Circulation Research

HYPERTENSION COMPENDIUM

Hypertension

Do Inflammation and Immunity Hold the Key to Solving this Epidemic?

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ABSTRACT: Elevated cardiovascular risk including stroke, heart failure, and heart attack is present even after normalization of blood pressure in patients with hypertension. Underlying immune cell activation is a likely culprit. Although immune cells are important for protection against invading pathogens, their chronic overactivation may lead to tissue damage and high blood pressure. Triggers that may initiate immune activation include viral infections, autoimmunity, and lifestyle factors such as excess dietary salt. These conditions activate the immune system either directly or through their impact on the gut microbiome, which ultimately produces chronic inflammation and hypertension. T cells are central to the immune responses contributing to hypertension. They are activated in part by binding specific antigens that are presented in major histocompatibility complex molecules on professional antigen-presenting cells, and they generate repertoires of rearranged T-cell receptors. Activated T cells infiltrate tissues and produce cytokines including interleukin 17A, which promote renal and vascular dysfunction and end-organ damage leading to hypertension. In this comprehensive review, we highlight environmental, genetic, and microbial associated mechanisms contributing to both innate and adaptive immune cell activation leading to hypertension. Targeting the underlying chronic immune cell activation in hypertension has the potential to mitigate the excess cardiovascular risk associated with this common and deadly disease.

Key Words: autoimmunity ■ cytokines ■ dendritic cells ■ hypertension ■ immunity ■ inflammation ■ T-lymphocytes

Hypertension is the worldwide leading cause of mortality and disability, accounting for nearly half of all strokes, heart failure, myocardial infarction, kidney damage, increased maternal mortality, and cognitive dysfunction.[1–6] By calendar year 2000, the worldwide prevalence of hypertension was estimated as 31.1%, affecting 1.39 billion people. By 2016, an elevated blood pressure (BP) was ranked as the leading risk factor for global burden of disease in both developed and underdeveloped countries.[7] The annual increase in the worldwide prevalence of hypertension has accelerated over the last decade, becoming responsible for 10.8 million or 19.2% of all attributable deaths in 2019.[8] This increase is in part due to the aging population, particularly in Western, high-salt consuming societies, since about 70% of adults develop hypertension by age 70. Recent recognition of the prognostic significance of lower levels of BP elevation led the American Heart Association and American College of Cardiology to reclassify hypertension as starting at 130/80 mm Hg.[9,10] According to this reclassification, nearly half of the adult United States population currently suffers from hypertension.

Hypertension Compendium

Major advances in the pharmacological treatment of an elevated BP occurred over the past 5 decades. However, despite the effort of major national and international societies and public health organizations, rates of control of BP have been dismal. In the United States, where hypertension accounts for $46 billion in annual health care costs, data from the National Health and Nutrition Examination Survey show that control rates increased from 31.8% in 1999 to 2000 to a maximum which

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Nonstandard Abbreviations and Acronyms

ACE2	angiotensin-converting enzyme 2
Ang II	angiotensin II
AP-1	activator protein 1
ARB	angiotensin receptor blocker
ART	antiretroviral therapy
BAFF-R	B-cell activating factor receptor
BP	blood pressure
C5aR1	C5a receptor 1
CANTOS	Canakinumab Anti-Inflammatory Thrombosis Outcome Study
COVID-19	coronavirus disease 2019
COX	cyclooxygenase
DASH	dietary approaches to stop hypertension
DC	dendritic cells
DOCA	deoxycorticosterone acetate
ENaC	epithelial sodium channel
Foxp3	forkhead box P3
GATA4	GATA-binding protein 4
GFP	green fluorescent protein
GM-CSF	granulocyte-macrophage colony-stimulating factor
GPR43	G-protein coupled receptor 43
GWAS	genome-wide association studies
HsCRP	high sensitivity C-reactive protein
IFN-γ	interferon gamma
IL	interleukin
ILCs	innate lymphoid cells
IsoLGs	isolevuglandins
LPS	lipopolysaccharide
LysM iDTR	myelomonocytic cells expressing lysozyme M
MHCI	major histocompatibility complex I
MIP-1a	macrophage inflammatory protein 1α
NCC	sodium chloride co-transporter
NFAT	nuclear factor of activated T cell
NF-κB	nuclear factor-kappaB
NLRP3	NOD-like receptor family pyrin domain containing 3
NOD	nucleotide oligomerization domain
PLWH	people living with HIV
RA	rheumatoid arthritis
SGK1	serum and glucocorticoid- regulated kinase
SIGLEC-6	sialic acid-binding Ig-like lectin-6
SLE	systemic lupus erythematosus
SNP	single nucleotide polymorphism
SR	salt resistant
SS	salt sensitive
SSBP	salt sensitivity of blood pressure
Tc	T cytotoxic
TCR	T cell receptor
Tfh	T follicular helper
Th	T helper
TMAO	trimethylamine-N-oxide
TNF-α	tumor necrosis factor α
Tregs	T regulatory cells
VEGF	vascular endothelial growth factor
WT	wild type

barely exceeded half all hypertensives (53.8%) in 2013 to 2014, and unfortunately declined again most recently to 43.7% in 2017 to 2018 (or to 38.9% if applying the cutoffs in the new American Heart Association-American College of Cardiology guideline).[11] These values in the community at large are very disappointing because in certain health care systems, it has been shown that control can be achieved in >80% of the patients.[12] The reasons for poor rates of control of hypertension include those pertaining to the health care system: (1) overestimation of office BP by improper recording techniques, which may occur in up to one-third of apparent resistant patients with hypertension in primary care[13]; (2) lack of recognition of the white-coat phenomenon (ie, uncontrolled hypertension during the office visit but controlled the rest of the day) in about a third of apparently resistant patients[14,15] which although suspected due to lack of target organ damage or from discordance between home and office BP can only be diagnosed with a 24-hour ambulatory monitor, infrequently available in community health care settings; (3) lack of recognition of the pressor effect of illicit drugs or medications to treat concomitant disorders, including but not limited to nonspecific and COX (cyclooxygenase)-2-selective nonsteroidal anti-inflammatory agents, sympathomimetics (decongestants, diet pills, and cocaine), stimulants (methylphenidate, dextroamphetamine, amphetamine, methamphetamine, and modafinil), excessive alcohol consumption, oral contraceptives, cyclosporine, erythropoietin, VEGF (vascular endothelial growth factor) inhibitors, and licorice-containing products[16]; (4) undertreatment, as shown in a study of 150 000 uncontrolled hypertensive subjects among whom only 30% were on at least 3 antihypertensive agents and only 15% on a regimen considered optimal[17]; and (5) underdiagnosis of secondary forms of hypertension.

There are also social determinants of lack of control and patients' medication adherence such as stable income, housing, availability of healthy food, transportation, education, access to health care, health insurance, and barriers owing to racial bias. Medication adherence is also affected by the fact that hypertension is mostly an asymptomatic disease, whereas its treatment may produce untoward symptoms. Recent methods to investigate patients' adherence include administration of medications in the office followed by a 24-hour ambulatory recording[18] and measurement of drug concentrations by high pressure liquid chromatography–mass spectrometry in urine or serum. A pooled analysis of 9 high pressure liquid chromatography–mass spectrometry trials in apparently resistant hypertension estimated that poor adherence ranged from 13% to 46% of the subjects and full nonadherence from 2% to 35%.[19]

Taken together, the data above may suggest that solving the issue of uncontrolled hypertension falls within the realms of public policy, public health, health care organizations, health education, and the social sciences only. However, this would ignore 3 facts that belong exclusively in the biological realm and may contribute to either lack of control of hypertension or to suboptimal protection from hypertensive target organ damage by current therapies. These include (1) the existence of a group of subjects with truly resistant (or even refractory) hypertension, despite optimal treatment[20]; (2) the fact that half the hypertensive population belongs to the salt-sensitive phenotype or phenotypes, in whom salt may be a cardiovascular risk factor independent of BP, particularly in terms of target organ damage[21]; and (3) the puzzling observation that the residual risk of well treated and controlled hypertensive subjects, assessed by longitudinal study of outcomes, is higher than that of untreated normotensive subjects at the same BP level.[22] The goal of this review is to highlight the role of inflammation as an important underlying mechanism that confers cardiovascular risk, even in controlled hypertension (Figure 1).

RESISTANT AND REFRACTORY HYPERTENSION

Truly resistant hypertension is defined as uncontrolled BP while on 3 antihypertensive agents of different classes including a diuretic, or as BP controlled with 4 or more agents. A more severe subgroup of patients is defined as having refractory hypertension when they remain uncontrolled after 6 months of treatment by a hypertension specialist, usually despite 6 or more antihypertensive agents. Both resistant and refractory hypertension are more common among Black individuals living in the southern United States stroke belt. After excluding all causes of pseudo-resistance described above, the prevalence of truly resistant hypertension is about 6% of all patients with hypertension and that of refractory hypertension about 5% to 10% of all individuals with resistant hypertension.[23] The intuitive explanation for lack of BP control in these patients is that the prevailing

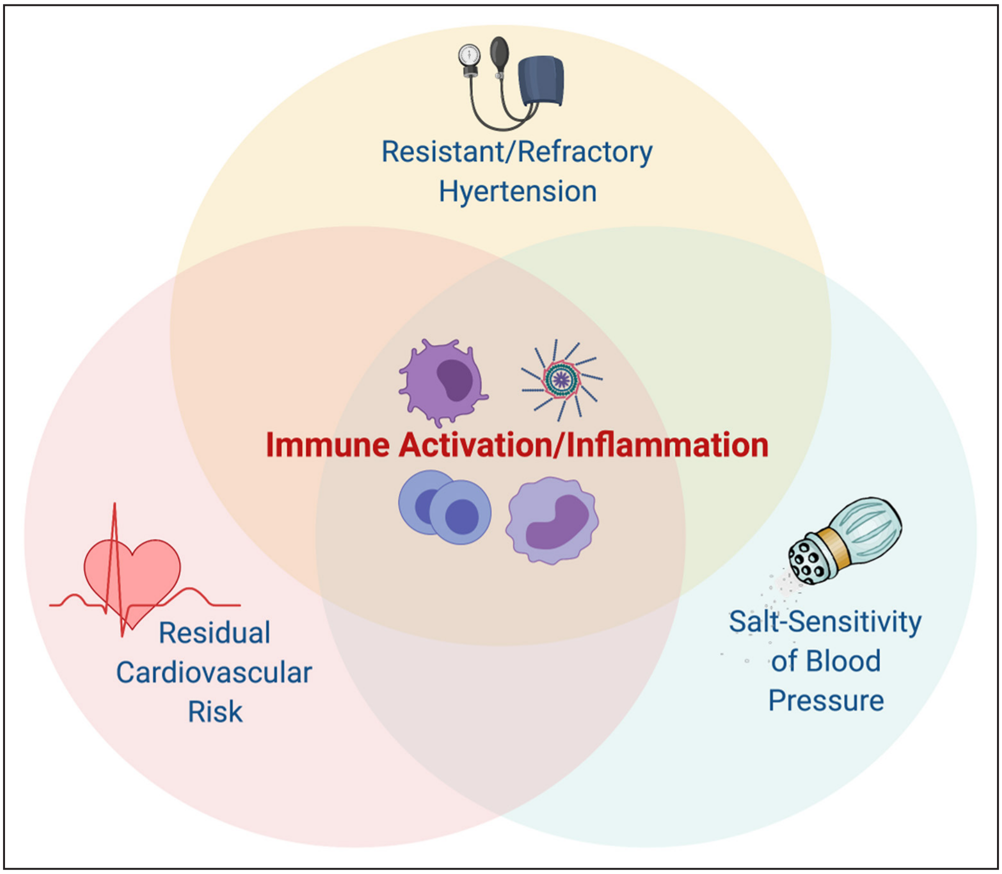

Figure 1. Proposed role of immune activation in hypertension.
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pressor system (or deficient depressor system) underlying their BP elevation has not been addressed by any of the mechanisms of action of the employed medications. A historical precedent for this assumption exists because spironolactone, an agent previously used mostly as a potassium sparing diuretic, became the most useful add-on drug for resistant hypertension, once it was understood that many of these subjects had aldosterone levels inappropriately high for their salt balance or level of activation of the renin-angiotensin system.[24]

Analogously, recent recognition that some patients with severe hypertension do not respond to spironolactone but exhibit depressor responses to amiloride suggests that another as of yet uncommonly treated mechanism underlying their hypertension is a mineralocorticoid-independent excessive activation of the EnaC (epithelial sodium channel). These patients have a variant single nucleotide polymorphism (SNP) in the CYP4A11 gene, which codes for a monooxygenase.[25] Deletion of the monooxygenase *Cyp4a10* in mice leads to diminished expression of renal epoxygenases, with ensuing decreases in vasodilator and natriuretic epoxyeicosatrienoic acids and development of salt-sensitive hypertension.[26] A mineralocorticoid-independent activation of ENaC is also supported by the facts that BP reduction produced by spironolactone in refractory subjects was half that observed in resistant ones, despite their equal renin and aldosterone plasma levels, and that in severe, low renin hypertension in Blacks, responses to amiloride were twice as potent as those to spironolactone.[20,27] It is, therefore, likely that lack of BP control in a large number of hypertensive subjects may be due to still unrecognized, therefore untreated, additional mechanisms. A possible role for these drugs in dampening the inflammation associated with hypertension is discussed below.

SALT SENSITIVITY OF BP

Salt sensitivity of BP (SSBP) is a phenotype of humans and other mammals whereby a certain proportion of the population exhibits changes in BP that parallel changes in salt intake or salt balance. In normotensive humans, about one-quarter of subjects exhibit significant increases in BP with salt loading and decreases in BP with salt depletion. In hypertensive humans, the prevalence is about 50% and even higher in certain subpopulations (eg, Blacks, 75%–80%). The SSBP phenotype has genetic and environmental components. The former was suspected from studies in siblings and twins but finally demonstrated by the ability to inbreed purely salt sensitive (SS) and salt resistant (SR) strains of rodents, such as the Dahl rats.[28] The latter was supported by a major effect of aging in increasing SSBP over time, as well as additional effects of race, sex, and measures of adiposity.[29] In the DASH (Dietary Approaches to Stop Hypertension) low sodium trial, women sustained ≈2 mm Hg greater BP reduction than men and the prevalence of SSBP in women increases significantly with menopause, which has been attributed to loss of beneficial effects of estrogens on the nitric oxide vasodilator system.[30]

There is an ongoing controversy on whether the primary abnormality in SSBP is a defect in the sodium excretory functions of the kidney or in the ability of vascular smooth muscle cells to normally respond to a salt load with vasodilation. The renal excretory hypothesis prevailed for many years, based on the concept of the infinite gain of the renal function curve proposed by Guyton and coworkers. Within this construct, derived from mathematical modeling, it was impossible to sustain the pressor effect of any hypertensive stimulus if a normal kidney managed to excrete enough salt to restore normotension.[31] Consistent with this hypothesis, abnormalities in about 100 genes, the products of which participate somehow in regulation of sodium excretion have been described.[21] However, differences in cardiac output or plasma volume in response to salt loading of SS and SR humans or animals have not been observed, and they are a prerequisite to accept that ensuing total body autoregulation is responsible for the increased total peripheral resistance of essential hypertension. The vascular hypothesis is based on the observation that when humans are exposed to a salt load, the SR subjects sustain rapid vasodilation for maintenance of normal BP whereas the SS ones fail to vasodilate and develop salt-dependent hypertension. These changes have been observed as rapidly as 24 hours, and without differences in cardiac output between the SS and SR groups, making it highly unlikely that autoregulation underlies the vasoconstriction.[32]

Regardless of its mechanism, SSBP is a cardiovascular risk factor with a similar pattern of target organ damage in rodents and humans, characterized by predominant renal damage, stroke, and left ventricular hypertrophy, somewhat different from the predominant atherosclerotic disease observed in SR forms of hypertension. The role of SSBP as a risk factor is independent of BP, and results in increased cardiovascular morbidity and mortality,[33,34] which cannot be tackled therapeutically owing to lack of understanding of its causation. The genetic abnormalities mentioned above involve multiple vasoactive and natriuretic regulatory systems, including renal transporters and metabolic-, angiogenic-, and inflammation-related substances. Because many of these systems interact, it has not been possible to date to define a primary abnormality. It is also possible that SSBP is not one but several phenotypes instead, with different polygenic causation. The question of how salt ultimately raises BP and produces target organ damage in SS subjects is obviously not settled. However, recent developments about the effects of sodium on immune function may be important in this regard as discussed below.

RESIDUAL CARDIOVASCULAR RISK

Long-term follow-up of thousands of well treated and well controlled patients with hypertension has clearly shown that their risk for cardiovascular complications is not reduced by antihypertensive treatment to the level expected from epidemiological observations in normotensive subjects with the same level of BP. This nonreversible excess residual risk was found to be 50% for any cardiovascular event, 46% for coronary disease, 75% for stroke, and 62% for cardiovascular death.[35] In this study, residual risk for coronary events was greater for calcium channel blockers, whereas that for stroke was greater for angiotensin-converting enzyme inhibitors, suggesting that at least in part, residual risk may depend on specific effects of pharmacological agents with different mechanisms of action on protection from organ damage or its lack thereof.

Also, high-risk individuals with most severe BP elevation benefit the most from therapy in terms of absolute number of events because antihypertensive agents produce the same relative risk reduction across any level of severity of hypertension. Paradoxically, these high-risk subjects with the most benefit from therapy are also left with the worst residual risk. It has, therefore, been proposed that preexisting or nonreversible target organ damage may be a major determinant of residual risk,[36] which is supported by the observation that up to one-third of optimally treated patients with hypertension have silent asymptomatic cardiac abnormalities.[37] However, when investigators of the Framingham Offspring Cohort analyzed the multivariate calculated hazard ratios for residual risk excluding and including a covariate score representing the preexisting burden of cardiovascular disease (left ventricular hypertrophy, systolic dysfunction, carotid ultrasound abnormality, peripheral artery disease, and microalbuminuria), they showed that preexisting target organ damage contributed at most 20% to the variability of the residual risk.[38] In other words, about 80% of the residual excess risk of optimally treated patients with hypertension remains unexplained. This strongly suggests that some fundamental pathophysiological mechanism that underlies the organ damage of hypertension is not reversed, or even remains ongoing despite normalization of BP, because currently available antihypertensive therapies do not address it. In this regard, we discuss below the role of inflammation in hypertensive target organ damage, which we believe is both a cause and consequence of tissue injury in hypertension.

INFLAMMATION IN HYPERTENSION

Inflammation is a critical component of immune activation normally required to eliminate invading pathogens. However, chronic low-grade inflammation contributes to the pathogenesis of an array of human diseases. Immune cells and their cytokines have been associated with BP elevation and end-organ damage for several decades, yet no therapies targeting inflammation in hypertension have been developed, and there is a paucity of clinical trials to understand the impact of anti-inflammatory agents on hypertension. In the recent CANTOS trial (Canakinumab Anti-inflammatory Thrombosis Outcome Study), inhibition of IL (interleukin)-1β using the human monoclonal antibody canakinumab reduced inflammatory markers including hsCRP (high sensitivity C-reactive protein) and IL-6 and cardiovascular events, but did not reduce development of incident hypertension or modify the relationship between hypertension and cardiovascular events. This suggests that the cardiovascular benefit of canakinumab was directly due to reduction in inflammation, not hypertension.[39–42] While these studies seem inconsistent with prior evidence suggesting a role of inflammation in the causation of hypertension, a secondary analysis of the CANTOS trial revealed a trend for greater reductions in major adverse cardiac events in people belonging to the highest BP quartile, suggesting that perhaps those with the most severe hypertension had the highest levels of inflammation.[43] Further studies are necessary to determine if finer stratification of hypertension status or the use of other inflammatory markers might identify those likely to benefit the most from IL-1β inhibition. In keeping with this, we recently performed an RNA sequence analysis of circulating monocytes from normotensive and hypertensive humans. We identified 60 genes that were differentially expressed in monocytes from hypertensive humans, many of which are related to IL-1β and IL-18, products of the inflammasome.[44] Together, these studies suggest a potentially important role for the inflammasome in the pathogenesis of hypertension and cardiovascular disease.

THE INFLAMMASOME IN HYPERTENSION

During hypertension, the potent vasoactive molecules such as endothelin-1, aldosterone, and Ang II (angiotensin II) act as priming stimuli able to activate the inflammasome (Figure 2).[45] Triggering of NLRP3 (NOD [nucleotide oligomerization domain]-like receptor family pyrin domain containing 3) activation and inflammasome assembly occur through either ATP-induced K^+ efflux or generation of reactive oxygen species, which are considered classical activators of the NLRP3 inflammasome during hypertension.[46] The NLRP3 inflammasome plays a pivotal role in the chronic, uncontrolled inflammation that is present in hypertension and other cardiovascular diseases, as supported by the fact that NF-κB (nuclear factor-κB) activity is increased in experimental and human hypertension, with consequent increases in tissue and circulating levels of the proinflammatory cytokines IL-1β and IL-18.[47,48] These cytokines exert effects on immune cells, including monocytes, macrophages, and dendritic cells (DCs) and also nonimmune cells, such as vascular endothelial and smooth muscle cells.[46] Moreover,

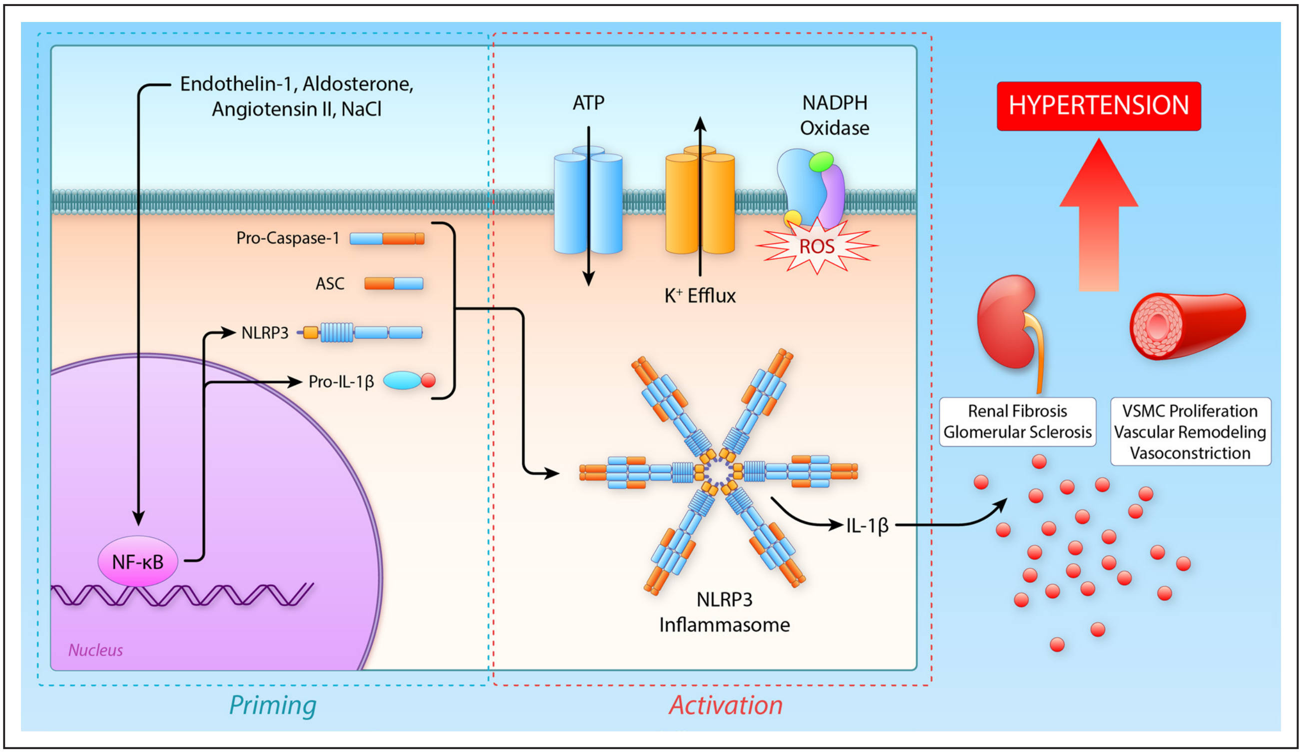

Figure 2. The NLRP3 (NOD-like receptor family pyrin domain containing 3) inflammasome in hypertension.
The NLRP3 inflammasome begins its activation through a priming step mediated by the transcription factor NF-κB (nuclear factor-κB), which upregulates inflammasome components NLRP3 and pro-IL (interleukin)-1β. Multiple endogenous vasoactive molecules including endothelin-1, aldosterone, angiotensin II, and NaCl can serve as priming stimuli. A second activation step is needed to trigger the formation of the components into the NLRP3 inflammasome signaling complex. Once assembled, caspase-1 proteolytically cleaves pro-IL-1β into the released IL-1β. NLRP3 inflammasome activation has been shown to play a role in the induction of renal injury and vascular remodeling, ultimately leading to hypertension (Illustration Credit: Ben Smith). ASC indicates apoptosis-associated speck-like adaptor protein; ROS, reactive oxygen species; and VSMC, vascular smooth muscle cell.

NLRP3 gene polymorphisms have been associated with hypertension, and elevated IL-1β expression has been observed in patients with essential hypertension.[49–51]

Actions on the vasculature and kidney contribute to the role of the inflammasome in cardiovascular disease. A phenotypic switch in vascular smooth muscle cells plays a major pathophysiological role in vascular disease, including hypertension, as an important initiating factor in vascular remodeling. Deletion of the NLRP3 gene attenuated Ang II–induced vascular inflammation and most importantly, it inhibited vascular remodeling and hypertension in mice.[52] Also, NLRP3 deficiency in spontaneously hypertensive rats attenuated vascular smooth muscle cell phenotypic transformation and proliferation, which in turn reduced BP.[53] Moreover, inhibition of SGK1 (serum and glucocorticoid- regulated kinase), with consequent negative regulation of NLRP3, reduced the cardiovascular inflammatory response associated with Ang II hypertension.[54]

Renal inflammation is another typical feature of hypertension and strongly correlates to the severity of increased BP.[55,56] Inhibition of NF-κB with resultant negative regulation of NLRP3 expression abolished the hypertension and renal cortex inflammation of spontaneously hypertensive rat.[57] Mice deficient in NLRP3 were protected against Ang II–induced podocyte injury and mitochondrial dysfunction,[58] and genetic deletion of NLRP3 attenuated aldosterone-induced podocyte injury and glomerular sclerosis.[59,60] On the contrary, excessive aldosterone-induced NLRP3 inflammasome activation in podocytes was abolished by treatment with antioxidants and eplerenone.[59] The renal NLRP3 inflammasome also has a role during salt-sensitive hypertension,[61,62] perhaps because NaCl is a priming stimulus for its activation.[63] Consistent with this, inhibition of NLRP3 reduced BP, renal fibrosis, and inflammation in the murine deoxycorticosterone acetate (DOCA) salt model.[62] Finally, ongoing studies of our group aim to investigate a possible role for immune-specific inflammasome expression in hypertension, particularly in antigen-presenting myeloid cells.

GWAS STUDIES OF HYPERTENSION SUGGEST A PATHOGENIC ROLE FOR INFLAMMATION

Familial studies have provided estimates of substantial heritability of BP at ≈30% to 60%.[64] While a limited number of monogenic disorders involving mutations in ≈30 genes have been identified to promote hypertension development, these disorders are exceedingly rare.[65] Most genetic contribution to hypertension is, therefore, believed to be polygenic. Recent approaches have centered on large-scale evaluation of common genetic variations through the use of genome-wide association studies (GWAS). Beginning in 2007, GWAS of hypertension first became large enough to identify genome-wide significant associations of about 8 genomic loci.[66,67] Further studies have confirmed and extended these findings with increasingly larger populations. To date, these studies have revealed nearly 1000 genetic variants associated with hypertension and BP.[68] Though individual SNPs make small overall contributions to alterations in BP, together these SNPs explain about 27% of the estimated heritability of BP.[65] Clearly, additional heritability remains to be discovered; however, the large number of identified polymorphisms and genetic loci associating with hypertension from GWAS provide tremendous potential to enhance our understanding of the genetic contributions and novel pathogenic mediators of the disease.

While GWAS have identified SNPs in genetic loci with roles in classical mechanisms of hypertension such as vasoconstriction, sodium reabsorption, and sympathetic nervous system activity, identified genetic loci are also associated with inflammation and immunity. A recent meta-analysis by Rodriguez-Iturbe et al[69] demonstrated that of 97 distinct genes containing SNPs associated with hypertension from multiple GWAS, 81 of these have direct or indirect roles in inflammation and immunity. This includes SNPs associated with major histocompatibility complex alleles which are classically linked with autoimmunity, and SNPs associated with genes involved in myeloid and T-cell activation such as GATA4 (GATA-binding protein 4), RELA proto-oncogene NF-κB subunit, SGK1, and NFAT5 (nuclear factor of activated T cells 5). These findings suggest an important role for inflammation and immunity in hypertension. However, one of the challenges in determining the importance of hypertension-associated polymorphisms is in determining causality. Most lead SNPs in GWAS studies are in intergenic and noncoding regions, making determination of their potential functional role challenging. As a result, only a very limited number of SNPs and associated genetic loci have undergone direct testing for causal or mechanistic roles in hypertension.[65]

Meta-analyses of GWAS results combined with integration of clinical, transcriptomic, epigenomic, and protein interaction networks have helped prioritize candidate causal SNPs.[68] One such approach by Huan et al identified several genes including *SH2B3*, *ATXN2*, *NMT1*, and *NSF* as key drivers of hypertension. Of these, SH2B3 is of particular interest as an intracellular adaptor protein that negatively regulates inflammatory cytokine and growth factor signaling. A polymorphism in *SH2B3*, rs3184504, is strongly associated with hypertension in multiple GWAS studies, and also with a variety of autoimmune diseases.[66,70–72] This polymorphism is a missense SNP that converts an arginine encoded by the major allele to a tryptophan encoded by the minor allele within the plekstrin homology domain of the protein. Although the effect of this polymorphism on SH2B3 protein function and hypertension development is unknown, genetic deletion of *Sh2b3* in mice results in increased Ang II–induced BP, enhanced renal and endothelial injury, and enhanced T-cell IFN-γ production. Increases in BP were most prominent with selective deficiency of SH2B3 in bone marrow-derived cells.[73] These findings suggest that SH2B3 plays an important role to limit BP elevation and end-organ damage through reduced inflammatory signaling and T-cell activation. Interestingly however, deletion of a 6 base pair region in the SH2 domain of SH2B3 in rats led to a decrease in BP,[74] suggesting that genetic alterations in discrete portions of the protein may have differing effects. These findings indicate the importance of determining the direct effect of the rs3184504 missense SNP in hypertension, as well as the multitude of other identified inflammation-related SNPs and genetic loci that to date have remained untested.

In summary, GWAS studies have provided powerful insights into the genetic basis of hypertension and suggested an important role for inflammation and immunity. The large number of genetic loci identified to date has the potential to provide key insights into pathophysiological mechanisms. Because hypertension is a complex, multisystem disease, it necessitates testing for causal roles of individual SNPs and genetic loci in in vivo models. Use of technology such as CRISPR-Cas9 to directly introduce polymorphisms into mice and other animal models holds the potential to test causal roles and determine mechanisms for SNPs identified in humans as a reverse translational approach. Combining these approaches with bioinformatic methodologies to prioritize SNPs most likely to play causal roles has the potential to greatly inform our fundamental understanding of the pathogenesis of hypertension and the search for new therapies.

MYELOID IMMUNE CELL POPULATIONS IN HYPERTENSION

Monocytes and Macrophages

The importance of innate immunity in the development of hypertension and its associated end-organ damage has been demonstrated over the last several decades.[75,76] Seminal studies investigated the role of myeloid cells, specifically monocytes, macrophages, and DCs, in antigen presentation and production of proinflammatory cytokines that promote hypertension (Figure 3).[77–81] Ablation of myelomonocytic cells expressing lysozyme M (LysM iDTR) by low-dose administration of diphtheria toxin completely abrogated the rise of BP in response to a pressor dose of Ang II. Moreover, deletion of LysM$^+$ monocytes prevented

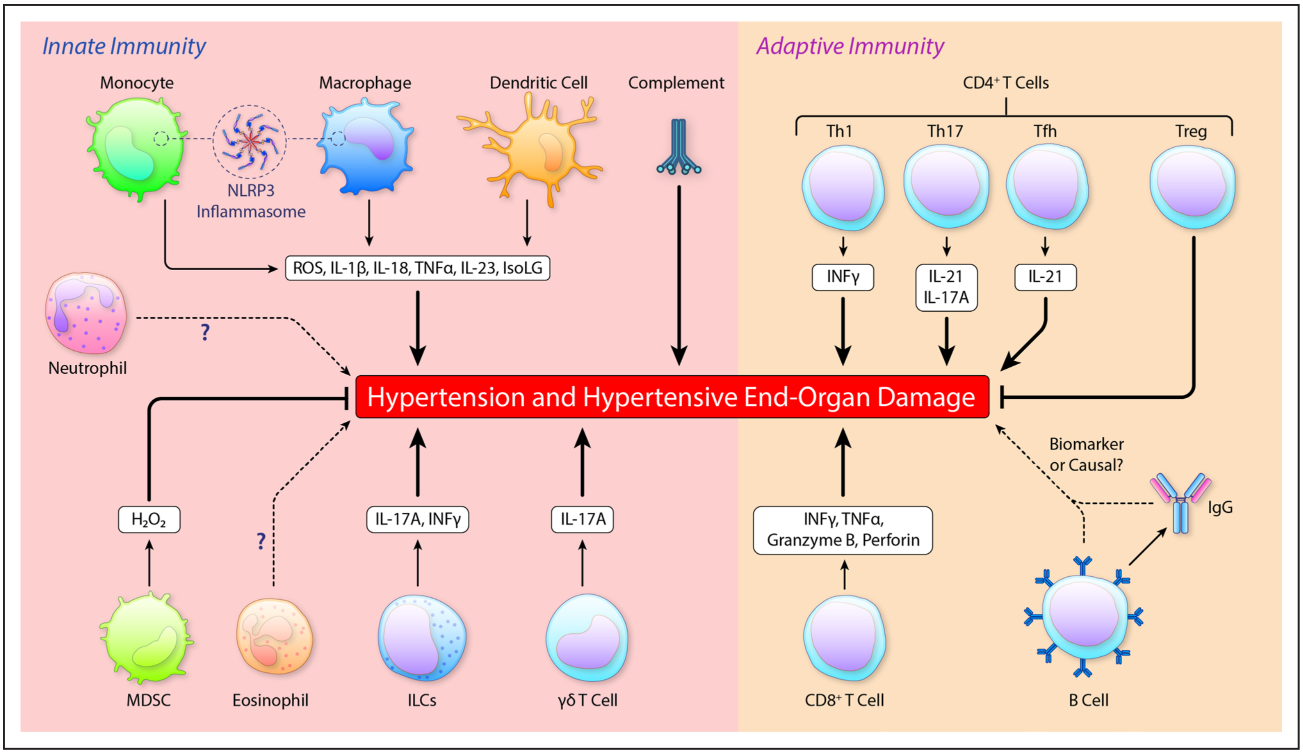

Figure 3. Innate and adaptive immune cells that have been implicated in hypertension pathophysiology.

Cells of the innate and adaptive immune system secrete factors including reactive oxygen species (ROS), hydrogen peroxide (H_2O_2), and cytokines that promote or inhibit hypertension and hypertensive end-organ damage. The role of eosinophils and B cells, which secrete immunoglobulins such as IgG, is still unclear (Created with BioRender.com; Illustration Credit: Ben Smith). IFN-γ indicates interferon γ; IL, interleukin; ILC, innate lymphoid cell; MDSC, myeloid-derived suppressor cell; NLRP3, NOD-like receptor family pyrin domain containing 3; and TNF-α, tumor necrosis factor α.

both vascular endothelial and smooth muscle dysfunction through a reduction in vascular superoxide formation.[81] In a translational study, Loperena et al[79] showed that human aortic endothelial cells undergoing uniaxial hypertensive stretch (10% stretch; 1 Hz) for 48 hours promoted conversion of human classical monocytes (CD14^{++}/CD16^{-}) to an intermediate monocyte phenotype (CD14^{+}/CD16^{++}) which produces proinflammatory cytokines (IL-6, IL-1β, IL-23, and tumor necrosis factor α [TNF-α]) and drive T-cell proliferation from the same human volunteers. This demonstrated a critical role for immune and endothelial cell crosstalk in the promotion of inflammation during hypertensive stimuli (Figure 4). This phenotypic conversion to intermediate monocytes was hydrogen peroxide and IL-6 dependent, as shown by its prevention by scavenging of hydrogen peroxide with catalase or neutralization of IL-6. Interestingly, 10% stretch of human aortic endothelial cells promotes the upregulation of cluster of differentiation 209 (CD209; DC-SGN), demonstrating a critical role of the endothelium in monocyte and monocyte-derived DC activation in an ex vivo model of hypertension.[79] In keeping with this, we demonstrated that in response to exposure to high salt (190 mmol/L NaCl) in vitro, human monocytes are activated by accumulation of highly reactive isolevuglandins (IsoLGs), with upregulation of co-stimulatory molecules (CD83 and CD86) and secretion of the proinflammatory cytokines IL-1β, TNF-α, and IL-6.[82] This sodium dependent activation of monocytes was mediated by the nicotinamide adenine dinucleotide phosphate oxidase. Immunodeficient (NOD-scid IL2Rγ null; NSG) mice fed a high-salt (4%) chow diet before receiving adoptive joint transfer of human monocytes and T cells demonstrated a profound T-cell proliferation and activation of T cells by IFN-γ and IL-17A production compared with mice fed a normal-salt diet. Taken together, these studies demonstrate a critical role of monocytes and macrophages in the development of hypertension and end-organ damage.

Prohypertensive DCs and the Role of ENaC

DCs have been demonstrated to play a critical role in the promotion of hypertension and its associated inflammation.[77,78,80] We found that immunogenic IsoLG-modified peptides were presented by activated DCs which secreted IL-6 and IL-1β and drove proliferation of T cells, hypertension, and of its associated end-organ damage. Scavenging of IsoLG-adducts with 2-hydroxybenzilamine, abrogated the increase in systolic BP in response to both Ang II-induced and DOCA-salt hypertension.[78] More recently, we found that genetic deletion of SGK1 in antigen-presenting cells and DCs prevented vascular dysfunction and the

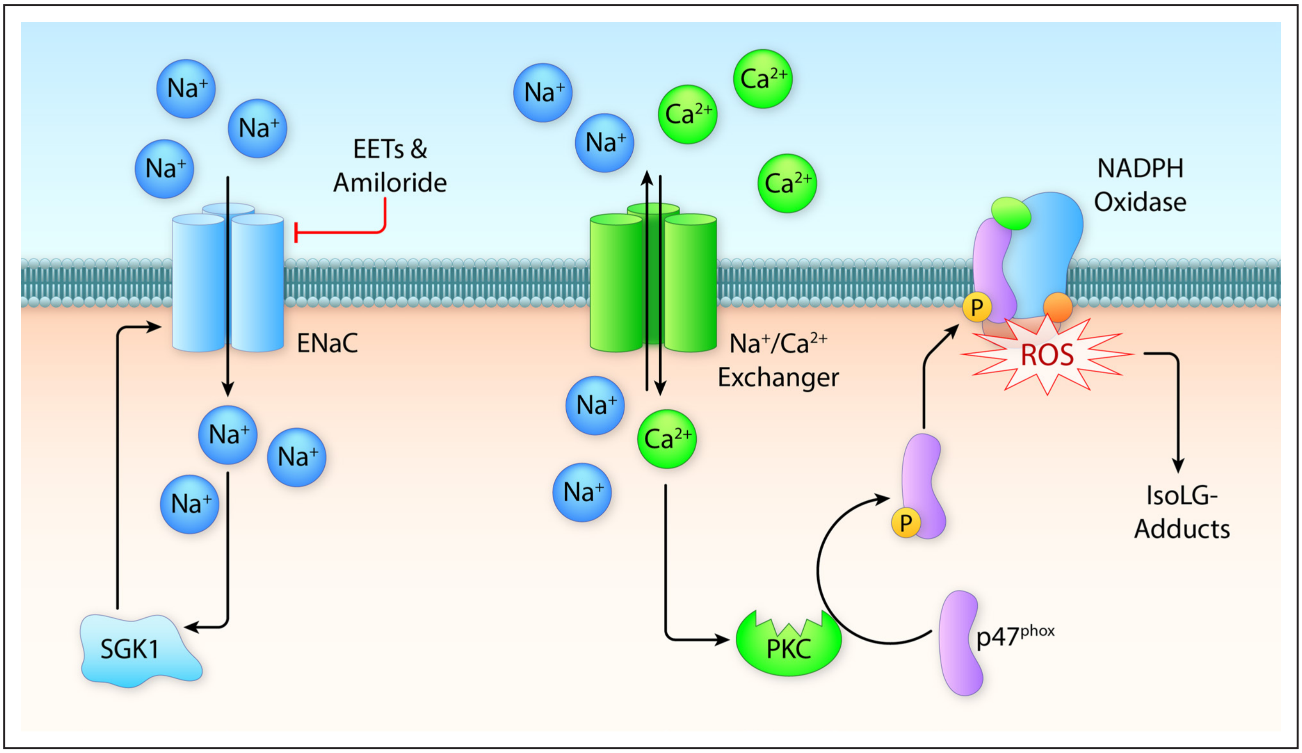

Figure 4. Aldosterone-independent activation of EnaC (epithelial sodium channel) in immune cells.
Extracellular Na$^+$ activates the amiloride-inhibitable channel ENaC, which leads to influx in intracellular calcium via the sodium-calcium exchanger. This influx of Ca2$^+$ activates PKC (protein kinase-C). PKC then phosphorylates p47*phox* leading to the assembly and activation of NADPH oxidase and subsequent production of superoxide and isoLG-adducted proteins. Increased intracellular sodium influx stimulates SGK1 (serum and glucocorticoid–regulated kinase) mediates expression and assembly of ENaC in immune cells. Additionally, epoxyeicosatrienoic acids (EETs) inhibit ENaC channel activity in these cells (Illustration Credit: Ben Smith).

development of salt-sensitive hypertension through an nicotinamide adenine dinucleotide phosphate oxidase mechanism. Also, in vitro SGK1 inhibition with GSK650934 prevented the salt-dependent increase in IsoLG-adducts in CD11c$^+$ cells.[80] Moreover, Hevia et al[83] found that cell-specific expression of the diphtheria toxin receptor under the control of the CD11c promoter prevented mice from developing Ang II plus a high-salt diet-induced hypertension. This was in part due to modulation of the intrarenal renin–angiotensin system components and natriuresis and tubular sodium transporters.

We have shown that sodium enters DCs through ENaC, because such entry is blocked by amiloride, but not by diuretics that act on different transporters. Sodium is then exchanged for calcium via the sodium hydrogen exchanger. Also, sodium entry leads to increased expression of SGK1. Both calcium and SGK1-induced subunit assembly lead to activation of the nicotinamide adenine dinucleotide phosphate oxidase and accumulation of IsoLGs.[77] SGK1 also enhances assembly of ENaC subunits into active channels, which closes a feed forward loop for activation of DCs by salt. These DCs, after exposure to high (190 mmol/L) salt in vitro, prime an increase in systolic BP by a sub-pressor dose of Ang II, when adoptively transferred into naive recipient mice.[77]

Our observations about a role for DC ENaC in salt-induced hypertension are consistent with previous knowledge about the role for this ubiquitous channel in human hypertension. For example, although the reason for increased prevalence of SSBP in Black subjects is not fully understood,[84–86] these patients exhibit greater antihypertensive responses to amiloride compared with Whites, suggesting overactivity of ENaC. In addition to the ENaC gain-of-function and loss-of-function mutations described in Mendelian disorders of hypertension or hypotension,[87–97] numerous variants have been identified by gene sequencing among the 3 genes encoding ENaC subunits (dbSNP and TOPMed databases). Individuals who harbor gain-of-function variants may be at increased risk for salt-sensitive hypertension.[98]

Many human ENaC nonsynonymous SNPs affect channel function by altering the sodium self-inhibition response, whereby extracellular Na$^+$ binds to and inhibits ENaC. Numerous sites have been identified in different domains of the extracellular regions of mouse and human ENaC where amino acid substitutions alter channel activity by changing the sodium self-inhibition response.[99–107] Although many missense mutations are mostly silent or inhibit protein function,[108–110] a number of variants have been identified that have a gain-of-function phenotype reflecting a loss of sodium self-inhibition. Also, siblings with a mild Liddle syndrome phenotype and ENaC gain-of-function mutation (αC479R) have been reported.[98] The CYP-epoxygenase metabolite 11,12-epoxyeicosatrienoic acid inhibits ENaC by reducing channel open probability[111,112] and SNPs in epoxygenases associate with SSBP. Also, the BP of Blacks who are homozygous for the variant CC allele of a SNP (rs3890011) in the CYP4A11 monooxygenase responds to amiloride but not spironolactone, suggesting an aldosterone-independent activation of their ENaC.[25] All observations above, taken together, suggest that ENaC overactivity in immune cells and nonimmune tissues may exert a major role in severe and in salt-sensitive hypertension.

The characterization and definition of myeloid cells has evolved through advances in technology in recent years. Using single-cell RNA sequencing Villani et al[111] recently reclassified DC and monocyte populations in the circulation of normal human participants. They identified a new subset of DCs with surface expression of the receptor tyrosine kinase Axl, and SIGLEC-6 (sialic acid-binding Ig-like lectin-6) and termed them AS DCs. These AS DCs produce copious amounts of IL-1β, TNF-α, and IL-6 in response to Toll-like receptor stimulation, potently driving both $CD4^+$ and $CD8^+$ T-cell proliferation.[111] They also reclassified human classical ($CD14^+$) and nonclassical ($CD16^+$) monocytes into 4 different populations. The role of these novel monocyte and DC subsets in the development of inflammation and human hypertension is unknown and requires future investigation.

Anti-Inflammatory Myeloid Cells

Although the studies above demonstrate a crucial role of DCs in the promotion of inflammation and the development of hypertension, there are DC subsets that are anti-inflammatory and attenuate hypertension. Expression of A20 (a ubiquitin-editing protein involved in maintenance of immunologic homeostasis) in DCs prevents Ang II–induced hypertension,[113] with concomitant prevention of the activation and accumulation of T cells in the kidney.[113] Another subset of myeloid cells, myeloid-derived suppressor cells, also prevent the increase in BP and its associated inflammatory response in multiple models of murine experimental hypertension.[114] Adoptive transfer of these myeloid-derived suppressor cells improved vascular relaxation and prevented both renal and vascular immune cell infiltration in a murine model of hypertension.[115] These studies demonstrate that myeloid cell subsets can provide a crucial immunologic break to prevent inflammatory cascades in the development of hypertension.

Innate Lymphoid Cells and Natural Killer T Cells

Natural killer cells or innate lymphoid cells (ILCs) are activated and exert cytotoxic effects in hypertension. ILCs have been classified into 3 groups by their surface expression markers, cytokine production, and transcription factors.[116] ILC1s produce IFN-γ and the transcription factors *T-Bet*, *NFIL3*, and *Runx3.* ILC2s produce type 2 cytokines (IL-4, IL-5, IL-13, and IL-9) and the transcription factors *RORα*, *BCL11B*, *GATA3*, and *GFI1*. ILC3s express *RORγT*, *AHR*, and *ID2* and produce type 3 cytokines, (IL-22, IL-17, and GM-CSF [granulocyte-macrophage colony-stimulating factor]).[116] A role for ILCs in hypertension remains to be determined.

Natural killer T cells are innate lymphocytes that respond to the MHCI (major histocompatibility complex I)-related glycoprotein CD1d that specializes in presentation of lipid antigens. Although IsoLG-adducted proteins could represent lipid-modified antigens, we found that mice lacking Jα18 ($Ja18^{-/-}$ mice), an invariant α chain of the T-cell receptor on natural killer T cells, developed similar degrees of hypertension in response to Ang II as those observed in wild-type (WT) mice. Similarly, we found that the hypertensive response to Ang II in $Cd1d^{-/-}$ mice was identical to that observed in WT mice.[78] These studies indicate that Natural killer T cells or lipid antigens do not play a role in Ang II–induced hypertension and that IsoLGs do not act via the CD1d/natural killer T-cell axis.

Eosinophils

Eosinophils, which play a role in a number of immune-mediated diseases[117] are another innate immune cell-type that has recently been associated with hypertension. We found that people with hypertension had increased eosinophil counts compared with normotensive participants,[118] and that they were associated with increased body mass index. In contrast, virally suppressed HIV^+ persons with hypertension had increases in the eosinophil maturation and differentiation factor IL-5 but their eosinophil counts, also elevated, were independent of body mass. These studies suggest that HIV infection is accompanied by adipose tissue dysfunction that mimics that of obesity. The ultimate mechanisms by which eosinophils contribute to hypertension has not been elucidated.

Complement and Hypertension

The complement system is a lytic cascade of plasma and membrane bound proteins that plays key roles in homeostasis and host defense as an immune surveillance system. However, it is becoming increasingly recognized that complement also contributes to chronic inflammation. Complement activation leads to cleavage of complement proteins including C3 and C5 by C3 and C5 convertase, respectively.[119] Complement proteins produced by antigen-presenting cells and T cells regulate both innate and adaptive immune functions.[120–123] Complement activation has been implicated in experimental and human hypertension with effects on various cell types important for vascular and renal function.[124]

Circulating levels of C3 have been linked to incident hypertension and BP in humans.[125–127] Elevations in renal complement levels precede the onset of albuminuria in Ang II–induced hypertension.[128] C3 is increased in glomeruli of spontaneously hypertensive rats, and C3 inhibition blunts mesangial cell proliferation, indicating a role for C3 in renal remodeling.[129] Additionally, mice lacking C3 show decreased renal fibrosis and tubular atrophy in a unilateral ureteral obstruction model.[130] In a DOCA-salt model, perivascular adipose tissue was found to produce C3, which was required for proinflammatory macrophage phenotypes and adventitial remodeling.[131,132] These studies point to C3 as playing a critical role in renal and vascular damage. Circulating levels of C5a are also increased in human hypertensive subjects compared with controls.[133] There are conflicting reports on the role of C5aR1 (C5a receptor 1) in experimental hypertension. Weiss et al[134] reported that mice deficient in C5aR1 display decreased albuminuria in a uninephrectomy and Ang II model despite no change in BP. Paradoxically, cardiac fibrosis and heart weight are elevated in C5aR1-deficient mice. In contrast, Zhang et al[133] reported decreased cardiac fibrosis in C5aR1 deficient mice after Ang II infusion. Bone marrow transfer showed that hematopoietic C5aR1 expression is critical for protection from cardiac fibrosis. Intriguingly, mice deficient in both C3aR1 and C5aR1 have a blunted response to Ang II infusion which is associated with increased renal and circulating T-regulatory cells (Tregs).[125] Meanwhile, inhibition of C3 and C5 convertases in the Dahl salt-sensitive rat model did not affect BP or albuminuria.[135] While the cell-type specific effects of each element of the complement system remain to be fully elucidated, growing evidence suggests an important role for complement in hypertensive end-organ damage.

INFLAMMATORY CD4+/CD8+ T CELLS AND CYTOKINES IN HYPERTENSION

The critical role of T cells in hypertension was demonstrated in 2007 when Guzik et al[136] showed that recombinase activating gene 1 deficient (*Rag1*$^{-/-}$) mice, which lack T and B lymphocytes, are protected from the full development of hypertension and end-organ damage. Importantly, the hypertensive phenotype was restored by adoptive transfer of T but not B lymphocytes. Although some recent investigations using the *Rag1*$^{-/-}$ mice from Jackson Laboratory (United States) fail to show this protective phenotype,[137,138] a large body of literature published since then (see below) using different mouse models as well as human samples has firmly established an important role for T cells in hypertension. Possible explanations for this change in the *Rag1*$^{-/-}$ mice are discussed in Madhur et al[139] and underscores the complexity and plasticity of the immune system. Briefly, these include an expansion of a population of natural killer cells that compensate for the lack of adaptive immune cells by releasing cytokines normally released by T cells as well as potential changes in the microbiome.

T cells are classified by their surface markers, cytokine profile, and lineage determining transcription factors, with each subset exhibiting precise functions in health and disease. Major T-cell classes are CD4$^+$ T helper (Th) cells, CD8$^+$ T cytotoxic (Tc) cells, and CD4$^-$CD8$^-$ T cells, which includes the innate-like gamma delta ($\gamma\delta$) T cells (Figure 3). In response to signals from antigen-presenting cells or other environmental factors including the local cytokine milieu, CD4$^+$ Th cells further differentiate into pro- or anti-inflammatory subtypes including Th1 cells that produce interferon γ (IFN-γ) and respond to intracellular pathogens; Th2 cells that produce IL-4 and IL-5 and are involved in allergic disorders and parasitic infections; Th17 cells that produce IL-17A and IL-21 and are involved in autoimmunity and the response to extracellular pathogens; T follicular helper cells that produce IL-21 and signal to B cells to promote antigen-specific immunoglobulin production; and Tregs that produce IL-10 and suppress immune responses. CD8$^+$ T cells are similarly classified as Tc1, Tc2, Tc17, and CD8 Treg cells. With the exception of Th2 cells, which have not been well characterized in hypertension, and Treg cells which likely play a protective role (described below), the remaining Th subtypes (Th1, T follicular helper, and Th17) are primarily pathogenic in hypertension. Hypertension is associated with a skewing of Th cells into these proinflammatory subsets and away from the protective Treg phenotype. The signature cytokines of these proinflammatory T cells, namely IL-17A, IFNγ, and IL-21, have been shown to be elevated in hypertensive mouse models and in humans with hypertension.[140–143]

We first demonstrated a critical role for IL-17A in hypertension in 2010 by showing that IL-17A$^{-/-}$ mice develop blunted hypertension in response to Ang II infusion.[144] It is important to note that while the reduction in BP of ≈20 mm Hg seen in the IL-17A$^{-/-}$ mice compared with WT mice is a clinically significant reduction, the IL-17A$^{-/-}$ mice are still hypertensive. Despite this residual hypertension, the end-organ damage normally caused by Ang II is virtually abolished in these mice. They are protected from increases in vascular superoxide production and inflammation, endothelial dysfunction, aortic stiffness, and glomerular injury.[144–146]

Mechanistically, IL-17A acts on multiple cell types to promote increases in BP and target organ damage. In endothelial cells, IL-17A inhibits nitric oxide production via phosphorylation of the inhibitory site threonine 495 on endothelial nitric oxide synthase.[147] In vascular smooth muscle cells, IL-17A in conjunction with tumor necrosis factor α induces inflammatory cytokine and chemokine expression, thus promoting the recruitment of other inflammatory cells to the vessel wall.[144] IL-17A promotes aortic stiffening via increased collagen synthesis from aortic fibroblasts.[145] While the effects of IL-17A on aortic stiffness appear to be BP-dependent, IL-17A has BP-independent effects on small vessel remodeling and stiffness. Orejudo et al[148] showed that IL-17A infusion increases BP and promotes inward hypertrophic remodeling and stiffness of small mesenteric arteries even when hydralazine and hydrochlorothiazide are used to prevent the BP increase. In the kidney, IL-17A acts on proximal and distal tubular cells to increase renal sodium transporter abundance or activity.[146,149] In fact, this is a potential mechanism by which a number of inflammatory cytokines regulate salt and water balance and BP (reviewed in detail in Norlander and Madhur[150]). IL-17A also upregulates chemokines in the kidney and induces renal damage.[151]

As discussed above, salt-sensitivity of BP is an independent cardiovascular risk factor. In addition to its effects on DCs, salt can directly increase IL-17A production from Th17 cells and inhibit Treg cells in an SGK1 dependent manner.[152–154] We showed that deletion of SGK1 specifically in T cells attenuates Ang II and DOCA-salt induced hypertension, prevents the upregulation of Th17 cells in the spleen in response to Ang II, and abrogates hypertension–induced renal and vascular inflammation and end-organ damage.[155]

In an elegant study by Amador et al[156] using a DOCA salt-induced hypertensive rat model, the authors demonstrated an increase in Th17 cells and downregulation of Treg cells in the heart and kidneys. Interestingly, spironolactone treatment prevented the Th17 cell activation and increased numbers of Tregs. Antihypertensive therapy with reserpine, hydralazine, and hydrochlorothiazide, however, did not abrogate the Th17 response in this model, indicating that mineralocorticoid receptor activation and not the BP per second, underlies the Th17/Treg imbalance.[156]

Mineralocorticoid receptor signaling also plays an important role in increasing T-cell IFNγ production. While Th1 cells make IFN-γ, the major T-cell source of IFN-γ in hypertension is CD8$^+$ Tc1 cells.[73,143] Sun et al[157] showed that mineralocorticoid receptor deficiency specifically in T cells decreases Ang II–induced hypertension, attenuates renal and vascular damage, and mitigates hypertension-induced accumulation of IFNγ producing T cells, particularly CD8$^+$ T cells, in the aorta and kidney. Treatment of WT mice with eplerenone, a mineralocorticoid receptor antagonist, attenuated Ang II–induced hypertension and the accumulation of IFN-γ producing T cells.[157] In cultured CD8$^+$ T cells, these authors showed that the mineralocorticoid receptor interacted with the IFN-γ regulating transcription factors NFAT1 and AP-1 (activator protein 1), suggesting a potential mechanism by which mineralocorticoid receptor activation increases IFN-γ production in these cells.

We previously showed that IFN-γ deficient mice are protected from Ang II–induced hypertension, and that like IL-17A, IFN-γ has effects on renal sodium transporters.[73,149] Furthermore, we showed that IFN-γ production, particularly from CD8$^+$ T cells, likely underlies the increased hypertension and renal and vascular damage caused by deficiency of the lymphocyte adaptor protein, LNK/Sh2b3, which is described in more detail below.[73] However, it is important to note that the effects of IFN-γ signaling on BP and target organ damage are somewhat inconsistent between studies, suggesting that IFN-γ may have both beneficial and detrimental effects depending on the context. For example, Markó et al found that IFN-γ receptor deficiency had no effect on BP in response to a much higher dose of Ang II than used in our studies. Importantly however, despite a lack of BP protection, IFN-γ receptor deficiency resulted in reduced cardiac hypertrophy, inflammation, fibrosis, and arrhythmogenic electrical remodeling. In the kidney, IFNγ receptor deficiency reduced inflammation and tubulointerstitial damage.[158] In a hypertensive chronic kidney disease model characterized by a high dose of Ang II infusion combined with uninephrectomy, Zhang et al[159] did not observe an effect of IFN-γ deficiency on BP or albuminuria. In contrast, Garcia et al showed that IFNγ may actually play a protective role in the heart. In an aldosterone-dependent hypertensive model, these authors showed that although IFN-γ deficiency decreased BP, it was associated with increased cardiac hypertrophy and worse diastolic dysfunction.

Although IFNγ signaling seems to have mixed effects on target organ damage, CD8$^+$ T cells do seem to play an important role in hypertension, which may be mediated in part by their other functions involving both secreted factors and direct cell contact. Youn et al[160] profiled T cells from humans with and without hypertension and found an increase in immunosenescent, proinflammatory CD8$^+$ T cells in hypertensive subjects. These cells are characterized by loss of the surface marker CD28 and presence of CD57. These authors also noted an increase in CD8$^+$ T cells expressing perforin, granzyme B, IFNγ, and TNF-α. Interestingly, hypertensive subjects also had higher circulating levels of granzyme B and CD4$^+$ T cells expressing perforin. How perforin and granzyme B might contribute to hypertension pathology is not entirely clear. Perforin creates pores in target cell membranes, and granzymes cleave both extracellular and intracellular proteins. These effects could result in matrix remodeling, cell detachment, and cell death. Granzyme B can cause rapid caspase-dependent apoptosis. In keeping with this, Shen et al[161] found that Granzyme B deficiency protected against Ang II–induced cardiac hypertrophy, fibrosis, and inflammation. In vitro, Granzyme B cleaved vascular endothelial-cadherin resulting in disruption of endothelial barrier function. A similar process may underlie the vascular remodeling and microvascular rarefaction that occurs in hypertension. Trott et al[162] demonstrated that CD8 deficient mice exhibit a blunted hypertensive response to Ang II and are protected against Ang II–induced endothelial dysfunction as well as vascular remodeling and microvascular rarefaction in the kidney. Furthermore, following Ang II infusion, WT mice demonstrate an impaired ability to excrete an intraperitoneal saline load, but this ability was preserved in CD8$^{-/-}$ mice, suggesting that CD8$^+$ T cells contribute to renal sodium retention. The mechanism for this may be related to the effect of CD8$^+$ T cells on vascular remodeling/rarefaction, the effect of IFNγ on renal sodium transporters,[149] and direct effects of CD8$^+$ T cells on renal tubular cells to increase sodium transporters. In support of the latter, CD8$^+$ T cells were shown to stimulate the NCC (sodium chloride co-transporter), in distal convoluted tubule cells through a mechanism that involves direct cell-cell contact.[163]

IL-21, produced by Th17 and T follicular helper cells, appears to function upstream of T-cell IL-17A and IFNγ production. We showed that mice deficient in IL-21 do not exhibit Ang II–induced increases in IL-17A from CD4$^+$ T cells or IFNγ from CD8$^+$ T cells and are protected from hypertensive end-organ damage.[141] In humans, peripheral blood CD4$^+$ T-cell production of IL-21 correlated with CD4$^+$ T-cell production of IL-17A and with systolic BP at the time of blood draw.[141] Importantly, we and others demonstrated that neutralizing antibodies to IL-17A, the IL-17A receptor, or IL-21 administered after the onset of hypertension in rodents, lowers BP, and reduces target organ damage.[141,156,164] These data suggest that anticytokine therapies targeting the IL-21/IL-17A pathway may be potential adjunct therapies for reducing the inflammatory damage associated with hypertension. While several therapeutics have recently been developed to target IL-17A signaling in the setting of autoimmune diseases,[165,166] no long-term studies evaluating the effect of these drugs on hypertension or other cardiovascular end points has been conducted. However, shorter studies do show promise. For example, von Stebut et al[167] demonstrated in a randomized, double-blind, placebo-controlled exploratory trial that anti-IL-17A treatment with secukinumab improves endothelial function in patients with moderate-to-severe plaque psoriasis after 52 weeks. Mehta et al showed in a prospective observational study that biologic therapy including inhibitors of TNFα, IL-23, and IL-17A is associated with favorable modulation of coronary plaque characteristics in one year.[168] Larger and longer clinical trials to investigate therapies aimed at modulating proinflammatory T-cell phenotype and function may offer new strategies to mitigate the inflammatory end-organ damage and residual cardiovascular risk associated with hypertension.

REGULATORY T CELLS IN HYPERTENSION

Tregs are a Th cell subset defined by their immunosuppressive function and ability to promote immunologic tolerance and homeostasis. Natural Tregs are the most well studied and are a subset of CD4$^+$ T cells initially defined by the presence of cell surface marker CD25 and absence of CD127. Foxp3 (forkhead box P3) was later identified as the canonical transcription factor and master regulator of natural Treg differentiation and function. The discovery of Foxp3 also permitted more definitive identification of these immunosuppressive cells.[169] Tregs are functionally marked by the ability to suppress the activation of conventional effector T cells to limit excessive immune responses and promote tolerance to self-antigens. Genetic deletion of Foxp3 in mice or inactivating mutations in humans lead to Treg deficiency and spontaneous autoimmune pathology termed scurfy in mice and autoimmune immunodysregulation, polyendocrinopathy, and enteropathy X-linked syndrome in humans.[170,171] Evidence suggests that loss of Treg number and function contributes to a variety of autoimmune diseases through defects in immune tolerance.[172] As a result, approaches of adoptive Treg administration and Treg activation are currently in clinical trials for the treatment of a variety of autoimmune diseases.[173]

Given the emerging role of inflammation and immunity in hypertension, and the immunosuppressive functions of Tregs, multiple studies have investigated the role of Tregs in the pathogenesis of hypertension. Animal models of hypertension have demonstrated decreased Tregs in the blood and kidneys coincident with elevations in BP.[125,174] In humans, some studies have demonstrated decreases in circulating Tregs in those with hypertension,[175] while others have shown no difference in circulating Treg numbers.[125,176] To date, most studies testing roles for Tregs in hypertension have performed adoptive transfer of CD4$^+$CD25$^+$ splenic Tregs in animal models. While multiple studies have demonstrated reductions in BP after Treg adoptive transfer,[162,174,177] these reductions have not been observed uniformly.[178–181] Reasons for these differences may relate to different Treg isolation and preparation methodologies and the duration and timing of Treg transfer and BP monitoring. Although Treg adoptive transfer has not consistently decreased BP, more robust reductions in hypertension-induced end-organ damage such as vascular stiffness and cardiac hypertrophy have been observed,[174,177–181] suggesting particular benefit to limit end-organ damage. As an alternative approach to adoptive transfer, Treg expansion using low-dose IL-2 infusion has been tested, which both reduced BP and renal injury in a mouse model of lupus.[182] While approaches to transfer or activate Tregs suggest potential beneficial roles in hypertension, a more limited number of studies have tested the effect of Treg depletion. These studies have primarily used anti-CD25 antibodies to deplete Tregs and have shown either increased BP[183] or no effect.[184] Interestingly, a recent study by Belanger et al[185] showed that anti-CD25-mediated Treg depletion increased BP in female but not male mice, suggesting that sex differences alter Treg function in the regulation of BP. Mechanisms of the observed beneficial effects of Tregs in hypertension remain unclear, however, at least some of the benefit may be through improved vascular endothelial function via Treg production of the anti-inflammatory cytokine IL-10.[186–188] In addition, Treg injection in hypertensive mice has been shown to reduce renal neutrophil content through enhanced CD39-dependent neutrophil apoptosis.[183]

On the whole, studies performed to date suggest that Tregs likely play protective roles in hypertension with variable effects to limit BP elevations but more consistent beneficial roles to limit hypertension-related end-organ damage. These findings suggest a potential for therapeutic use of Treg activation and expansion in hypertension. However, improved understanding of the fundamental biology and role of Tregs in hypertension is needed. Given that CD25 can be expressed at least transiently in activated conventional T cells,[172] adoptive transfer of $CD4^+CD25^+$ cells can include a limited number of conventional T cells in addition to Tregs, which may explain some of the negative results with Treg adoptive transfer described above. Future studies using more specific markers to identify $Foxp3^+$ cells such as GFP (green fluorescent protein) from Foxp3-GFP expressing mice can help clarify the effect of Treg transfer on BP.[189] Similarly, using diphtheria toxin to specifically deplete Tregs in mice with insertion of the diphtheria toxin receptor into the Foxp3 locus can permit more specific Treg depletion than anti-CD25 antibodies.[190] In addition, recent evidence has demonstrated that some Treg subsets may play pathogenic roles in diseases such as type 1 diabetes,[191] lung fibrosis,[192,193] and ischemic heart failure[194] through reducing angiogenesis and promoting fibrosis. Combined with findings that Treg subsets may have distinct functions in different tissues such as skin, adipose tissue, and colon,[195,196] these studies suggest that particular subsets of Tregs may exhibit subtype- and context-specific roles in hypertension. Identifying hypertension-associated Treg subsets in humans and animal models will be critical to determine roles of these distinct cell populations in the pathogenesis of hypertension. These efforts to advance our fundamental understanding of Treg function in hypertension have the potential to advance new therapeutic options targeting activation and expansion of these cells as a novel therapy.

GAMMA DELTA T CELLS IN HYPERTENSION

Most T cells (96%–99%) possess a conventional α/β TCR (T-cell receptor). However, a small subset of unconventional, innate-like T cells expresses the $\gamma\delta$ TCR (1%–4%). These cells are generally negative for the CD4 and CD8 surface receptors. Like other T cells, there is considerable heterogeneity among $\gamma\delta$ T cells in terms of surface marker expression, cytokine secretion, and function. Unlike conventional T cells, these cells do not recognize specific protein antigens bound to classic MHCI and MHCII and are activated instead by factors such as nonprotein phosphoantigens, isoprenoid pyrophosphates, and heat shock protein-derived peptides without antigen processing and MHC presentation. These cells localize in nonlymphoid tissues where there are poised to respond quickly. A subset of $\gamma\delta$ T cells make IL-17A and in certain pathological conditions, are the most prominent source of IL-17A. We found by flow cytometry combined with intracellular staining that both $\gamma\delta$ T cells and Th17 cells contribute approximately equally to IL-17A production in the kidney and aorta of Ang II-infused animals.[164] Consistent with an important role for $\gamma\delta$ T cells in hypertension, Caillon et al[197] demonstrated that mice with genetic deletion or pharmacological depletion of $\gamma\delta$ T cells exhibit blunted hypertension and preserved endothelial function in response to Ang II. Thus, $\gamma\delta$ T cells may represent a novel therapeutic target for the treatment of hypertension.

B CELLS IN HYPERTENSION

While we have made significant advances over the past 2 decades in exploring the role of innate immune cells and T cells in hypertension, very little is known about the role of B cells and immunoglobulins in hypertension. This is an important area since B cell involvement and specific immunoglobulin production would suggest an antigen-mediated humoral immune response and open up additional avenues for immune modulating therapies in the management of hypertension. For over 50 years, modest elevations in specific subsets of serum immunoglobulins, particularly IgG, have been observed in hypertensive animals and humans,[141,198–201] but the precise targets of these immunoglobulins and whether they play a causal role in hypertension is unknown. Interestingly, Khamis et al[202] showed that elevated total serum IgG levels are actually an independent predictor of freedom from adverse cardiovascular events in patients with hypertension, suggesting that IgG may play a protective role.

As described above, Guzik et al[136] demonstrated in 2007 that *Rag1*$^{-/-}$ mice, that are deficient in T and B cells, develop blunted experimental hypertension and that adoptive transfer of T but not B cells restores the hypertensive response. This finding led the scientific community to focus almost exclusively on T cells, while B cells were largely ignored. In 2015, Chan et al[201] revisited the role of B cells in hypertension and demonstrated that pharmacological depletion of B cells using anti-CD20 antibodies or genetic deletion of BAFF-R (B-cell activating factor receptor) in mice reduced Ang II–induced hypertension and vascular end-organ damage. Although not exclusively expressed on B cells, BAFF-R plays a critical role in normal B cell maturation and survival. Subsequently, Dingwell et al[203] demonstrated that mice unable to produce functional B cells due to deletion of the gene for the heavy chain joining region (J_HT) have a modest reduction in baseline BP. However, these authors did not study the response to hypertensive stimuli in J_HT mice. Using a similar model consisting of deletion of the IgM heavy chain (μMT$^{-/-}$) as well as activation-induced cytidine deaminase (*Aicda*$^{-/-}$) mice that are unable to produce high affinity class-switched immunoglobulins, we recently showed that neither B cells nor high affinity class-switched immunoglobulins are necessary for experimental hypertension.[204]

One potential explanation for these disparate findings is the type of B cells targeted in the various studies. B cells are divided into 2 major classes: B1 and B2. B1 cells are innate-like cells found predominantly in the peritoneal and pleural cavities that produce natural IgM antibodies. B2 cells are the conventional B cells. Peritoneal B1 cells are relatively resistant to anti-CD20 treatment.[205] In addition, BAFF-R$^{-/-}$ mice have a preferential reduction in B2 B cells.[206] Thus, both of the models used by Chan et al only confers partial B-cell depletion, primarily of the B2-cell subtype, with some retention of B1 cells. In contrast, our models are characterized by virtually absent or defective B1 and B2 cells. It is, therefore, possible that innate-like B1 cells play a protective role in hypertension that might be masked by global B cell deficiency. However, further studies are needed to test this hypothesis. Alternatively, B-cell activation and immunoglobulin production may not be causal to the pathophysiology of hypertension and instead may simply be a biomarker reflective of immune activation. In keeping with this, it is important to note that IL-21 produced by T follicular helper cells is a potent inducer of germinal center B cell proliferation and differentiation into immunoglobulin secreting plasma cells. Thus, the increased immunoglobulins observed in hypertension may be reflective of increased IL-21 signaling. Nevertheless, it is important to determine whether specific B cell subsets have an immunomodulatory role in hypertension, and thus further studies are critically needed in this area. Given the limitations and risk of compensatory changes that can occur with genetically modified animals, methods that involve acute pharmacological depletion or inducible genetic deletion of individual B cell subsets will be very valuable and informative.

AUTOIMMUNE COLLAGEN VASCULAR DISEASE AND HYPERTENSION

Numerous collagen vascular diseases are associated with a significant increase in risk of cardiovascular disease. Specifically, patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) experience increased cardiovascular events. Initial observations revealed a significantly increased risk of death from cardiovascular and cerebrovascular diseases in patients with RA.[207] They exhibit early atherosclerosis as measured by carotid artery ultrasound and also augmented coronary-artery calcium scores when compared with control subjects.[208,209] Young women with SLE aged 35 to 44 are 52× more likely to experience a myocardial infarction when compared with matched controls from the Framingham Offspring Study.[210] Inflammation plays an important role in the development of CVD in both RA and SLE subjects, since their CVD is associated with systemic inflammation (elevated inflammatory markers and cytokine secretion). Importantly, subclinical atherosclerosis in RA correlates with elevated erythrocyte sedimentation rate, TNF-α, and IL-6 levels,[209,211] and atherosclerosis development in SLE is associated with augmented type I interferon levels.[212]

Hypertension is one of a multitude of risk factors for cardiovascular disease in patients with systemic autoimmunity. There is mounting evidence that hypertension is a direct and specific effect of immune activation independent of additional organ involvement. In SLE, hypertension occurs independently of renal disease and of markers of systemic inflammation. In a study of 235 patients with SLE, hypertension could not be correlated with renal disease or serum complement levels.[213] The importance of hypertension as a primary driver of cardiovascular disease in collagen vascular diseases has been highlighted by numerous studies. In a prospective study of 229 subjects with SLE, the requirement for antihypertensive treatment was associated with coronary artery disease.[214] Moreover, a recent study by Tselios et al[215] showed that BP reduction below 130/80 in patients with SLE reduces atherosclerotic vascular events. Hypertension is also highly prevalent in RA.[216] Panoulas et al[217] described the presence of hypertension in over 70.5% of patients with RA as defined by systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg.

Additional evidence for a role of inflammation in the hypertension observed in collagen vascular diseases arises from the study of animal models of SLE. The *NZBWF1* mouse strain develops systemic autoimmunity characterized by immune complex formation and autoantibody production. Female mice develop systemic hypertension at to 9 months of age and have been extensively studied as a model of SLE associated hypertension. Importantly, cells of both the adaptive and innate immune system have been implicated in the pathogenesis of hypertension in this model. B-cell depletion by different methods revealed the importance these cells in the development of SLE-associated hypertension. For example, treatment of *NZBWF1* animals with anti-CD20 abrogates the development of hypertension[218] and treatment with bortezomib, a proteasome inhibitor that exhibits plasma cell toxicity, also attenuates mean arterial pressure in these SLE prone mice.[219]

A role for oxidative stress in the immune activation observed in the hypertension of autoimmune disorders has been demonstrated by treatment of *NZBWF1* animals with the superoxide scavenger tempol, or the nicotinamide adenine dinucleotide phosphate oxidase inhibitor apocynin; both reduced BP and renal injury in this model.[220] This occurred in the absence of a reduction in SLE disease activity as measured by the accumulation of antidouble-stranded DNA antibodies. We have shown that scavenging of isoLGs, a product of lipid peroxidation, with the specific scavenger 2-hydroxybenzilamine attenuates SLE-associated hypertension in both the *NZBWF1* and *B6.SLE123* models of SLE. In contrast to the above, 2-hydroxybenzilamine reduced SLE severity as measured by antidouble-stranded DNA antibodies and renal immune complex deposition.[221] These data suggest that specific products of reactive oxygen species-mediated lipid peroxidation contribute to the genesis of hypertension in SLE.

Treatment of collagen vascular diseases is based on global immunosuppressants despite the fact that their mechanisms are heterogeneous. Investigation of the factors driving disease heterogeneity and their associations with CVD will allow for future therapeutic approaches that target such specific factors.

VIRAL INFECTIONS AND HYPERTENSION

Numerous studies have found that people with hypertension have increased susceptibility to viral infections with worse outcomes. Hypertension is among the comorbidities that worsen the prognosis for the recent coronavirus pandemic (coronavirus disease 2019 [COVID-19]).[222] Other studies have linked hypertension with incidence and outcomes of influenza infection.[223,224] Perhaps, the most studied viral infection and its relation to hypertension is that by the HIV.

Coronavirus Disease 2019

The recent COVID-19 pandemic, caused by the novel severe acute respiratory syndrome-coronavirus 2, has led to an unprecedented medical crisis worldwide. People with hypertension are at a heightened risk for severity and mortality due to COVID-19. Because severe acute respiratory syndrome-coronavirus 2 uses the ACE2 (angiotensin-converting enzyme 2) receptor to infect cells, there has been a debate as to whether use of antihypertensive drugs including the ARBs (angiotensin receptor blockers) and ACE inhibitors, which increase expression of ACE2, would increase the risk for infectivity and severity of COVID-19 in people with hypertension.[225] However, a recent study by Trump et al[226] found that augmented immune cell activation might explain the adverse COVID-19 outcomes in patients with hypertension and that ACE inhibitors could be the more beneficial antihypertensive treatment during COVID-19. They found that in people with hypertension, there is a delayed viral clearance and an exacerbated airway inflammation in patients with COVID-19. Treatment with ACE inhibitors was associated with a reduced COVID-19-related inflammation and with increased cell intrinsic antiviral responses, whereas ARB treatment related to enhanced epithelial–immune cell interactions.[226] Macrophages and neutrophils of patients with hypertension, exhibited higher expression of the proinflammatory cytokines *CCL3* and *CCL4* and the chemokine receptor *CCR1*.[226] These studies suggest that the worse outcomes in patients with COVID-19 who have hypertension may stem from an exaggerated immune response.

HIV

Studies of BP in people infected with HIV may provide a unique window into the role of the immune system in human hypertension. Over 36 million adults are now living with HIV. Currently, 25 million people living with HIV (PLWH) are on antiretroviral therapy (ART) and 2 million start ART each year. As a result of ART, PLWH are living longer and healthier lives with less morbidity and mortality from opportunistic infections. According to a 2018 meta-analysis, the risk of CVD in PLWH is ≈2.5-fold higher than HIV-uninfected adults of similar age.[227] According to one recent study of the largest cohort of PLWH in North America, ≈42% of the variability of CVD is attributable to high office BP.[228] More than one-third (35%) of PLWH on ART have hypertension, and they develop CVD at lower office BP levels than HIV-uninfected adults.[229]

Several findings support that immune activation and chronic inflammation contribute to hypertension and CVD in PLWH. Macrophage-derived serum IL-6 and soluble CD14 are both elevated in PLWH and precede incident hypertension.[230] Soluble CD163, a marker of monocyte activation, is also elevated and has been associated with vascular damage in this population.[231] T-cell secreted cytokines such as IL-17A and IFNγ and, the eosinophil maturation cytokine, IL-5, are significantly elevated in hypertensive PLWH.[118]

HIV-specific proteins are known to directly trigger inflammatory cascades. The transcriptional regulator Tat induces expression of endothelial cellular adhesion molecules (intercellular adhesion molecule, vascular cell adhesion molecule, and E-selectin) and primes the vasculature for inflammatory cell migration.[232] Additionally, Tat upregulates T-cell derived interleukin-17A expression, and elevated serum IL-17A is associated with hypertension in PLWH.[118] Expression of the NLRP3 inflammasome is upregulated in the peripheral blood immune compartment of PLWH compared with HIV-uninfected controls,[233] which may contribute to their hypertension. Moreover, CD4$^+$ T cells of PLWH increase during the first 2 years after ART initiation in parallel manner to a concomitant rapid increase in BP.[234] Eosinophil counts are associated with hypertension in PLWH but not in HIV-uninfected controls after adjustment for traditional risk factors.[118] Dysfunctional production of the T-cell derived, eosinophil maturation factor IL-5 has been suggested as a possible underlying mechanism; although the macrophage/monocyte derived MIP-1α (macrophage inflammatory protein 1α), and others, may also contribute.

In summary, PLWH are at increased risk of hypertension and CVD. Neither traditional risk factors such as obesity and age nor HIV-specific factors such as ART type, lipodystrophy, and HIV viral load account for this risk. Recent insight into the complex interplay of these factors and HIV-specific inflammatory pathways have shed light on the pathophysiology of hypertension in PLWH. However, further studies are needed to outline a unifying theory on mechanisms and so identify potentially actionable targets.

THE GUT MICROBIOME, INFLAMMATION, AND HYPERTENSION

The gut microbiome, made of trillions of microbes and their genetic material, is now widely acknowledged to affect host physiology and disease.[235] Of all microbes, bacteria and their metabolites are the best understood for their role in cardiovascular disorders like hypertension.[236] Evidence from human studies indicates that hypertension is associated with different microbial composition in terms of taxa, gut-derived metabolites, and intestinal mucosa structure. Hypertensive individuals have reduced microbial richness, diversity, and display a microbial shift with greater abundance in pathogenic taxa compared with normotensive individuals.[237,238] Beneficial metabolites such as short-chain fatty acids are decreased in hypertension, and the gut barrier integrity is compromised.[239] Animal models have played a substantial role in elucidating mechanisms of the microbiome beyond associations. For instance, fecal microbial transplantation from hypertensive subjects into germ-free mice elicits hypertension suggesting a direct role of the gut microbiome in modulating host BP.[240,241]

The gastrointestinal tract houses the largest immune organ of the body, the gut-associated lymphoid tissue. The gut microbiome regulates inflammatory pathways that contribute to the pathogenesis of hypertension. Metabolites produced by bacteria in the gut including TMAO (trimethylamine-N-oxide), LPS (lipopolysaccharide), and short-chain fatty acids are known mediators of these inflammatory pathways.[236] Short-chain fatty acids attenuate hypertension, gut dysbiosis, and restore a balance between Th17 and Treg cells in animal models of hypertension.[242,243] They promote Th1 but prevent Th17 cell differentiation through GPR43 (G-protein coupled receptor 43).[244,245] The gut microbiome is highly dynamic and can be influenced by factors such as dietary composition. For instance, a diet rich in fiber confers antihypertensive benefits whereas a high-salt diet increases BP and causes a shift in microbial composition.[238,246] In mice, a high-salt diet decreases the Firmicutes to Bacteroidetes ratio, promotes gut barrier dysfunction, and disrupts inflammatory responses.[238,247] Interestingly, high salt increases Th17 cells by mechanisms directly dependent on the gut microbiome,[247] and exacerbates gut inflammation by increasing the expression of inflammatory markers such as IFN-γ and some Toll-like receptors in the colon.[248] Mucosal DCs, which normally regulate gut homeostasis tightly,[249] influence gut dysbiosis and hypertension in response to a high salt stimulus when activated.[238]

SEX DIFFERENCES

There is an established sexual dimorphism in hypertension. Hypertension is more prevalent in men than in women younger than 60 years of age; whereas the opposite trend is present in older subjects.[250] While both men and women exhibit SSBP, men have higher mortality from SSBP for unclear reasons.[33,251] Experimental animal studies indicate that SSBP is more pronounced in males than females.[252] It is not known if sex/gender differences exist in monocyte activation and how this impacts SSBP. Gender differences have been identified in Na$^+$ storage between muscle and skin: men exhibit higher Na$^+$ content in skin than in muscle, whereas women accumulate Na$^+$ to greater levels in muscle.[253]

The observed associations between HIV and hypertension appear to be similar in males and females. Few published data exist for HIV-infected women, though, since most studies of HIV and hypertension have mainly enrolled homosexual men. Studies report that HIV-infected women on long-term ART have significantly elevated sCD14 and sCD163 as compared with HIV-infected males,[254] and higher sCD14 levels are strongly linked with higher BP in PLWH.[255] Further studies are needed in HIV-infected women and should investigate both the premenopausal and postmenopausal period.

There are also sex differences in factors that influence gut microbiota such as salt. Women exhibit greater BP changes in response to high-salt consumption.[256] While direct evidence on sex differences in the gut microbiota in humans is lacking, studies in preclinical models have shown sex-dependent differences in the gut microbiome. In mice, there is differential abundance in taxa and metabolites between males and females, and there is a role for sex hormones in modulating gut microbiota composition.[257,258] Testosterone and estrogens play a substantial role in sex differences and both hormones are differentially affected by gut-related mechanisms.[259–261]

Germ-free mice also exhibit sex differences in vascular function, an important regulator of BP; for example young male germ-free mice exhibited increased vascular stiffness that was not observed in females.[262] More studies on the impact of sex differences in the gut microbiome on hypertension are warranted because of the therapeutic implications for management of sex-specific diseases such as hypertensive disorders of pregnancy. Growing evidence suggests a role for gut microbiome disruption in the pathophysiology of adverse pregnancy outcomes such as preterm birth and preeclampsia.[263] Preeclampsia is associated with gut dysbiosis with an increase in proteobacteria and greater fecal and plasma TMAO and LPS compared with healthy pregnant controls.[264] LPS activates an inflammatory response through Toll-like receptor 4 and is used to induce preeclampsia-like phenotypes in rodents.[265] Better characterization of the involvement of the gut microbiome in hypertensive disorders of pregnancy may improve our understanding of their elusive causes. Furthermore, preeclampsia is an established risk factor for adverse maternal and offspring cardiovascular outcomes later in life,[266] and there is growing evidence that maternal dysbiosis can be transferred to the fetus in utero, programming the offspring for susceptibility to illness.[267,268] The specific role of the gut microbiome in determining maternal and offspring prognosis needs further investigation.

CONCLUSIONS AND PERSPECTIVES

The inability to control hypertension in some subjects who are compliant with medications, the effect of salt to raise BP in certain individuals regardless of hypertension status, and the presence of residual cardiovascular risk in those with treated and controlled hypertension strongly suggest that current pharmacological therapies leave some underlying pathogenic mechanism of the disorder unaddressed. In this review, we summarize the now overwhelming evidence that immune-mediated inflammation may be such a mechanism and discuss the genetic and environmental risk factors, such as viral infections, high-salt diet, and the microbiome, which can modulate inflammation and cardiovascular risk (Figure 5). In some individuals, the magnitude of vascular and renal inflammation may preclude total resolution of vasoconstriction or normalization of sodium handling by current therapies, hence leading to refractory uncontrolled hypertension. In the majority of nonrefractory patients with hypertension, current therapies may control BP, but the unaddressed underlying inflammatory processes may perpetuate target organ damage and explain their excess residual cardiovascular risk.

Therefore, the ultimate aim of investigating immunity in hypertension is to develop therapies that can be tested for control of BP or for reduction of cardiovascular risk in clinical trials. Conventional immunosuppressants, such as mycophenolate mofetil, reduce BP in experimental models and humans, and more recently, the anti-IL-1β monoclonal antibody canakinumab reduced cardiovascular events in patients with established atherosclerotic disease. However, ubiquitous suppression of immunity by these type of

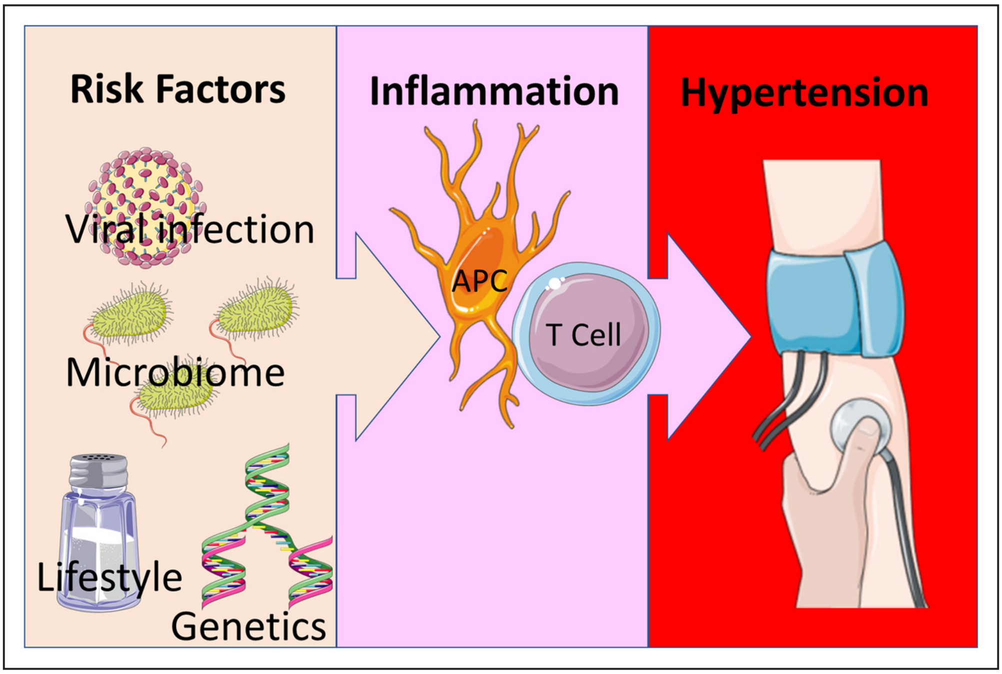

Figure 5. Risk factors contributing to inflammation and hypertension.
Risk factors including viral infections, high-salt diet, genetics, and the microbiome lead to an inflammatory milieu that contributes to hypertension.

agents increases infectious complications, limiting their widespread use for a disease that affects almost half of the adult population of the world. Thus, a more granular understanding of the immune mechanisms of hypertension may allow for more targeted and personalized therapeutic approaches. In addition, approaches that restore the balance of proinflammatory and anti-inflammatory immune cells in hypertension without causing global immunosuppression will be important to develop and test in clinical trials. Rigorous and routine measurement of BP and cardiovascular events should be considered in current and future trials of anti-inflammatory medications being tested for other diseases to determine their potential in decreasing cardiovascular events in at-risk populations. Furthermore, more studies using existing drugs such as amiloride and spironolactone which seem to have anti-inflammatory effects will help determine if they should perhaps be used more widely or selectively in certain populations such as those with salt-sensitive hypertension or hypertension driven by excess aldosterone, respectively. Finally, novel technologies, such as targeted nanoparticles, may be able to inhibit or overexpress certain factors in specific subsets of immune cells, thus delivering precise and targeted therapies without the risks of global immunosuppression. Accomplishing these goals will require a coordinated effort among cardiovascular physiologists, immunologists, biomedical engineers, and clinical trialists. It is our hope that these efforts will continue and that 1-day, immune modulation will be added to our arsenal to eradicate this deadly epidemic.

ARTICLE INFORMATION

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Sources of Funding

This study was supported by the National Institutes of Health grants DP2HL137166 (M.S. Madhur), K01HL130497 (A. Kirabo), R01HL147818 (T.R. Kleyman and A. Kirabo), K08 HL153786 (M.R. Alexander), T32HL144446 (A. Pitzer), F32HL142937 (J.P. Van Beusecum), P30DK079307 (T.R. Kleyman), K08 HL153789 (D.M. Patrick), K23 HL152926 (J.R. Kleyman) and the American Heart Association EIA34480023 (M.S. Madhur).

Disclosures

None.

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