retention, vasoconstriction, and overthypertension. Abbreviations: DC, dendritic cell; IFN, interferon; IL, interleukin; ROS, reactive oxygen species; TCR-MHC, T-cell receptor-major histocompatibility complex; TNF, tumor necrosis factor.

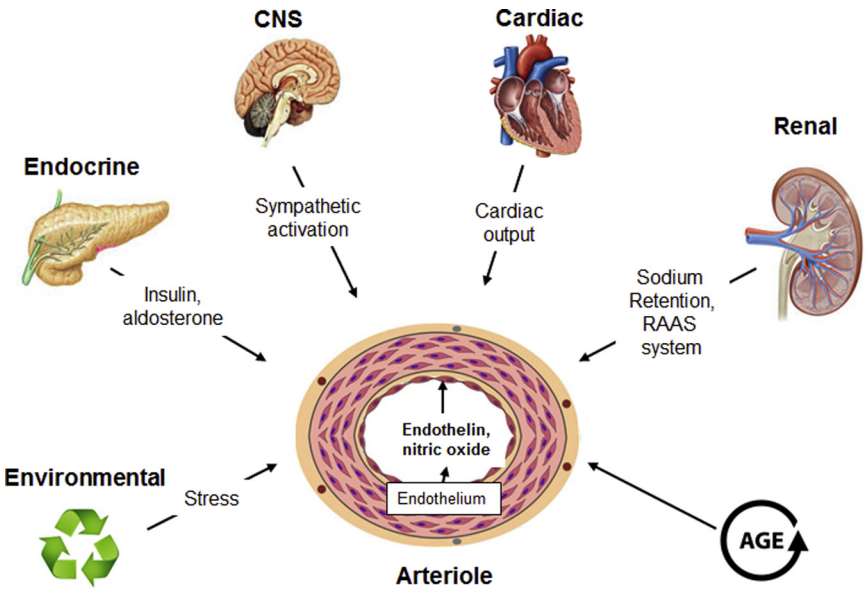

Figure 3. Some of the factors that play a key role in control of blood pressure by affecting the basic equation blood pressure = cardiac output × peripheral resistance. Increase in blood pressure is medicated by the collective contribution of a number of genetic, environmental (including diet), and physiological factors. Both excess sodium intake and renal sodium retention would presumably work primarily on increasing fluid volume and cardiac output. Various hormonal mediators, including angiotensin II, NO, and endothelin may initiate the increased peripheral resistance. Abbreviations: CNS, central nervous system; RAAS, renin-angiotensin-aldosterone system.

important signaling molecules that mediate activation of transcription factors, induction of immune response genes, and phosphorylation of kinases.[54] They regulate endothelial function and vascular tone and vascular remodeling through proliferation and apoptosis.[55] Chronic inflammation is known to promote oxidative stress and vice versa by activating transcription factors such as nuclear factor κB.[56] Nicotinamide adenine dinucleotide phosphate oxidase is a major source of ROS in immune cells and also in the vasculature.[57]

NO and prostacyclin released from endothelial cells inhibit platelet aggregation, the neutrophil attachment to endothelial cells, expression of adhesion molecules, and inhibition of smooth muscle cell proliferation.[58] Ang II also contributes to the production of ROS through increased activity of nicotinamide adenine dinucleotide phosphate oxidase.[59] Oxidative stress is an important cause of endothelial dysfunction, primarily through reducing NO bioavailability through chemical reaction of superoxide with NO, resulting in the formation of peroxynitrite.[60] Peroxynitrite may further increase oxidative stress by inhibiting endothelial nitric oxide synthase (eNOS) activity through oxidation of 4-tetrahydrobiopterin (BH4), a cofactor of eNOS. This leads to eNOS uncoupling, where eNOS produces superoxide instead of NO.[61] Inhibition of NO-induced ROS generation using pharmacologic and gene-targeted approaches results in regression of vascular remodeling, improved endothelial function, and lowering of BP.[62] Despite the consistent and promising findings from experimental studies clinical studies investigating beneficial effects of antioxidants have largely been disappointing.[63,64] Currently, researchers are advocating for the use of more disease-specific, target-directed, and highly bioavailable antioxidants instead of nonspecific antioxidant vitamins.[65]

MICROBIOME AND HYPERTENSION

Advances in sequencing techniques have revealed that the human gut microbiome plays a vital role in human health and disease. Experimental and human studies suggest that gut microbiome is altered and possibly etiologically linked to HTN. Compared with the healthy control subjects, hypertensive individuals have decreased microbial richness and diversity, with abundance in Prevotella enterotype.[66] Furthermore, fecal microbial transplant from hypertensive humans to germfree mice resulted in increased BP.[66] The microbiota of salt-sensitive rats has a distinct gut microbiome profile with abundance in phylum Bacteroidetes.[67] SHRs have higher Firmicutes/Bacteroidetes ratio and reduced Actinobacteria compared with normotensive Wistar Kyoto control rats.[68] Ang II–treated rats also have an increased Firmicutes/Bacteroidetes ratio.[68] Short chain fatty acids (SCFAs) are byproducts of gut microbial metabolism that have been known to influence several aspects of host physiology, including BP regulation.[69] SCFAs have an anti-inflammatory effect on both colonic epithelium and immune system,[70-72] which is mediated through activation of the G protein receptor family.[73] SCFAs bind to the aryl hydrocarbon receptor to increase transcription of IL-10R and reduce gut inflammation.[74,75] This is significant because about 70% of the body's immune cells reside in the gut-associated lymphatic tissue. As discussed previously, excess IL-17A production is

associated with HTN.[32,76] Th17-producing cells are known to be affected by the abundance of specific commensal bacteria.[77] High salt intake depletes *Lactobacillus murinus* and treatment of mice with *L. murinus* prevented salt-sensitive HTN by modulating TH17 cells.[78] Interestingly, some symbiotic bacteria produce angiotensin-converting enzyme inhibitors, renin inhibitors, and antioxidant molecules during the digestion of mucin.[79] A recent meta-analysis provided preliminary support that *Lactobacillus*-rich probiotics might affect BP in hypertensive subjects.[80]

SALT SENSITIVITY AND INFLAMMATION

Sodium is the major cation that maintains extracellular fluid volume. Epidemiologic, clinical, and experimental studies have demonstrated that excess dietary salt intake contributes to HTN and reductions in salt intake lowers BP.[81,82] However, the effect of salt intake on cardiovascular disease and death is nonlinear.[83] Salt sensitivity is defined as a change in BP of 5% to10% or at least 5 mm Hg, in response to a change in NaCl intake.[84] In salt-sensitive HTN, the accumulation of sodium in tissue is accompanied by retention of water to maintain the isotonicity. High-salt diet in rats leads to sodium accumulation in interstitium of skin, resulting in increased density of lymphatics mediated by activation of tonicity-responsive enhancer binding protein in mononuclear phagocyte system cells infiltrating the interstitium of the skin.[85] Both Dahl salt-sensitive rats fed high salt and hypertensive humans are found to have infiltration of macrophages and $CD4^+$ and $CD8^+$ T cells in the kidneys.[86] Mycophenolate mofetil, an immunosuppressive agent, was able to prevent the infiltration of T cells into the kidneys and reduce the development of salt-sensitive HTN and kidney damage.[87] It has been suspected that apart from the classical systemic RAAS an independently functioning RAAS exists within the kidney that regulates sodium excretion and BP.[88] As noted previously T cells express angiotensinogen, angiotensin-converting enzyme, and renin and produce Ang II.[29,30] This could explain the intrarenal activation of RAAS in salt-sensitive HTN.

BRAIN INFLAMMATION IN HYPERTENSION

Sympathetic premotor neurons controlling vasomotor activity are located predominantly in the rostral ventrolateral medulla. SNS stimulation increases BP by increasing cardiac output, vascular resistance, and fluid retention. Recent findings suggest that SNS also acts as an integrative interface between the brain and the immune system.[89] Perivascular macrophages in the blood-brain barrier can transfer peripheral inflammatory signals to the brain.[90] Inflammation of forebrain and hindbrain nuclei controlling the SNS efferent output from the brain is important in the development of neurogenic HTN. Interestingly, lymphoid organs have an abundant supply of sympathetic innervation, and norepinephrine released into the lymphoid tissue by the autonomic nerves has an immunomodulatory function.[91] Furthermore, Ang II–induced HTN is dependent on the activation of nuclear factor κB in the paraventricular nucleus,[92] and direct injection of IL-1β into the paraventricular nucleus or via the intracerebroventricular route increases BP.[92,93] Thus, inflammation in specific regions of the brain is linked to systemic HTN.

TREATMENT STRATEGIES

A number of clinical studies have reported a strong association between inflammation and HTN. In a prospective cohort study, baseline levels of C-reactive protein were found to be independently associated with an increased risk for incident HTN.[94] Also, increased levels of inflammation-sensitive plasma protein fibrinogen, α1-antitrypsin, haptoglobin, ceruloplasmin, and orosomucoid are associated with a future increase in BP among healthy middle-aged men.[95] Despite the evidence for immune activation, anti-inflammatory drugs are not in general used to treat HTN. Experimental evidence supporting use of anti-inflammatory agents in the treatment of HTN is described throughout the review. In the clinical setting, preliminary findings suggest that minocycline, a centrally penetrating anti-inflammatory antibiotic, produces sustained BP reduction in a hypertensive individual.[96] Mycophenolate mofetil, which blocks T cell and B cell proliferation, reduces HTN in experimental models of HTN.[22,97] Preliminary reports show that treatment with mycophenolate mofetil resulted in a significant reduction in BP in patients with psoriasis and rheumatoid arthritis.[98] Another observational study suggested that long-term use of immunosuppressive medication may reduce arterial stiffness and improve BP control in patients with CKD.[99] Statins are known to have anti-inflammatory properties, which result in modest reduction in BP in hypercholesterolemic patients.[100] Monoclonal antibodies against IL-17A or IL-17RA, the IL-17A receptor has shown promising results in patients with psoriasis.[101,102] However, a meta-analysis examining the effect of anti–TNF-α agents in patients with rheumatoid arthritis is associated with increased risk of developing HTN.[102,103] Similarly, clinical trials have not demonstrated beneficial effect of vitamin antioxidants in HTN.[104,105] Despite convincing evidence linking inflammation to HTN, reducing inflammation has not been uniformly successful in reducing BP.

CONCLUSION

Evidence from human and animal studies strongly suggests an association between inflammation and HTN. It could very well be that HTN could be etiologically linked to abnormal immune response, which also plays a vital role in HTN-associated end organ damage. The cause-effect relationship is further confounded by the fact that a number of factors that are associated with HTN, such as obesity, insulin resistance, aging, and SNS activation, are also associated with inflammation. Evidence from experimental models of HTN supports the beneficial effects of immunomodulatory agents in the treatment of HTN. Further studies are required to identify the target for intervention and most effective agent with optimal risk-benefit ratio. Furthermore, whether such therapies could be effective in all types of HTN irrespective of

underlying etiology remains to be elucidated. Encouraging results from the Canakinumab Anti-inflammatory Thrombosis Outcome study[106] and the Low Dose Colchicine for Secondary Prevention of Cardiovascular Disease[107] study in reducing cardiovascular mortality and morbidity support the safety and efficacy of anti-inflammatory therapies in human subjects. At the present time, however, anti-inflammatory therapy for HTN remains an attractive concept, but not ready for prime time.

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