REVIEW

Update on Immune Mechanisms in Hypertension

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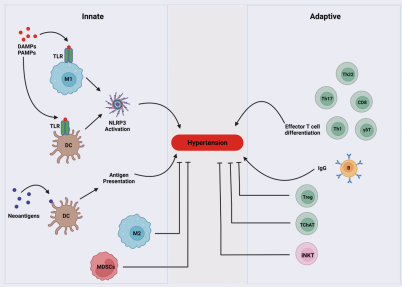
The contribution of immune cells in the initiation and maintenance of hypertension is undeniable. Several studies have established the association between hypertension, inflammation, and immune cells from the innate and adaptive immune systems. Here, we provide an update to our 2017 *American Journal of Hypertension* review on the overview of the cellular immune responses involved in hypertension. Further, we discuss the activation of immune cells and their contribution to the pathogenesis of hypertension in different *in vivo* models. We also highlight existing gaps in the field of hypertension that need attention. The main goal of this review is to provide a knowledge base for translational research to develop therapeutic strategies that can improve cardiovascular health in humans.

GRAPHICAL ABSTRACT



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The immune system plays a fundamental role in the intricacies of the human body with varying responses dependent on daily attributions. New immunological breakthroughs have demonstrated an indisputable and increasingly prevalent role of immune cells in the pathogenesis of hypertension. Extensive studies have demonstrated a strong relationship between hypertension, immune cells, and inflammation. Imbalance between different pro-inflammatory and anti-inflammatory immune cells determines the severity of inflammation. This updated review presents potential mechanisms of immune cell-mediated pathology of hypertension using various *in vivo* models.

IMMUNE SYSTEM

The immune system encompasses entire organ systems and provides protection from pathogens and foreign bodies.[1] These defense mechanisms are arbitrated by successive and organized responses known as the innate and adaptive immune responses. The innate immune response is present at birth and acts as the first line of defense by rapidly engaging in protective measures against pathogens. The adaptive immune response acts as a delayed secondary antigen-specific response. It is regulated by innate immune cell crosstalk with the ability to retain memory of antigens, correlating to a rapid response during future encounters.[2] The intricacies of immunological mechanistic links in diseases such as hypertension remain relatively obscure.

INNATE IMMUNITY

The innate immune response becomes activated via infection from microbial invasion or tissue injury.[3] Defenses of the innate immune system include anatomic and physiologic barriers, endocytosis, phagocytosis, inflammation, and the complement system.[4] Antigen presenting cells

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(APCs) and natural killer (NK) cells play crucial roles in the innate immune response. Innate immune cells express pathogen recognition receptors (PRRs), such as Toll-like receptors (TLRs), that allow the cell to activate immunological responses in response to pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs).[5]

APCs, including monocytes, macrophages, and dendritic cells (DCs), digest pathogenic antigens via phagocytosis. These cells identify digestible apoptotic cells or microbial pathogens via opsonic or nonopsonic receptors on the cell's plasma membrane.[6] Presentation of processed antigens on the surface of APCs, in conjunction with a major histocompatibility complex (MHC) molecule, to cells of the adaptive immune system elicits an adaptive immune response. Monocytes arise from bone marrow and circulate through the blood and differentiate into macrophages after entering the tissue. Macrophages are able to live for long periods in the tissue, and their main function is to ingest and destroy microbes while removing damaged tissues.[1] Macrophages are categorized as classically activated M1 pro-inflammatory or alternatively activated M2 anti-inflammatory cells. DCs are tissue resident sentinel cells that bridge the innate and adaptive immune response by activating T lymphocytes. DCs present antigen to T cells via PAMPs or express membrane costimulatory molecules that promote T cell responses or differentiation into effector cells.[1]

NK cells develop mainly in the bone marrow; however, recent evidence has provided support of maturation in secondary lymphoid tissues.[7] They recognize self from non-self as well as mediate antitumor and antiviral responses due to healthy cells expressing MHC Class I molecules whereas infected/damaged cells lose MHC Class I expression.[8] They directly eliminate targets via NK cell-mediated cytotoxicity or indirectly through pro-inflammatory cytokines.[8]

ADAPTIVE IMMUNITY

Adaptive immunity is facilitated by a T cell-mediated cellular response and a B cell-mediated humoral response, aided by innate immune cell presentation of antigens.[9] The adaptive immune response primarily functions to distinguish non-self antigens from self-antigens, produce responses based upon memory established via previous antigen interactions, and respond with high specificity.[4,9] The adaptive response is the basis for immunization against diseases by eliciting quick and effective memory responses.

T cells are derived from hematopoietic stem cells and migrate to the thymus to mature, and subsequently circulate among lymphoid organs.[4] T cells express T cell receptors (TCRs) on their cell membranes to bind antigens and are activated via APCs. The presentation of antigens by MHC molecules allows for differentiation of T cells into cytotoxic T cells, helper T cells (Th), memory T cells, or regulatory T cells (Tregs). CD8+ cytotoxic T cells are activated via interactions of their TCRs with MHC Class I molecules and destroy tumor cells and virus-infected cells via phagocytosis; a few retained cells are kept to achieve a memory response.[4] CD4+ Th cells coordinate the immune response through activation of other immune cells such as macrophages, B cells, and CD8+ T cells. Th cells are activated via TCR MHC Class II recognition and differentiate into several subtypes. Th1-derived cytokines, like interferon (IFN)-γ, activate macrophages and increase their bactericidal components, increase immunity, and contribute to B cell differentiation to aid in phagocytosis via the production of opsonizing antibodies.[4] Th17 cells produce IL-17 and are associated with pro-inflammatory responses in chronic infections and diseases.[4] Th22 cells play a role in inflammation and autoimmune diseases, secrete the cytokines IL-22, IL-13, TNF-α, and express chemokine receptors CCR4, CCR6, and CCR10.[10] Treg cells limit and suppress immune responses and are of 2 types: natural (nTregs) and induced (iTregs) regulatory cells.[4] nTregs develop in the thymus, whereas iTregs originate from peripheral naive conventional T cells.[11] Newly discovered choline acetyltransferase-expressing T (TChAT) and γδ T cells have been implicated in blood pressure regulation.[12,13]

B cells play an active role in the antibody-mediated immune response and are generated from hematopoietic stem cells in the bone marrow. They can serve as APCs and express TLRs to monitor for DAMPs and PAMPs. After maturation in the bone marrow, B cells leave with unique antigen binding receptors on their cell membranes. B cells recognize antigens directly via antibody expression on the cell's surface and get activated via CD40 interactions after they encounter antigens.[4] Then they proliferate and differentiate into antibody-secreting plasma cells or memory B cells.[4] Plasma cells are short lived and undergo apoptosis when the threat that stimulated them is gone, ensuring a controlled early humoral response.[4] They secrete 5 major antibodies into circulation (IgA, IgD, IgE, IgG, and IgM) to aid in protection.[4] Memory B cells are able to survive past infection, aiding in re-exposure via rapid production of antibodies.[4]

IMMUNE SYSTMEM ACTIVATION IN HYPERTENSION

The immune system is activated by exogenous or endogenous stimuli and the degree to which the system is activated is highly dependent on the individual. Upon activation, immune cells release cytokines and other pro-inflammatory factors, inducing inflammation in the interstitium and blood vessels. Given the chronic inflammatory nature of hypertension, this inflammation fails to rescue blood pressure and instead leads to endothelial dysfunction, impaired renal sodium handling, arterial remodeling and stiffening, and end-organ damage. Inflammation and immune responses are critical to the initiation, progression, and maintenance of many types of hypertension, and most immune cell types play some role in the disease process (Figures 1 and 2).[14–18]

APCs use PRRs to detect foreign antigens and apoptotic signals. Upon exposure to DAMPs and PAMPs, PRRs are activated and begin to recruit leukocytes to their location. TLRs are the most well known of the PRRs and are expressed on most types of APCs. TLRs play a major role in inducing and sustaining inflammation in hypertensive conditions by initiating pro-inflammatory signaling pathways.[19–21] In hypertension, TLRs are activated via

nuclear proteins, cytosolic proteins, and neoantigens.[5] Different subtypes of TLRs participate in different signaling pathways and produce unique downstream effects. Further investigation into the roles of TLRs in hypertension is underway. Recently, Ishikawa *et al.* demonstrated that inhibition of TLR9 decreased blood pressure and lessened side effects of hypertension in the vasculature and lungs of rats.[19] Additionally, Pushpakumar *et al.* reported that TLR4-deficient mice experienced a blunted blood pressure response to angiotensin II (AngII) infusion and protection from kidney damage.[22] These studies, among others, have identified TLRs as a potential target for hypertensive therapies.

Presentation of antigens and neoantigens by APCs is required for activation of T and B cells and contributes to the pathogenesis of hypertension (Figures 1 and 2).[17,23–25] Recently, it has been reported that MHC Class II-expressing monocytes present antigens to effector CD4+ T cells and induce inflammation in glomeruli.[26] Hypertensive stimuli induce differentiation of naive T cells into cytotoxic, helper, regulatory, and memory T cell subsets. Due to their many phenotypes, T cells can play different roles in the pathogenesis of hypertension, including roles that are pro-inflammatory and anti-inflammatory. B cells tend to play a pro-inflammatory role, as their activation and IgG production is necessary for the development of hypertension.[25]

The primary mechanism that drives immune cell activation under hypertensive conditions remains unclear, but several have been implicated in this process. Increases in sympathetic outflow, renal perfusion pressure, reactive oxygen species, salt levels, and splenic activity have been observed to induce immune cell activation in hypertension.[27–32] Immunomodulation is a promising option to rescue blood pressure, resolve inflammation, and improve patient outcomes; however, due to the wide variety of factors that influence blood pressure in hypertension, potential therapeutic targets are challenging due to their immunosuppressive effects. We pursued an alternative strategy in which we aided in immune cell exfiltration of the kidneys through augmenting lymphatics. This was able to decrease renal pro-inflammatory immune cells and blood pressure in mice with various forms of hypertension.[33,34]

Pharmacological or genetic manipulation of immune cells such as monocytes, pro-inflammatory T cells (CD8+, CD4+ Th17, Th22, and γδ, among others), and plasma cells have been shown to prevent and/or improve hypertension, while depleting immune cells such as invariant natural killer T (NKT) cells, Tregs, TChATs, and myeloid-derived suppressor cells exacerbates the condition.[24,35–43] A recent study reported that depleting plasma cells in hypertensive mice decreased circulating autoantibodies, prevented IgG deposition, prevented renal damage and pro-inflammatory immune cell infiltration, and decreased blood pressure.[39] Another study highlighted the protective role of CD1d-dependent NKT cells in hypertension and cardiac remodeling.[40] The number of different immune cells playing instrumental, yet varied, roles in hypertension makes finding an ideal target for immunotherapy challenging. Additionally, certain types of immune cells cannot be modified without risking system-wide consequences. Continued investigation of immune cell roles is needed to determine appropriate therapeutic options for hypertensive patients while maintaining a strong immune system.

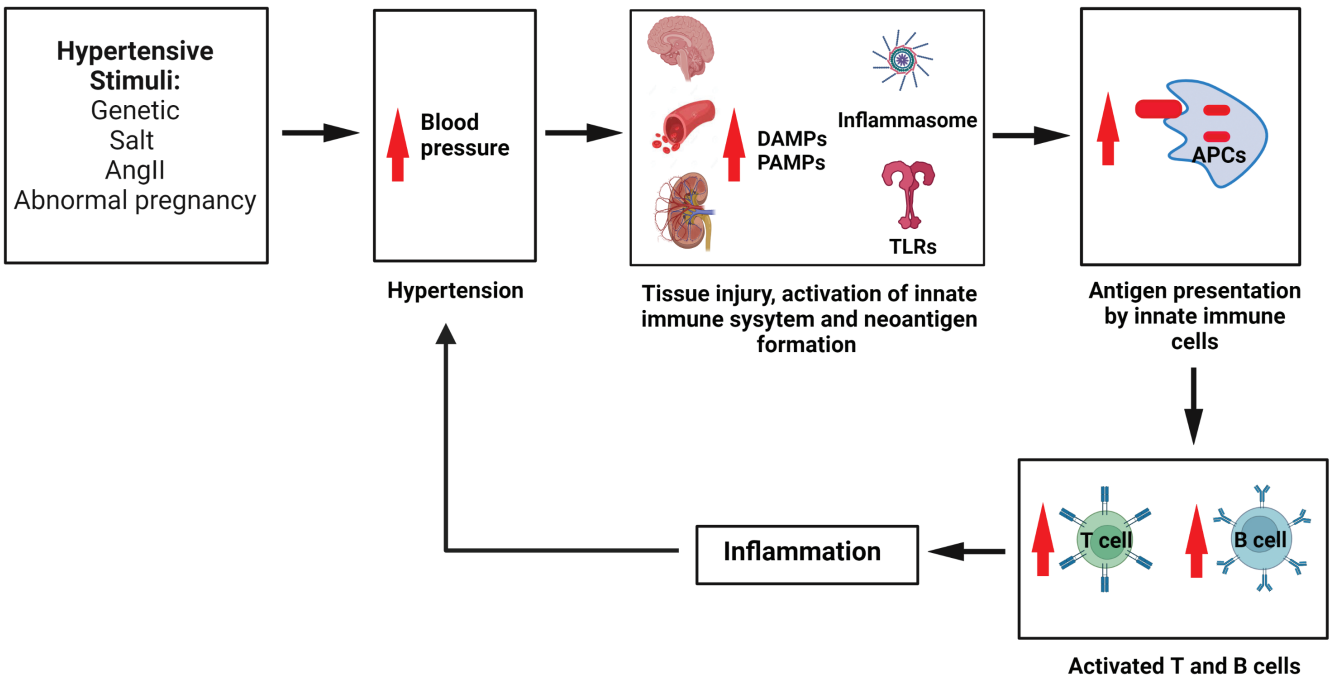

Figure 1. Summary of immune cell involvement in hypertension.

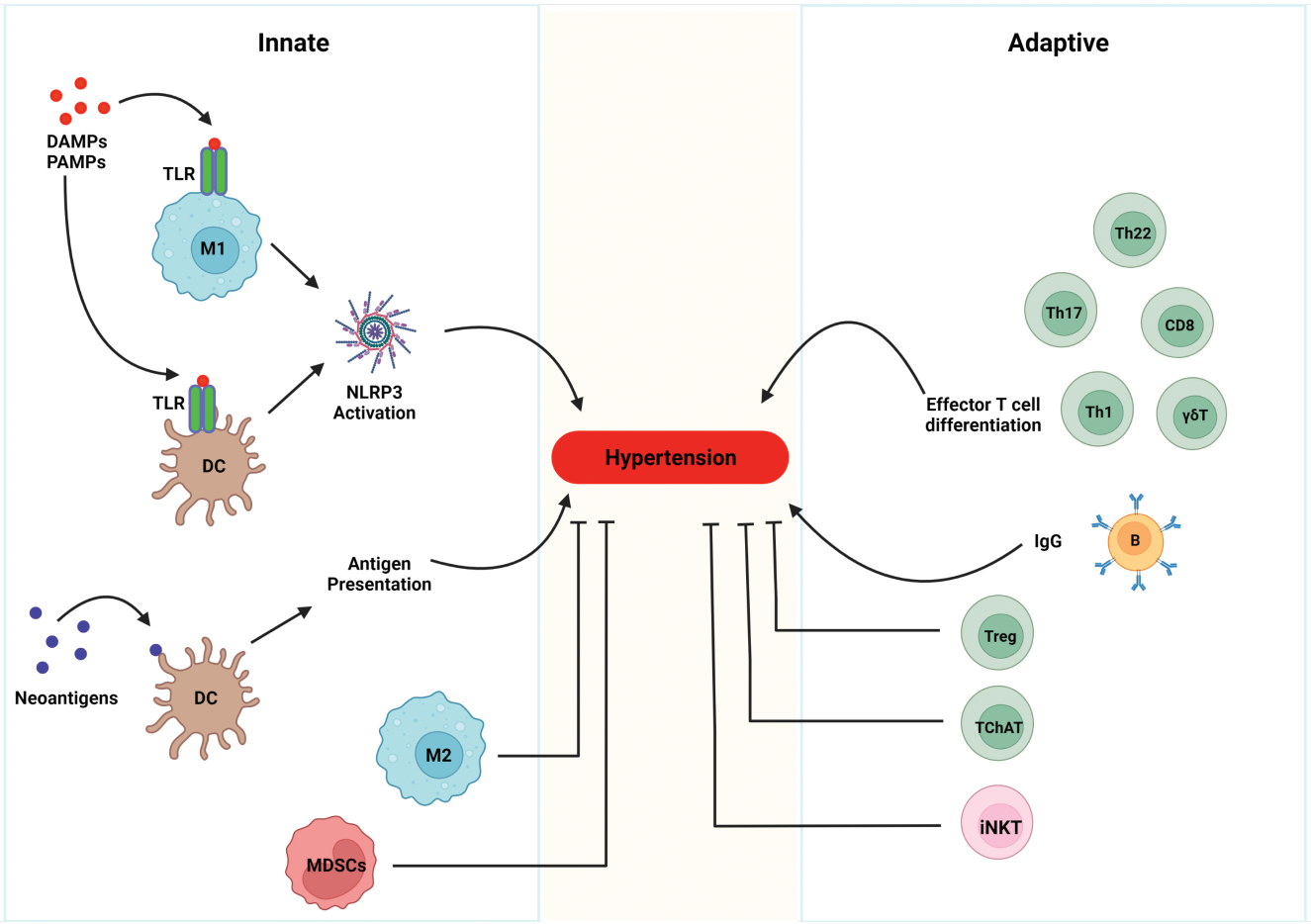

Figure 2. Role of immune cells in the pathogenesis of hypertension. Hypertension-related DAMPs and PAMPs activate TLRs and NLRP3 inflammasomes in M1 macrophages and DCs contributing to inflammation. Neoantigens are processed and presented by DCs to B and T cells that lead to differentiation of plasma cells and effector T cell subsets (CD8+ T cells, Th1, Th17, Th22 cells, and γδ T cells). MDSCs, M2 macrophages, Tregs, TChAT, and iNKT cells prevent the formation of pro-inflammatory cytokines, attenuate inflammation, and attenuate hypertension. Abbreviations: DAMPs, danger-associated molecular patterns; DC, dendritic cells; iNKT, invariant natural killer T cells; M1, pro-inflammatory macrophages; M2, anti-inflammatory macrophages; MDSCs, myeloid-derived suppressor cells; NLRP3, NOD-, LRR-, and pyrin domain-containing 3 inflammasomes; PAMPs, pathogen-associated molecular patterns; TChAT, choline acetyltransferase-expressing CD4+ T cells; Th, T helper cells; Treg, regulatory T cells.

SPONTANEOUSLY HYPERTENSIVE RATS

The spontaneously hypertensive rat (SHR) is a well-established genetic model of hypertension that develops hypertension at a young age and exhibits pathological changes including impairment of renal function and a dysregulated immune system. SHR showed a drastic increase in splenic pro-inflammatory CD161+ (a C-type lectin-like receptor that serves as a marker for NK cells and type 17 phenotype across T cell populations) immune cells at birth that increased with age, along with infiltration of these cells in the kidneys and aortas.[44] In neonatal spleen, CD4+CD161+ and CD8+CD161+ cells were reported to be elevated and attributed to elevated expression of master transcription factor RORγt transcription that induces the production of the pro-inflammatory cytokine IL-17F contributing to salt-induced hypertension.[44] Interestingly, chloroquine reduced blood pressure in young SHR by impairing TLR9 signaling, reducing circulating T cells, and recruiting CD45+ immune cells to the vasculature.[45] Recently, it has been reported that increased expression of renal TLR4 in male SHR, in comparison to female SHR, is not implicated in the relative increase in the blood pressure and pro-inflammatory renal T cell profile in male rats.[46,47] In addition, splenectomy in SHR demonstrated that the higher abundance of renal Tregs in females was due to infiltration into the kidneys, rather than increased production of Tregs.[48]

The association of the gut microbiome and hypertension has been studied extensively in the past decade. In SHRs, increased wall permeability, altered expression of tight junction proteins, and microbial dysbiosis was reported in the gut, along with increased expression of *Cd68*, *Cd3*, *Il-1β*, and *Tlr4* in the small intestine and proximal colon, further supporting the role of gut health in the pathogenesis of hypertension.[49] Altered composition of gut microbiota of SHR in the early neonatal period was restored by cross-fostering SHR rats by normal WKY mothers. Cross-fostering improved gut microbiota dysbiosis in SHR and decreased pro-inflammatory CD161+ cells in the spleen and aorta, thereby lowering blood pressure at adulthood.[50]

Another study showed that fecal microbiota transplantation from SHR to WKY rats induces gut microbiota dysbiosis (characterized by an increased *Turicibacter* and decreased *S24-7_g*), upregulation of DC maturation and activation markers (CD80 and CD86), imbalance in Th17/Tregs ratio in mesenteric lymph nodes, aortic T cell infiltration, and hypertension.[51] Supplementation of probiotics and short chain fatty acids restored Th17/Treg imbalance in mesenteric lymph nodes and decreased endotoxemia and blood pressure in SHR. These changes resulted from increased Treg infiltration and decreased activation of the lipopolysaccharide (LPS)/TLR4 pathway in the vasculature.[52] Taken together, it is evident that gut microbiota dysbiosis is associated with immune cell changes and hypertension.

SALT-INDUCED HYPERTENSION

The role of the innate and adaptive immune systems in salt-sensitive hypertension (SSHTN) has been well established by utilizing low renin, high salt animal models, including uni-nephrectomized deoxycorticosterone acetate (DOCA)/salt-induced hypertension, Dahl salt-sensitive rats (DSS), and L-arginine methyl ester hydrochloride (L-NAME)/high salt-induced hypertension.

High salt triggers activation of the innate immune complex NLRP3 inflammasome, which releases pro-inflammatory cytokines IL-1β and IL-18.[53,54] DOCA/salt mice with a knockout of a critical inflammasome adaptor protein showed decreased expression of renal IL-1β-induced cytokines *Il6* and *Il17a*.[55] NLRP3 inhibition significantly reduced renal expression of pro-*Il1β*, pro-*Il18*, *Il17a*, and *Tnfa*, as well as a decrease in T cells that produce IFN-γ.[56] IL-18, produced by renal tubular epithelial cells of DOCA/salt-treated mice, contributes to increased blood pressure and renal inflammation by stimulating the production of IFN-γ by T cells.[57]

APCs demonstrate a pro-inflammatory phenotype in SSHTN. DSS rats fed a high salt diet demonstrated a significant increase in renal M1 macrophages, with upregulation of TLR4, CD14, Ly96, and IL-6 receptor, when compared with consomic SSBN13 controls.[58] Excess salt primes DCs for IL-1β to promote pro-inflammatory T cell cytokines after co-culture with splenic T cells from L-NAME-treated mice. High salt enters DCs through epithelial sodium channel (ENaC) and activates NADPH oxidase, which in turn increase isolevuglandin (IsoLG) production. [55,59] DCs then produce IL-1β and promote T cell production of IL-17A and IFN-γ.[59] Serum/glucocorticoid regulated kinase 1 (SGK1) mediates assembly of ENaC and formation of IsoLG.[60] SGK1 knockout in CD11+ cells of L-NAME-treated mice was associated with reduction of renal CD4+ and CD8+ T cells.[60]

T cell involvement in SSHTN has been further defined. SGK1 deficiency in CD4+ T cells reduced vascular CD45+ cells and CD3+ T cells in DOCA/salt mice.[31] Na^+-K^+-$2Cl^-$ cotransporter 1 (NKCC1) is upregulated in Th17 cells and may help mediate T cell salt sensing.[31] CD8+ T cells infiltrate distal convoluted tubules in DOCA/salt mice, leading to upregulation of sodium chloride cotransporter and increased sodium retention.[61] An increase in renal Tregs in female DOCA/salt rats that was not seen in male rats highlight sex differences in T cell-mediated protection from DOCA/salt-mediated hypertension.[62]

Excess sodium alters gut dysbiosis and production of metabolites like short chain fatty acids, which play a role in inflammation. A high salt environment reduces *Lactobacillus* spp., which synthesize indole metabolites that have been shown to reduce blood pressure and inhibit Th17 polarization.[63] Supplementation of *L. murinus* significantly reduced splenic Th17 cells in L-NAME-treated mice.[63] Supplementation of sodium butyrate reduced blood pressure and renal expression of *Tnfa* and *Il6* in DOCA/salt mice.[64] Other dietary interventions such as time-restricted eating has been reported to reduce inflammation and blood pressure in people with hypertension.[65] Time-restricted feeding significantly decreased blood pressure in mice with nitro-L-arginine methyl ester hydrochloride-induced hypertension.[66] There was a significant decrease in activated macrophages and DCs in the kidneys of these mice.[66] As the incidence of SSHTN continues to grow, the role of excess sodium in inflammation should continue to be investigated. Further studies focusing on altering gut flora and supplementation of metabolites would be promising for developing therapeutics for the treatment of hypertension.

ANGIOTENSIN II-INDUCED HYPERTENSION

Angiotensin II-induced hypertension (A2HTN) models continue to be utilized to further investigate the role of innate and adaptive immunity in hypertension. Recently, it was demonstrated that TLR3 and its intracellular adaptor TRIF are the primary TLR signaling pathway needed for A2HTN in the heart and kidneys.[67] Neutrophil extracellular traps (NETs) are prothrombotic meshes of protein and chromatin that are involved in inflammation and adaptive immunity and have also been implicated in the early stages of hypertension, increasing in an AngII-dependent fashion.[68] While the mechanism behind still remains largely unknown, decrease in DNase I resulting in impaired NET clearance or the presence of hypomethylated CpG regions in NET DNA activating Toll-like receptor 9 seems to be the most likely possible reasons.[69] Similar to NETs, circulating Axl+ Siglec-6+ DCs are increased in hypertensive humans, and mice with A2HTN had an increase in Axl-activating ligands, while an Axl inhibitor blunted the rise in the blood pressure. Further, Axl inhibition or deletion reduced infiltrating DCs and T cells in the kidney and aorta.[70] γδ T cells also increased in the spleen in A2HTN and mice deficient in TCRδ demonstrated minimal blood pressure response to AngII as well as reduced splenic T cell activation, with anti-TCRγδ treatment attenuating the increase in blood pressure.[71] Microglial cells similarly increase in A2HTN alongside changes in gut microbiota, with both reverting to normal with decreases in mean arterial pressure when treated with a tetracycline derivative.[72] Macrophage-produced 12/15-lipoxygenase has been shown to potentiate the vasoconstrictive effect of AngII, contributing to the development of A2HTN.[73] AngII infusion can lead to increased levels of plasma sphingosine-1-phosphate (S1P), an immune cell trafficking signal, and coupling a S1P receptor agonist with AngII infusion results in a lessened blood

pressure increase.[74] T cell subsets have been evaluated intensively, demonstrating the effects of interleukins and extracellular vesicles produced by T cells on A2HTN. Mice with deletions of IL-6 or Rag-1 showed resistance to thrombosis caused by A2HTN while extracellular vesicles derived from T cells increased in the kidney and in circulation as a result of A2HTN.[75,76] The activation of C3a/C3aR and C5a/C5aR signaling reduces the expression of Foxp3 in the Tregs and limits the immunosuppressive function.[77] Genetic deletion or pharmacological blockade of C3aR and C5aR have shown to promote the differentiation of FOXP3+ Tregs.[78] In A2HTN, the expression of C3aR and C5aR was increased in FOXP3+ Tregs, while mice deficient in both receptors experienced a blunted blood pressure in response to AngII with less renal damage and remodeling.[41] Th22 cells producing IL-22 were elevated in hypertensive patients and AngII-infused mice, and both anti-IL-22 treatment and STAT3 inhibition mitigated the increased blood pressure.[37] Macrophage and T cell infiltration into kidney has been implicated in the amplification of A2HTN and end-organ damage in Dahl salt-sensitive rats.[79] In addition, menopause, Treg depletion, or transfer of mixed splenocytes from hypertensive mice are each sufficient to cause premenopausal normotensive females to become hypertensive.[80,81] Notably, the mixed splenocyte transfer raises questions regarding which cell types (or combinations of cell types) are required for the premenopausal protection to be overcome, as T cell transfer alone is insufficient without the addition of B cells, macrophages, and DCs. Overall, the A2HTN animal model continues to be a valuable tool in determining the role of immunity in hypertension.

HYPERTENSIVE DISORDERS OF PREGNANCY

Hypertensive disorders of pregnancy account for more than 10% of pregnancy complications, leading to maternal and fetal morbidity and mortality.[82] These disorders are broadly categorized into chronic hypertension, preeclampsia (PE)–eclampsia, chronic hypertension with superimposed PE, and gestational hypertension.[83] Among these, PE is the most prevalent multiorgan disease characterized by new-onset hypertension and proteinuria after 20 weeks gestation in combination with hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, pulmonary edema, and kidney and liver dysfunction.[84] Improper trophoblast invasion and placentation along with defective remodeling of uterine spiral arteries incites placental ischemia, and abnormal maternal immune responses all lead to imbalanced immune cells contributing to the excessive inflammatory state contributing to the pathogenesis of PE and other hypertensive disorders of pregnancy.[85,86]

During early pregnancy, NK cells are the most abundant innate immune cells in the decidua and crucial for spiral artery remodeling.[87–89] Decidual NK (dNK) cells were elevated at maternal–fetal interface in PE when compared with normal pregnancies.[90,91] Elevated NK cells and cytolytic activation were observed in peripheral blood from women with PE as well as Reduced Uterine Perfusion Pressure (RUPP) rat model.[92–94] Anti-inflammatory compounds like IL-4 and 17-hydroxyprogesterone caproate have been reported to reduce total and cytolytic placental NK cells while improving blood pressure in RUPP rats, suggesting NK cell modulation for the treatment of PE.[95,96]

Macrophages, the second largest immune cell population in the decidua, exhibit an anti-inflammatory M2 phenotype.[97] An imbalance in M1/M2 macrophages has been documented at the maternal–fetal interface in PE, leading to a local pro-inflammatory state.[98–102] Vascular endothelial growth factor (VEGF) treatment enhanced macrophage migration and shifted polarization toward the M2 phenotype *in vitro*.[99] In LPS-induced PE-like rat model, the expression of T cell immunoglobulin mucin 3 (Tim-3), a checkpoint receptor regulating immune tolerance, and its ligand Galectin-9, were reduced at the maternal–fetal interface. Administration of Galectin-9 and TIM-3 ligand increased M2 macrophages and reversed the impairments at the maternal–fetal interface.[101] Notably, combined activation of PD-1/Tim-3 pathway with PD-L1/Galectin-9 proteins inhibited M1 macrophage polarization and ameliorated PE-like symptoms in LPS-treated rats.[102] The complement system has also been implicated in the pathogenesis of PE, where elevated levels of C5a in the placenta were associated with increased infiltration of CD11b+ macrophages and trophoblast dysfunction in PE.[103] Targeting these inflammatory macrophages may provide new therapeutic strategies to improve pregnancy outcomes in women with hypertensive disorders.

DCs play a crucial role in maternal–fetal tolerance during pregnancy.[104] Changes in DC populations and proportions in the circulation and at the tissue level have been implicated in disrupted maternal–fetal tolerance.[105–107] Notably, the decidua of women with PE had increased expression of DC-specific lnc-DC (long noncoding RNA that regulates DC maturation by phosphorylating STAT3)[108]; and p-STAT3, along with increased number of mature DCs suggesting the role of lnc-DC in the induction of DC maturation.[109] Mature DCs present antigens to T cells and stimulate proliferation of Th1/Th17 cells, resulting in pro-inflammatory responses consequently disrupting maternal–fetal tolerance.[109,110]

Tregs are the most critical adaptive immune cell type that help create an immunosuppressive environment for the maintenance of maternal–fetal tolerance during pregnancy.[111] Reduction in the percentage of Tregs and the expression of Treg-related transcription factors like FOXP3 and GATA3 along with an increase in the percentage of Th17 cells in the circulation were reported in women with PE.[106,107,112–119] Moreover, the Treg/Th17 imbalance observed at the maternal–fetal interface in women with PE has been attributed to decreased expression of programmed cell death-1 (PD-1) and PD-ligand 1 (PD-L1), altered proportions of DC subsets in the circulation and impaired lymphangiogenesis.[106,107,118,120] In PE, there is a significant decrease in clonally expanded populations of effector Tregs in the decidua during the third trimester.[121] In women with PE, there was increased expression of the transcription factors T-bet and retinoic acid receptor-related orphan receptor (ROR)γt (which regulates differentiation of Th cells into Th1 or Th17) in peripheral blood mononuclear cells.[122] siRNA-mediated knockdown of T-bet and RORγt in activated T cells *in vitro* ameliorated T cell imbalance by increasing FOXP3 expression.[122] The role of activated T cells in the pathogenesis of PE was supported by increased expression of activation markers

like HLA-DR and CD122 and increased placental γδ T cells.[123,124] Activated proportions of CD4+ memory, CD4+ effector memory (EM), and CD4+ central memory (CM) cells were reduced in the peripheral circulation of women with PE.[125] Similar to changes observed in circulating T cell populations, increased activated CD4+ and CD8+ memory cells were reported at the fetal–maternal interface in women with early-onset PE and decreased CD4+ CM and CD8+ memory cell populations in the decidua from both early- and late-onset PE groups.[126] Interestingly, there was an increase in decidual CD8+ EM cells lacking PD-1 expression in women with PE and miscarriages.[127] The contribution of B cells in the pathogenesis of PE came to light with the finding of auto-antibodies against AngII AT1R in preeclamptic women.[128] However, a study in the RUPP rat model reported no change in B1 and B2 cell populations in peripheral blood, spleen, and placenta, and B cell depletion with anti-CD20 antibody was found to be ineffective against PE symptoms.[129] Hence, extensive research is needed to provide deeper insights into the contributions of different immune cell subsets to local and systemic inflammation in women with pregnancy complications due to hypertension.

CONCLUSION AND FUTURE DIRECTIONS

Certain factors relating to induction and progression of hypertension were not presented extensively in this review such as the role of the complement system, oxidative stress, cytokines, chemokines, and MHC in immunological contributions to disease progression. The influence of the immune system and its role in hypertension can be further elucidated due to complex system interactions. A key area of developmental focus relates to the interface between the gut flora and metabolite alterations in hypertension. Current treatments for hypertension include lifestyle modifications or pharmacotherapies, often used in combination to reduce hypertensive effects; however, most therapeutics focus on inhibition of the renin–angiotensin–aldosterone system and in turn fail to prevent end-organ damage showcasing the need for further development in the treatment field of hypertension.

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DISCLOSURE

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