Review Article

Role of regulatory T cells and T helper 17 cells in the pathogenesis of hypertension: a review

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ABSTRACT

The discovery of autoantibodies in artery samples from cadavers with hypertension over 50 years ago suggested a potential link between the immune system and hypertension. Since then, research exploring the role of the immune system in hypertension has emerged. Animal studies have demonstrated a strong correlation between regulatory T cells (Tregs) and T helper 17 (Th17) cells in hypertension development, yet studies on human hypertension remain limited. Tregs produce inhibitory cytokines such as interleukin (IL)-10 and transforming growth factor-β to act as anti-inflammatory cells that protect against hypertension. In contrast, Th17 cells, by producing IL-17A, function as pro-inflammatory cells that promote hypertension. Recently, a subset of cells known as IL-17A+FOXP3+Treg cells have been identified, which can produce IL-17 and act as inflammatory cells under certain conditions. Understanding the basic mechanisms by which the immune system influences hypertension could lead to targeted immunotherapies for hypertension in the future. Thus, we highlighted the role of Tregs and Th17 cells in the development of hypertension and their potential as targets for therapy. Our findings confirmed the role of Tregs and Th17 cells in the pathogenesis of hypertension.

KEYWORDS hypertension, immune system, regulatory T cell, T helper 17 cell

Approximately one-third of people worldwide are affected by hypertension, which increases the risk of various cardiovascular diseases, such as peripheral and coronary artery disease, hypertrophy of the left ventricle, heart failure, non-hemorrhagic stroke, hemorrhagic stroke, and chronic kidney disease. More than 90% of hypertension cases are classified as essential or primary hypertension because their etiology remains unknown. A combination of hereditary variables might lead to hypertension.[1]

The pathophysiology of hypertension remains incompletely understood. More than 50 years ago, autoantibodies were discovered in arterial samples from hypertensive cadavers, suggesting a relationship between the immune system and hypertension. Since then, studies on the role of the immune system in hypertension have emerged.[2] Recent studies, mostly in rats and mice, have indicated that a putative key mechanism of hypertension is the dysregulation of various T lymphocyte subsets. Theoretically, both direct and indirect hypertensive stimuli increase the level of interleukin (IL)-6 in the renal and cardiovascular system, which can imbalance the ratio of T helper 17 (Th17) and regulatory T cells (Tregs) in the body. In perivascular adipose tissue (PVAT) and adventitia, this leads to an increase in IL-17 and a reduction in IL-10, contributing to higher blood pressure in animal models.[3] This review highlights the role of Tregs and Th17 cells in hypertension development, indicating their potential as therapeutic targets in hypertension.

Innate immunity and hypertension

Innate immunity is characterized by a rapid, nonspecific reaction to antigens and serves as the body's initial line of protection. This involves several effector cells, including dendritic cells (DC), natural killer (NK) cells, and macrophages. The inflammatory process initiated by these cells is localized to the region of injury, resembling low-grade inflammation in hypertension.[4] Pattern recognition receptors (PRRs) detect danger signals, such as pathogen-associated molecular patterns and danger-associated molecular patterns (DAMPs), as endogenously generated cellular stress signals, triggering an intracellular reaction that causes inflammasome formation, pro-inflammatory cytokine production, and activation of both innate and adaptive immune effector cells. Among PRRs, only toll-like receptors (TLRs) have been proven to be involved in the inflammation associated with hypertension.[5,6]

Macrophages contribute significantly to the development of hypertension and vascular diseases. De Ciuceis et al[7] used osteopetrotic mice with a mutation in the colony-stimulating factor 1 gene and found that these mice maintained normal blood pressure and experienced less endothelial dysfunction, oxidative stress, and vascular remodeling, even after receiving hypertensive doses of angiotensin (Ang) II. Despite these potential explanations, the precise mechanisms through which monocytes and macrophages cause hypertension remain unknown. Monocytes and macrophages possess activated Ang II and mineralocorticoid receptors. In response to these stimuli, monocytes and macrophages generate reactive oxygen species by activating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and cytokines.[8,9]

Kossman et al[10] found that the synergistic stimulation of NK cells and monocytes leads to Ang II-induced vascular damage. Monocytes secrete IL-12, which stimulates NK cell activation. Ang II increases the infiltration of both monocyte and NK cells, resulting in elevated expression of T-bet protein and IL-12, and interferon (IFN)-γ mRNA in the aorta, all of which contribute to vascular damage.[10]

Increased effector T cell activity is essential to antigen-presenting cells (APCs) in this process. As important APCs in the inflammatory process, DCs activate T cells by delivering an activation signal that includes antigenic peptide presentation to the T cell receptor and a co-stimulation signal. The most essential co-stimulatory signal is the interaction between T cell CD28 and B7 ligands on APCs, which is especially important for activating naive T cells.[11] Vinh et al[12] demonstrated that B7 ligand-induced T cell co-stimulation is essential to hypertension. The pharmaceutical drug abatacept, which inhibits the interaction of CD28/B7, was found to reduce deoxycorticosterone acetate (DOCA)-salt-induced hypertension and Ang II-inhibited T cell activation and infiltration in the aorta of mice.[12] Human hypertension is characterized by low-grade inflammation, as demonstrated by elevated C-reactive protein levels and cytokines in the blood. However, evidence supporting the role of the innate immune system remains limited.[13] All possible DAMPs are linked to hypertension and can stimulate TLRs on innate immune cells. Marketou et al[14] revealed that TLR4 gene expression in peripheral monocytes was higher in patients with non-diabetic hypertension than that in normotensive cases, although no difference was identified in TLR2 expression. Imakiire et al[15] found that angiotensin-converting enzyme inhibitors diminish glomerular CD68+ monocyte/macrophage infiltration in the glomeruli of patients with hypertensive nephrosclerosis.[15] The combination of observations in patients with hypertension and evidence from animal models indicate the involvement of the innate immune system in hypertension.

Adaptive immunity and hypertension

The adaptive immune system is defined by specific immune responses to fight endogenous or foreign antigens and is primarily mediated by T and B lymphocytes. For T cell activation, antigens must be presented by APCs.[16] Naïve CD4+ T cells can polarize into various phenotypes, including Th1, Th2, Th17, or Tregs, depending on the cytokine environment. The Th1 phenotype, produced by IL-12 and IFN-γ, primarily secretes IL-2, tumor necrosis factor-α (TNF-α), and IFN-γ. The IL-4 environment promotes the development of the Th2 phenotype, which mainly produces IL-4 and IL-10. In contrast, aldosterone activates the Th17 phenotype, thereby promoting the secretion of IL-17A, IL-17F, IL-21, and IL-22.[17]

Fifty years ago, researchers believed that T cell activation may be linked to hypertension. According to Okuda and Grollman,[18] the transfer of lymphocytes from hypertensive rats with renal infarction induced hypertension in control animals,

whereas immunosuppression targeting adaptive immunity reduced hypertension. Studies with Lyon hypertensive rats, hypertensive New Zealand Black mice, hypertensive mice with partial renal infarction, and spontaneous hypertensive rats proved that lymphocyte depletion through thymectomy slowed hypertension development.[3] Mattson et al[19] showed that deleting the recombination-activating gene-1 in Dahl salt-sensitive rats using zinc finger nuclease technology alleviated salt-induced hypertension, thus providing more evidence for T lymphocyte involvement in hypertension. Additionally, transferring CD4+ cells from preeclamptic rats to healthy pregnant rats raised the blood pressure of the recipient.[20] Overall, these results support the notion that T cell activation can cause various kinds of hypertension in mice and rats, thus emphasizing the need for animal studies to identify specific cell subsets that cause hypertension. Many animal studies have thus focused on the activation of Tregs and Th17 cells, which leads to hypertension.

Treg and hypertension

Tregs play various roles in regulating immunological balance. They are vital for modulating peripheral immune responses, suppressing inflammatory responses, and preventing autoimmune disease.[21] Few naive CD4+ T cells can develop into natural or inducible Tregs. Most circulating Tregs are natural and are produced by the thymus, while inducible Tregs are derived from CD4+ T cells in response to antigens and increased local levels of IL-6 and transforming growth factor-β (TGF-β), which inhibit naive CD4+ T cell transformation into Tregs. Tregs express forkhead box P3 (FOXP3), a transcription factor, and the surface marker CD25.[22] Mice lacking FOXP3 experience severe lymphoproliferative disease and loss of Tregs. Tregs are crucial for maintaining a healthy immune balance and self-tolerance to prevent autoimmune disorders by blocking innate and adaptive immune responses to various triggers, including self-antigens and pathogens.[23]

Tregs employ several suppression methods, which are categorized into four main modes of action: inhibition by cytokines, cytolysis, metabolic disruption, and modulation of DC function. Cytokines IL-10 and TGF-β are the most important in the suppressive mechanisms of Tregs. IL-10, an 18-kD protein produced by Tregs, inhibits the generation of pro-inflammatory cytokines such as IL-12 and IL-17, increases phagocytic activity, and increases debris cleaning at inflammation sites.[24] TGF-β, a multifunctional 25 kDa protein, regulates various immune cells through several mechanisms, such as inhibiting effector T cell activation, increasing Treg production, suppressing T cells and B cells proliferation, and inhibiting the activity of macrophages, DCs, and NK cells.[25]

Tregs were first discovered as novel regulators of hypertension by Dr. Schiffrin's team. They employed a genetically modified Brown Norway normotensive strain chromosome 2, which possesses quantitative trait loci for pro-inflammatory genes and hypertension, compared to those in the Dahl salt-sensitive genome. They found that these consomic rats had lower blood pressure, decreased vascular hypertrophy, and decreased effector T cells with increased Tregs in the aorta compared to those in Dahl salt-sensitive rats, as evidenced by the enhanced FOXP3 expression and increased CD4+CD25+ and CD8+CD25+ lymphocytes. Furthermore, genetic substitution in consomic rats led to higher local generation of the anti-inflammatory cytokines IL-10 and TGF-β. These results suggest that Tregs may reduce vascular inflammation and increase blood pressure in consomic rats.[25]

Several investigations from the same group support the theory that Tregs suppress hypertension and end-organ damage. Barhoumi et al[8] mentioned that Ang II infusion led to a 43% decrease in the number of FOXP3+ cells in the mouse renal cortex and an increase in systolic blood pressure (SBP) by 43 mmHg. Using telemetric measurements, the adoptive transfer of Tregs decreased Ang II-induced hypertension in C57BL/6 mice by 10–15 mmHg. This effect was accompanied by a decrease in vascular oxidative stress, in macrophage and T cell infiltration in the aortic adventitia and PVAT, and in plasma IFN-γ, IL-6, and TNF-α levels.[8] According to Matrougui et al,[26] three intraperitoneal Treg injections each week for 2 weeks lowered the mean arterial blood pressure by 12 to 15 mmHg. Treg injection entirely restored the IL-10 levels and Treg counts that Ang II reduced. The infusion significantly improved coronary arteriolar endothelial dysfunction and reduced the vascular macrophage infiltration and TNF-α expression induced by Ang II.[26]

Tregs are assumed to exert anti-inflammatory functions via IL-10 production, though additional pathways are also involved. IL-10 has strong anti-inflammatory properties, including decreasing the levels of IL-6 and TNF-α. According to Ryan et

al,[27] carotid arteries from IL-10-null mice exhibited considerable endothelial dysfunction and elevated levels of vascular superoxide when exposed to Ang II, unlike wild-type mice, which only showed a minimal effect.[28] In hypertensive IL-10-null mice, Kassan et al[29] transplanted cultured Tregs obtained from control mice, which resulted in decreased SBP and NADPH oxidase activity, and enhanced the relaxation of endothelium-dependent mesenteric arteries. Similar results were observed after IL-10 treatment in Ang II-induced hypertension animals.[29] All these investigations indicate that Tregs are powerful anti-hypertensive cells that produce IL-10 upon release.

In a human study, Hafeez et al[30] explored the role of regulatory T cells in preeclampsia. They revealed a significantly decreased Treg number and proportion compared to that in normal pregnancy and healthy non-pregnant participants, but a significantly increased number in normal pregnancy compared to that in non-pregnant healthy controls.[30] Gackowska et al[31] examined the levels of Tregs in children with untreated primary hypertension and sought its association with hypertensive target organ damage; they revealed a decreased percentage of the total Tregs in their left ventricular hypertrophy and increased arterial stiffness. Further, Alexander et al[32] used mass cytometry and observed a selective reduction in $CCR10^+$ Tregs and $PD\text{-}1^+CD57^+CD8^+$ memory T cells, showing a reproducible decrease in hypertension.

Th17 and hypertension

Another subset of CD4+ cells, Th17 cells, secrete the cytokine IL-17, which is linked to cardiovascular and autoimmune diseases. The increase in local IL-6 levels combined with TGF-β encourages the differentiation of CD4+ naive T cells into Th17 cells, and IL-17 contributes to an inflammatory response in the vascular system and mediates Ang II-induced hypertension.[33] Madhur et al[28] demonstrated a direct correlation between elevated Th17 cell levels, IL-17 production, and Ang II-induced hypertension. In their study, chronic Ang II infusion increased the blood pressure in both IL-17-null and wild-type mice in the first 7 days (120 *versus* 162 mmHg). However, after 4 weeks, blood pressure elevation was significantly lower in IL-17-deleted mice than in the controls (150 *versus* 170 mmHg). The arteries of IL-17-null mice show intact vascular function, decreased superoxide generation, and decreased aortic T cell infiltration, indicating that IL-17 is a crucial cytokine involved in hypertension.[28]

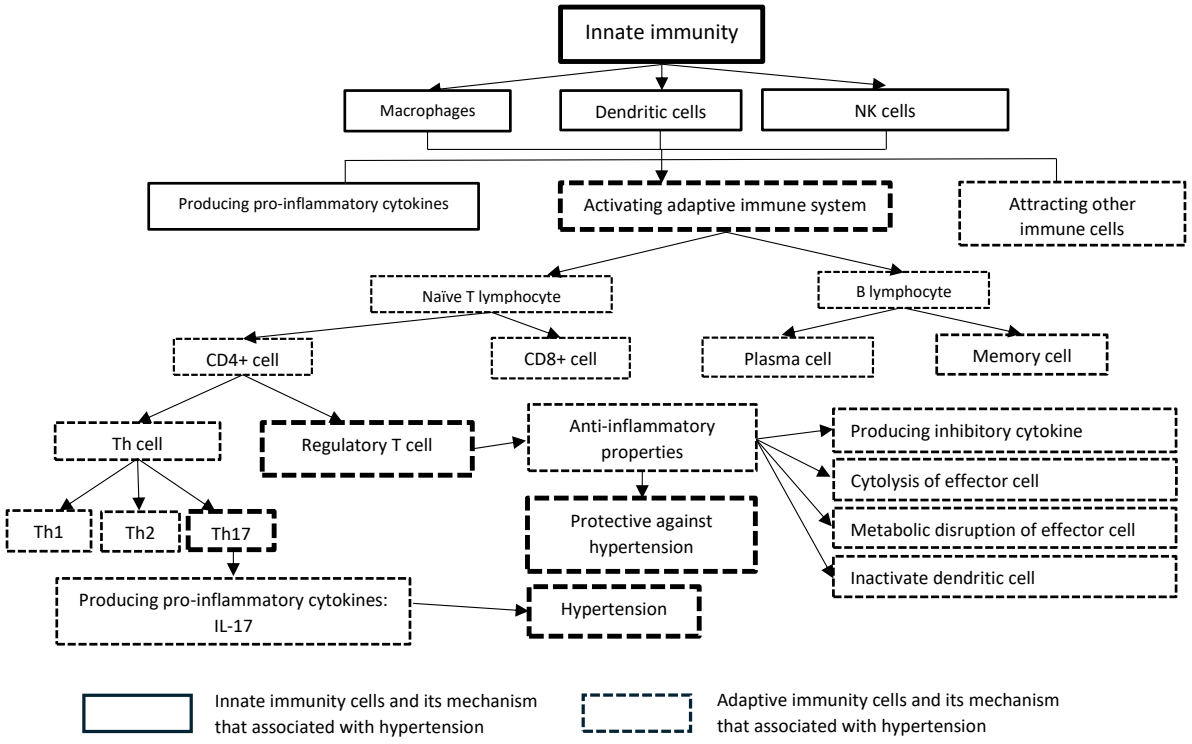

Figure 1. The immune system and its mechanism of action. IL=interleukin; NK=natural killer; Th=T helper

In another trial, intravenous administration of IL-17 to C57BL/6 mice increased the SBP and inhibited nitric oxide-mediated vascular relaxation. Th17 activation has been linked to DOCA salt-induced hypertension in rats, and treatment with an anti-IL-17 antibody was found to decrease hypertension in these rats. Furthermore, a high-salt diet promotes Th17 cells via the p38/mitogen-activated protein kinase pathway. These findings imply that Th17 cells contribute significantly to T cell activation-mediated hypertension by releasing IL-17 (Figure 1).[34]

The Th17/Treg ratio and hypertension

CD4+ T cells can differentiate into either Th17 cells or Tregs, depending on the local cytokine environment, with these processes being mutually exclusive. Increased IL-6 is critical for driving Th17 cell differentiation alongside TGF-β while inhibiting Treg generation from CD4+ T cells. This creates an imbalance between Th17 cells and Tregs. Additionally, IL-6 encourages CD8+ T cells to stimulate cytotoxic T cells.[6]

Hypertensive stimuli, such as Ang II, sympathetic overdrive, autonomic nervous dysfunction, and environmental factors, including obesity and vitamin D deficiency, increase IL-6 expression in the PVAT. This creates an imbalance in Th17/Treg differentiation, with increased IL-17 and decreased IL-10 levels, and attracts other activated immune cells, including macrophages. Overall, the development of hypertension is triggered by a sustained rise in IL-6, IL-17, and TNF- levels in PVAT and a fall in Treg and IL-10 levels.[3]

Xie et al[35] demonstrated the role of a Th17/Treg imbalance in atherosclerosis development. Amador et al[32] found that Th17 cells were activated and FOXP3 mRNA was downregulated in the peripheral tissues, heart, and kidneys of DOCA-salt hypertensive rats. Treatment with spironolactone, an aldosterone antagonist, resulted in lower Th17 cell counts and higher Treg levels, indicating that activation of mineralocorticoid receptors affects the Th17/Treg pathway in DOCA-salt hypertension. Another study showed that excessive dietary sodium increased the production of pro-inflammatory Th17 cells and affected autoimmunity by impairing Treg activity.[34]

IL-17A+FOXP3+Tregs and hypertension

Tregs and Th17 cells can significantly influence the pathogenesis of inflammation and autoimmune diseases despite their antagonistic properties. Recent research has suggested that Tregs can produce IL-17, although their ability to maintain their inhibitory functions in such cases remains uncertain. Beriou et al[36] discovered that a small but stable percentage of $CD25^{high}FOXP3^{+}DR^{-}CCR6^{+}$Tregs expressed IL-17 both *ex vivo* and in short-term cultures. This IL-17 production was enhanced by IL-2 and IL-6, with co-treatment with IL-1, and was inhibited by TGF-β. Their findings showed that a subset of human Tregs could generate the effector cytokine IL-17 both *in vivo* and *in vitro*. When secreting IL-17, these Tregs temporarily lose their suppressive action, as evidenced by both loss of suppression and the inability to reduce IFN-γ production under inflammatory conditions. This impairment of suppression was reversible, as FOXP3+/IL-17+ clones could restore regulatory function once stimulated to express IL-17.[36] Further, Putra et al[37] showed higher levels of IL-17A+FOXP3+ Tregs in the hypertensive group compared with those in normotension. They also found a moderate to strong correlation between IL-17A+FOXP3+Treg levels and both systolic and diastolic blood pressure. However, further studies are required to determine the association between IL-17+FOXP3+ Tregs and hypertension.

Clinical perspectives

The immune system has been implicated in the pathogenesis of hypertension by both animal and human studies. Nakagami et al[38] conducted a placebo-controlled dose-escalation study to investigate the safety, tolerability, and immunological response of an Ang II vaccine (AGMG0201). This study involved participants aged 18–79 years with mild-to-moderate hypertension, with 12 patients each in the low- and high-dose groups. Within each group, the subjects were randomly assigned to receive either the active vaccine or placebo at a 3:1 ratio. Each participant received a single intramuscular injection, followed by a second injection after 30 days and monitoring for 360 days post-injection. The results indicated that most treatment-related adverse events were mild to moderate, including pain and erythema, at the injection site. Further, Anti-Ang II antibodies were observed in patients receiving AGMG0201.[38] In the future, immune-targeted therapy will have the potential for hypertension treatment, including the Ang II vaccine that is under development.

A limitation of this review was the large number of animal studies included. Studies on the roles of Tregs and Th17 cells have been conducted more frequently in animals than humans. However, findings related to the immune system of animals may not be fully translated to humans. Further, the methods used in these studies were heterogeneous, with many animals having secondary hypertension, which may not be relevant to the pathogenesis of essential hypertension.

In conclusion, growing evidence links Tregs, Th17 cells, and the imbalance between these cell types with the onset and progression of hypertension, as well as targeting organ damage in various forms of hypertension, including Ang II-induced, salt-sensitive, and hereditary hypertension. Research on Th17/Treg balance offers promise for preventing and treating hypertension-related organ damage. Current developments in hypertension therapies are increasingly focused on targeting the immune system. Therefore, understanding the specific roles and mechanisms of immune cells in hypertension is crucial for advancing treatment strategies and improving patient outcomes.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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