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**REVIEW**
*Björn Folkow lecture*

# Dual opposing roles of adaptive immunity in hypertension†

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Hypertension involves remodelling and inflammation of the arterial wall. Interactions between vascular and inflammatory cells play a critical role in disease initiation and progression. T effector and regulatory lymphocytes, members of the adaptive immune system, play contrasting roles in hypertension. Signals from the central nervous system and the innate immune system antigen-presenting cells activate T effector lymphocytes and promote their differentiation towards pro-inflammatory T helper ($T_h$) 1 and $T_h17$ phenotypes. $T_h1$ and $T_h17$ effector cells, via production of pro-inflammatory mediators, participate in the low-grade inflammation that leads to blood pressure elevation and end-organ damage. T regulatory lymphocytes, on the other hand, counteract hypertensive effects by suppressing innate and adaptive immune responses. The present review summarizes and discusses the adaptive immune mechanisms that participate in the pathophysiology in hypertension.

**Keywords** Blood pressure • Adaptive immunity • Inflammation • T effector lymphocytes • T regulatory lymphocytes • Cytokines

## Translational Perspective

Evidence from experimental models of hypertension and hypertensive patients suggests an imbalance of T effector and regulatory subsets in hypertension, causing low-grade inflammation, and contributing to blood pressure elevation and progression of end-organ damage. Novel data increasingly identifies new potential targets within the immune system for therapeutic intervention. Interventions directed toward promoting immunosuppressive T regulatory activity and reducing pro-inflammatory T effector lymphocytes, or the products or targets thereof, could contribute to blood pressure control and limit target-organ damage.

## Introduction

It has been increasingly recognized, but may remain underappreciated, that an immune-inflammatory component participates in the pathogenesis of hypertension. Infiltration of innate and adaptive immune cells in the kidney, vessel wall and perivascular regions, together with other inflammatory processes such as elevated cytokine release, reactive oxygen species (ROS) production, and expression of adhesion molecules are a consistent feature of hypertension.[1–3] Aberrant activation of adaptive immunity, represented by T effector lymphocytes, appears to play a key role in the development of hypertension. Exactly how and why this occurs is still unclear, but may involve increased sympathetic activity and co-stimulation from innate cells.[2] T effector cells interact with innate immune mechanisms to exaggerate the inflammatory response via production of pro-inflammatory cytokines and ROS and, hence, contribute to the pathophysiology of cardiovascular disease and hypertension.[1] T regulatory lymphocytes (Tregs), on the other hand, counteract the elevation of blood pressure and associated kidney and vascular damage by limiting innate and adaptive immune responses.[1] This review will aim to comprehensively examine the evidence for the contrasting roles of T effector and regulatory subsets in hypertension.

## Immunity in hypertension: a historical perspective

Since the early 1980s, an increasing amount of evidence has accumulated that suggests a direct relationship between hypertension and

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immune dysfunction in experimental hypertensive animals. The chronic phase of hypertension was shown to be blunted in athymic mice undergoing partial infarction of one kidney and contralateral nephrectomy.[4] Thymus transplantation from wild-type mice restored the ability to maintain chronic hypertension in athymic mice. Similarly, spontaneous increase of systolic blood pressure was prevented by neonatal thymectomy in Lyon genetically hypertensive (LH) rats.[5]

Olsen first demonstrated that intravenous injection of splenic cells from deoxycorticosterone acetate (DOCA)-salt hypertensive and renal hypertensive rats induced arterial hypertension in normotensive rats.[6] Similarly, lymphoid cell injections from LH rat donors were also shown to be sufficient to cause blood pressure elevation in Lyon normotensive rats.[7] Hypertension was induced by transfer of syngeneic spleen lymphoid cells from mice suffering from systemic lupus erythematosus into normotensive mice, suggesting that hypertension could be an immunologic disease induced by an abnormal lymphoid system.[8] Implantation of thymus tissue from normotensive rats into young and developing spontaneously hypertensive rats (SHR) partially suppressed the development of elevated blood pressure.[9] In another study, SHR were shown to exhibit reduced suppressor T-cells activity.[10] Chronic immunosuppressive treatment with cyclophosphamide or cyclosporin induced a partial reduction in blood pressure in SHR.[11,12]

Together, these results supported the hypothesis that cellular adaptive immune reactions contribute to the pathogenesis of hypertension. More recently, experimental hypertension studies have identified roles for different subsets of T lymphocytes, an important component of adaptive immunity, in hypertension. First, it is important to introduce the various subsets of T lymphocytes.

## T-lymphocyte subsets

T lymphocytes can be distinguished from other lymphocytes by the presence of the T-cell receptor (TCR) complex containing two TCR chains (α and β), a CD3 co-receptor and a ζ-chain accessory molecule. The majority of T lymphocytes contain TCRs composed of α- and β-glycoprotein chains. During development in lymphoid tissues, $CD3^+$ T lymphocytes mature into either $CD4^+$ or $CD8^+$ single-positive cells, and leave the thymus and become immunocompetent. In a normal immune response, T lymphocytes require two signals for activation (*Figure 1*).[13] The first signal involves recognition by T cells via their TCR, of an antigenic peptide presented by antigen-presenting cells (APC) via their major histocompatibility complex (MHC) class II molecules. The second is a costimulatory signal, which is usually the interaction between B7 ligands (CD80 and CD86) on APC with the T-cell co-receptor CD28. In response to combined stimulation with antigen, costimulators, and particular cytokines, naïve $CD4^+$ T helper ($T_h$) cells ($T_h0$) have been classically described to differentiate into $T_h1$, $T_h2$ and $T_h17$ effector cells, each producing its own panel of cytokines and mediating separate functions.[14] $T_h1$ cells secrete interferon (IFN)-γ, interleukin (IL)-2, and tumor necrosis factor (TNF)-β and play roles in cell-mediated defense against intracellular microorganisms. $T_h2$ cells produce IL-4, IL-5, IL-10, and IL-13, which assist in B-cell activation and suppress cell-mediated immunity. $T_h17$ cells secrete IL-17 and IL-22 and participate in defense against extracellular bacteria and fungi and in autoimmune diseases. $CD8^+$ T effectors differentiate into cytotoxic ($T_c$) cells that secrete perforin, granzyme B, IFN-γ, and TNF-α. Perforin creates pores within the target cell membranes, through which the granzymes can enter and induce apoptosis.[15]

A small group of T lymphocytes express the γ/δ TCR instead of the conventional α/β TCR.[16] γ/δ T cells are unique since, in addition to effector functions shared with α/β T cells, these cells can perform professional antigen-presenting capacity similar to dendritic cells (DCs).[17] These 'innate-like' T lymphocytes spans across the biology of innate and adaptive immunity, and can rapidly produce IL-17A in response to the pro-inflammatory cytokines IL-1 and IL-23.[18] Interestingly, some γ/δ T lymphocytes that express CD39 carry out Treg functions.[19] Relatively, recent advances in immunology have also led to the identification of new T effector lymphocyte subsets including $T_h9$, which produce IL-9 and IL-10 in abundance, and $T_h22$, which primarily produce IL-22.[20]

$CD4^+$ naïve T lymphocytes can also differentiate into T regulatory lymphocytes (Tregs) (*Figure 1*).[14] T regulatory lymphocytes have the capacity to suppress innate and adaptive responses to autoantigens, alloantigens, tumor antigens, and infectious agents. Therefore, Tregs are important in the maintenance of immunologic self-tolerance and immune homeostasis. They express IL-2 receptor α-subunit (CD25), and the transcription factor forkhead box P3 (Foxp3), which controls the phenotype and function of Tregs. T regulatory lymphocytes include natural Tregs, which develop in the thymus and constitute the majority of circulating Tregs, and inducible Tregs (also known as adaptive or peripheral Tregs), which differentiate from conventional $CD4^+$ T cells in peripheral tissues in response to antigens, cytokines, and other cues. Tregs can suppress innate and adaptive immune responses mainly via the anti-inflammatory effects of IL-10, although other mechanisms may also be involved.[21]

It is important to realize that while T lymphocytes are traditionally classified into different subsets mentioned above in order to delineate their various functions, polarized T cells possess considerable plasticity, and can change their phenotype and cytokine secretion depending on the environment that the cells are in. For example, the ratio between Tregs and $T_h17$ cells, which are derived from the same precursor, depends on the amount of IL-6 present in the cytokine milieu.[22] $CD8^+$ T lymphocytes have also been known to be able to perform regulatory function.[23]

## T-effector lymphocytes in hypertension

Harrison's group first investigated the possibility that T and B cells might represent a novel therapeutic target for the treatment of hypertension.[24] They used C57BL/6 mice lacking recombination activating gene-1 ($Rag1^{-/-}$), an enzyme that plays an important role in the rearrangement and recombination of the genes of immunoglobulins and the TCR, and as a result are deficient in mature T and B cells. They showed that $Rag1^{-/-}$ mice exhibited a blunted development of hypertension, vascular oxidative stress in response to angiotensin (Ang) II infusion or DOCA-salt. Adoptive transfer of T cells, but not of B cells, restored the hypertensive phenotype in response to Ang II in $Rag1^{-/-}$ mice. However, if reconstitution was carried out with T lymphocytes from mice deficient in Ang II type 1a receptors ($AT_{1a}R$), or $Agtr1a^{-/-}$, or deficient in the reduced nicotinamide

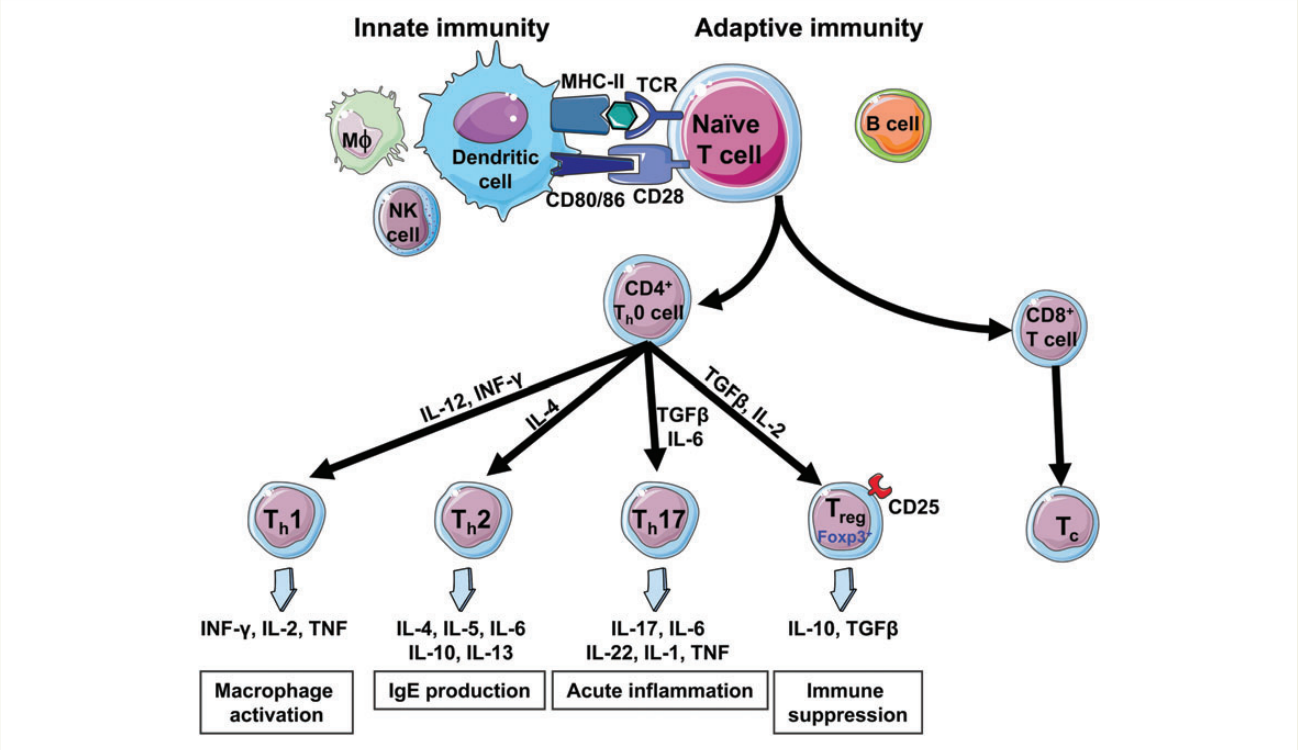


**Figure 1** Differentiation of naïve T lymphocytes into various subsets in a normal immune response. Antigen-presenting cells (dendritic cells and monocyte/macrophages) present antigens on major histocompatibility complex (MHC)-II to naïve T cells ($T_h0$) in secondary lymphoid tissues, leading to T-cell clonal expansion and differentiation into effector T cells, such as T helper ($T_h$)1, $T_h2$, and $T_h17$ or T regulatory ($T_{reg}$) cells according to combined stimulation by different cytokines. $T_h$ effector lymphocytes and Tregs migrate into tissues such as the vasculature, particularly at the level of the adventitia and perivascular fat. The effector lymphocytes ($T_h1$ and $T_h17$) cells activate other immune cells and participate in inflammation by producing pro-inflammatory cytokines such as interferon-γ, interleukin (IL)-6, and IL-17. T regulatory lymphocytes suppress innate and adaptive responses via production of anti-inflammatory cytokines IL-10 and transforming growth factor-β. CD, cluster of differentiation; DC, dendritic cell; MΦ, macrophage; NK cell, natural killer cell; $T_c$, cytotoxic T cell; TCR, T-cell receptor.

adenine dinucleotide phosphate (NADPH) oxidase subunit p47phox (*Ncf1*$^{-/-}$), the Ang II-mediated hypertensive response in *Rag1*$^{-/-}$ mice was partially blunted, and was not totally corrected, suggesting that T-cell $AT_{1a}R$ activation and NADPH oxidase-dependent ROS formation are important for the development of hypertension. Ang II-induced adventitial collagen deposition and aortic stiffening were also blunted in *Rag1*$^{-/-}$ mice.[25] Furthermore, adoptive transfer of T-cells to *Rag1*$^{-/-}$ mice restored the aortic stiffening and collagen deposition caused by Ang II. Interestingly, this restoration was not achieved through adoptive transfer of $CD4^+$ or $CD8^+$ T-cells alone, indicating that the combination of $CD4^+$ and $CD8^+$ T-cells is required for Ang II-induced vascular remodeling.[25]

Immunosuppressive therapy has also prevented blood pressure elevation in other experimental models of hypertension. Mycophenolate mofetil, which depletes B and T cells, protects against hypertension and renal disease in salt-sensitive,[26,27] DOCA-salt,[28] and SHR rats.[29,30] An increase in production of TNF-α by T cells was observed, and treatment with a TNF-α antagonist, etanercept, prevented Ang II-induced blood pressure rise and increase in vascular superoxide. These observations have since been corroborated and extended by others. Vital *et al.*[31] demonstrated that lymphocyte-deficient *Rag1*$^{-/-}$ mice and irradiated wild-type mice receiving bone marrow from *Agtr1a*$^{-/-}$ mice exhibit reduced blood pressure response to Ang II, thus also supporting a role for lymphocyte-associated $AT_{1a}R$ in Ang II-mediated hypertension. Crowley *et al.*[32] used severe combined immunodeficiency (*Scid*) mice on a C3H background, which also lack lymphocyte immune responses, and showed that these mice have blunted Ang II-induced hypertension, cardiac hypertrophy and renal injury, due to enhanced production of nitric oxide (NO), prostaglandin E2 and prostacyclin via stimulation of endothelial nitric oxide synthase and cyclooxygenase-2-dependent pathways. More recently, Mattson *et al.*[33] similarly found blunting of salt-sensitive hypertension and renal disease in rats with a genetic mutation in the *Rag1* gene.

Paradoxically, Coffman's group found that activation of $AT_{1a}R$ on bone marrow-derived cells is protective in Ang II-induced hypertension and renal damage. Transfer of bone marrow from *Agtr1a*$^{-/-}$ mice into irradiated wild-type 129/SvEv mice resulted in an augmented hypertensive response, elevated albuminuria and increased renal macrophage infiltration and inflammation after chronic Ang II infusion, compared with transfer of wild-type bone marrow.[34] Using a Cre/Lox approach, they showed that knocking out $AT_{1a}R$ specifically in $CD4^+$ T lymphocytes, potentiates Ang II-induced kidney injury, renal expression of chemokines, and accumulation of T cells in the kidney, despite similar blood pressure elevation compared with

wild type mice.[35] This was associated with increased differentiation of $CD4^+$ T cells towards a more pro-inflammatory ($T_h1$) phenotype. *Tbet*-deficient mice (*Tbx21*$^{-/-}$), which are incapable of mounting a $T_h1$ response, were protected from Ang II-induced kidney injury. It should be noted, however, that Coffman's group used the 129/SvEv strain, which are particularly susceptible to kidney injury, whereas most other studies used the C57BL/6 strain, which may explain the results obtained.

The respective roles of $CD4^+$ and $CD8^+$ T lymphocytes in hypertension are still under intense investigation. Gratze *et al.*[36] used *Id2*-knockout (KO) mice (*Id2*$^{-/-}$) lacking the gene for the inhibitor of differentiation 2 (ID2), which results in dysfunction of innate immune mechanisms through deficit of Langerhans and splenic $CD8a^+$ dendritic cells, decreased natural killer cells and altered adaptive immunity through lack of $CD8^+$ T memory lymphocytes. ID2 plays an important role in the differentiation, proliferation, invasion and apoptosis of various cell types. Although Ang II pressor responses were significantly blunted in *Id2*$^{-/-}$, bone marrow transplantation of ID2-containing marrow cells did not restore the Ang II responses, nor did transplantation of kidneys from *Id2*$^{-/-}$ into wild-type mice blunt Ang II-induced hypertension. Based on these data, the authors concluded that Langerhans dendritic, natural killer, and memory $CD8^+$ T cells do not play a major role in Ang II-induced hypertension. The investigators identified the vessel wall as the candidate tissue responsible for the insensitivity to Ang II-induced hypertension in *Id2*$^{-/-}$, as these mice present an altered gene expression of PPARα and PPARγ and an antisenescence phenotype in their vascular smooth muscle cells. Indeed, other studies have demonstrated the protective role that PPARα and PPARγ exert on the vascular wall response to Ang II in rodents.[37–39] In another study, Ang II-induced arteriolar thrombosis in cremaster arterioles was found to be greater in wild-type mice compared with *Rag1*$^{-/-}$, $CD4^+$ T-cell- or *Nox2* ($gp91^{phox}$)-deficient (*Cybb*$^{-/-}$) mice, whereas $CD8^+$ T-cell-deficient mice exhibited an intermediate phenotype.[40] Adoptive transfer of wild-type or *Cybb*$^{-/-}$ T cells into *Rag1*$^{-/-}$ restored the prothrombic effects of Ang II. Thus $CD4^+$, and to a lesser extent $CD8^+$, T lymphocytes participate in at least Ang II-mediated microvascular thrombosis. As mentioned previously, $CD4^+$ T lymphocytes differentiate into effector $T_h1$, $T_h2$, and $T_h17$ subsets, all of which seem to be involved in hypertension. The evidence for this will be discussed in the following subsections.

## Alteration of $T_h1/T_h2$ balance in hypertension

Several reports provide evidence for a direct role of Ang II in the modification of T-cell balance towards a more proinflammatory $T_h1$ phenotype, as indicated by increased $T_h1$ cytokine IFN-γ production,[41,42] and a decrease in $T_h2$-mediated responses, including IL-4 production, in Ang II-infused rats.[41] These effects can be blocked by $AT_{1a}R$ antagonists independently of haemodynamic responses to Ang II.[41] Interferon-γ seems to be required for the initiation of vascular inflammation, but not blood pressure elevation, since *IFN* γ KO mice have attenuated Ang II-induced vascular dysfunction, independently of blood pressure changes.[43] IL-2 treatment attenuated the development of hypertension in young and adult SHRs,[44] as well as reduced cardiac hypertrophy and improved renal dysfunction in Dahl salt-sensitive rats.[45,46] However, these findings are contradictory to reports from other groups. IL-2 did not demonstrate an antihypertensive effect in other studies in SHRs[45–47] and Dahl salt-sensitive rats.[46] Others have reported that IL-4 release contributes to the development of hypertension while IFN-γ is important for the maintenance of normal blood pressure values in hypertensive mice.[48] In one study, IFN-γ ameliorated the development of hypertension and vascular and renal injuries in Dahl salt sensitive rats.[49] This controversy may be derived from the differences in cytokines and hypertensive animal models used in the studies. It is likely that the pro-inflammatory state of low-grade inflammation promoting hypertension is determined by the total milieu of various cytokines rather than by a single one. There are several chemokine receptors characteristically found on the surface of $T_h1$-type T cells, one of which is C-X-C chemokine receptor type 6, which interacts with the chemokine ligand 16 (CXCL16). Chemokine ligand 16 deficiency was shown to inhibit infiltration of macrophages and $CD3^+$ T cells in the kidneys of Ang II-treated mice.[50] Thus, polarized $T_h1$-mediated responses may be important for the pathogenesis of hypertension.

## Role of $T_h17$ cells in hypertension

IL-17 promotes a vascular inflammatory response and is a critical mediator of Ang II-induced hypertension and vascular dysfunction. Madhur *et al.*[51] demonstrated that Ang II-induced hypertension is associated with increased $T_h17$ cells and IL-17 production. In their study, *IL17a* KO mice (*IL-17a*$^{-/-}$) receiving chronic infusion of Ang II displayed blunted hypertensive response, preserved vascular function, decreased superoxide production, and decreased aortic T-cell infiltration, and the authors suggested that IL-17 contributes to maintenance of elevated blood pressure. *IL-17a*$^{-/-}$ mice are also protected against aortic collagen deposition and stiffening in response to chronic Ang II infusion.[25] In another study, IL-17 infusion to C57BL/6 mice significantly increased systolic blood pressure and decreased aortic NO-dependent relaxation.[52] The authors identified activation of RhoA/Rho-kinase by IL-17 as a potential mechanism that contributes to endothelial dysfunction and hypertension. DOCA-salt-induced hypertension in rats was associated with $T_h17$ cell activation and decreased numbers of Tregs.[53] *In vivo* treatment of these DOCA-salt hypertensive rats with an anti-IL-17 antibody reduced arterial hypertension, expression of profibrotic and pro-inflammatory mediators as well as collagen deposits in the heart and kidney.[53] Moreover, it has been shown that a high-salt diet is able to induce $T_h17$ cell development through the p38/MAPK pathway in humans and mice.[54]

Placental ischaemic rats have been shown to exhibit lower levels of Tregs and higher autoimmune-associated $T_h17$ cells.[55] Adoptive transfer of $CD4^+$ T cells from pregnant reduced-uterine perfusion pressure (RUPP) rats, a model of preeclampsia, into normal pregnant rats induced a significant increase in mean arterial pressure, as well as circulating inflammatory cytokines. Administration of IL-17 soluble receptor C reduced circulating $T_h17$ cells, oxidative stress, and hypertension in RUPP rats.[56] In a model of Tacrolimus-induced hypertension, blood pressure elevation and endothelial dysfunction were found to be due, at least in part, to an increase in $T_h17$ and a decrease in Treg polarization.[57] Modulation of DC function by aldosterone enhances $CD8^+$ T-cell activation and promotes $T_h17$ polarization of $CD4^+$ T cells, which might contribute to the

inflammatory damage leading to hypertension and cardiovascular diseases.[58] Together, these studies underline the critical role played by $T_h17$ cells in different models of hypertension.

## Activation of T effector lymphocytes in hypertension

It is still unclear how T effector lymphocytes are activated during hypertension. In this section, the evidence for the roles of costimulation by innate APCs and the central nervous system (CNS) in activating T effector cells during hypertension will be discussed.

### Role of the costimulation in activation of T effector lymphocytes

Activation of T effector lymphocytes in hypertension suggests that antigen presentation by innate APCs plays a role. Recently, Vinh *et al.*[59] demonstrated a critical role for T-cell costimulation by APCs in hypertension. Ang II-induced hypertension increased the presence of activated ($CD86^+$) dendritic cells in secondary lymphatic tissues. Preventing T-cell costimulation either pharmacologically, using a CTLA4-Ig (which blocks CD28 interactions with B7 ligands), or by genetic deletion of B7 ligands in mice prevented Ang II and DOCA-induced hypertension, T-cell activation, vascular oxidative stress and inflammation. CTLA4-Ig also reversed established Ang II and DOCA-salt-induced hypertension.

### Role of the central nervous system

Emerging evidence supports the notion that the CNS may modulate innate and adaptive immune responses, and thereby influence the pathophysiology of hypertension. Ang II administration into the lateral cerebral ventricles was shown to increase mRNA expression of pro-inflammatory splenic cytokines, such as IL-1β and IL-6.[60] These responses were abrogated by splenic sympathetic denervation, suggesting that central Ang II may elicit a peripheral immune response through the autonomic nervous system. The role of central signalling in hypertension was investigated by causing anterior and ventral to the third ventricle lesions in mice, intervention which is known to prevent most forms of experimental hypertension by disrupting signals from the subfornical organ to the hypothalamus.[61] Third ventricle lesions in mice blunted Ang II-induced hypertension, T-cell activation, and vascular infiltration of leucocytes. Cre/Lox-mediated deletion of extracellular superoxide dismutase (*Sod3*) in the cicumventricular organs of mice increased central signalling.[62] This manipulation resulted in local increase in oxidative stress and elevated sympathetic outflow, causing a slight increase in baseline blood pressure and exaggerating hypertension in response to a low dose of Ang II. T-cell activation was also increased in *Sod3* KO mice infused with a sub-pressor dose of Ang II.[2] In agreement with these observations, Zimmerman *et al.*[63] reported a blunting of Ang II-induced hypertension in C57Bl/6 mice receiving intracerebroventricular injections of an adenovirus encoding for cytoplasmic SOD. Specific inhibition of the brain mitochondrial ROS also reduced the inflammatory cells within the bone marrow to control levels and attenuated Ang II-induced hypertension.[64] Accordingly, the increase in central superoxide may be an important mechanism mediating hypertension.

## T regulatory lymphocytes in hypertension

We first identified a role for Tregs in a rat model of genetic hypertension.[65] We used consomic rats that contained chromosome 2 from normotensive Brown Norway strain on a Dahl salt-sensitive background. Chromosome 2 bears several quantitative trait loci for hypertension and contains pro-inflammatory genes. We showed that chromosome 2-dependent modulation of immune responses in genetic hypertension occurred via Tregs. Consomic rats exhibited reduced blood pressure and vascular inflammation, increased aortic FOXP3 expression and activity of $CD4^+CD25^+$ and $CD8^+CD25^+$ lymphocytes, as well as elevated production of anti-inflammatory cytokines IL-10 and TGFβ by Tregs, compared with Dahl salt-sensitive rats.

We recently extended these findings by showing that adoptive transfer of Tregs in C57Bl/6 mice blunted Ang II-induced hypertension, vascular oxidative stress and stiffness, endothelial dysfunction, aortic macrophage and T-cell infiltration, and circulating levels of pro-inflammatory cytokines in the plasma.[66] We observed similar protective effects of Tregs adoptive transfer in a model of aldosterone-induced hypertension.[67] Kavakan *et al.*[68] demonstrated that adoptive transfer of Tregs prevented Ang II-induced cardiac hypertrophy and fibrosis, TNF-α expression, immune cell infiltration, and electric remodelling, independently of blood pressure-lowering effects. The discrepancy in blood pressure results between our Ang II study and theirs may be explained by differences in the Tregs adoptive transfer protocol and the mouse strains used in these studies. Consistent with our findings, Matrougui *et al.*[69] used C57Bl/6 mice receiving intraperitoneal injections of Tregs 3 times a week for 2 weeks, starting after Ang II infusion and showed a reduction in blood pressure elevation in these mice. They demonstrated that Ang II-induced apoptosis of Tregs is responsible for the induction of vascular inflammation and endothelial dysfunction. Adoptive transfer of Tregs reduced Ang II-induced Tregs apoptosis, macrophage activation and infiltration into coronary arterioles and the heart, local TNF-α release, and coronary arteriolar endothelial dysfunction.

T regulatory lymphocytes production of IL-10 has been shown to have vascular protective effects and limit Ang II-mediated oxidative stress and vascular damage. Ang II-induced endothelial dysfunction was exacerbated in *IL 10* KO mice (*IL* $10^{-/-}$).[70] Indeed, IL-10 released by Tregs plays an important cardiovascular protective role in hypertension.[71] The transfer into hypertensive *IL* $10^{-/-}$ mice of Tregs isolated from control mice reduced systolic blood pressure and NADPH oxidase activity, and improved endothelium-dependent relaxation in resistance arteries, whereas the transfer of Tregs isolated from *IL* $10^{-/-}$ had no effect on hypertensive wild-type mice. They further showed that IL-10 reduced oxidative stress through the inhibition of NADPH oxidase activity via activation of p38 MAP kinase. Whether other immune-suppressive mechanisms of Tregs participate in counteracting hypertension remains unknown.[1]

Together, these studies indicate that Tregs have potent antihypertensive properties, at least in part due to their ability to produce the anti-inflammatory cytokine IL-10.

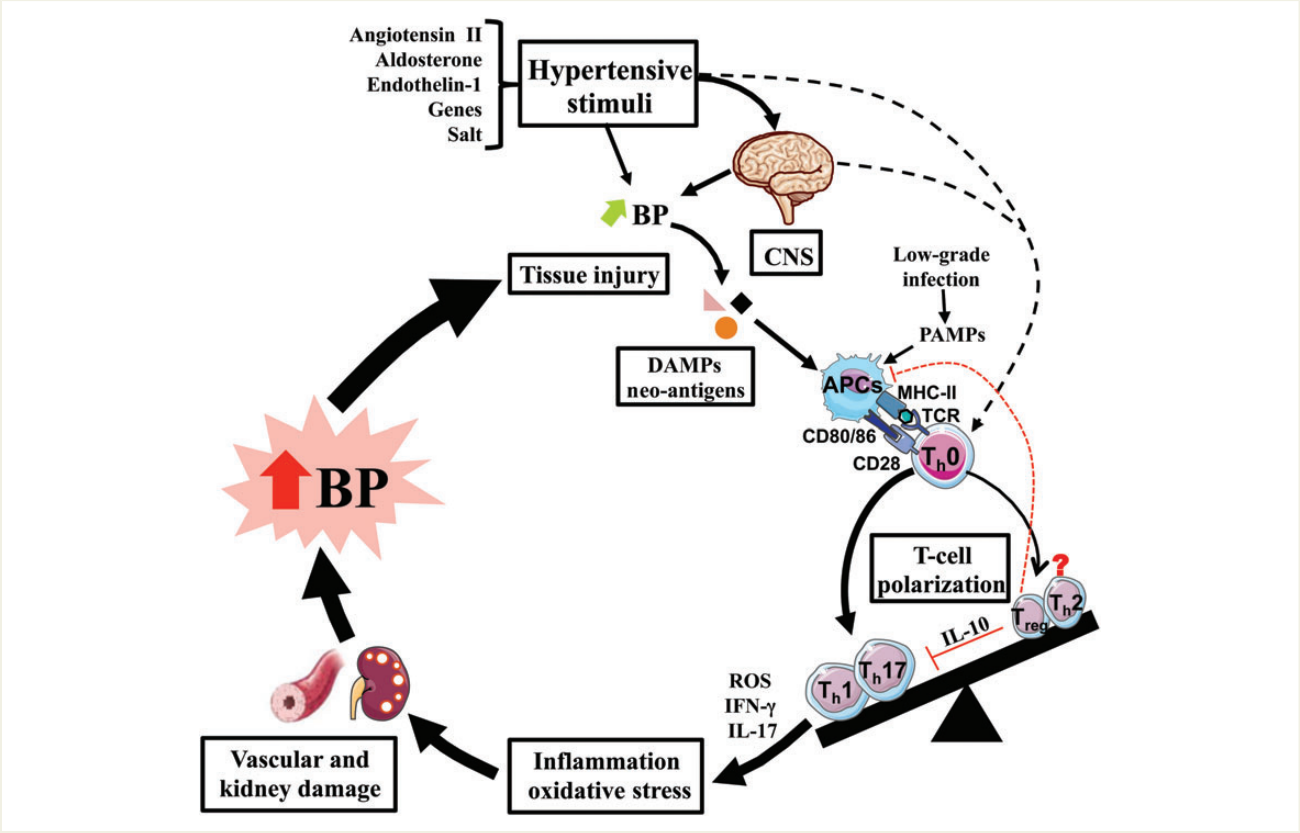


**Figure 2** Proposed role of T effector and regulatory lymphocytes in hypertension. Slight elevation in blood pressure (BP) in response to hypertensive stimuli (angiotensin II, aldosterone, endothelin-1, salt and genetic susceptibility) occurs due to increased central signalling, perhaps causing mild tissue injury and formation of damage-associated molecular patterns (DAMPs) and neoantigens. This may lead to activation of innate antigen-presenting cells (APCs) and, subsequently, activation and polarization of naïve $CD4^+$ T effector lymphocytes ($T_h0$) towards pro-inflammatory T helper ($T_h$)1/$T_h$17 phenotypes. $T_h1$/$T_h17$ may contribute to vascular and kidney damage via production of reactive oxygen species (ROS), interferon (IFN)-γ and interleukin (IL)-17 and lead to maintenance of hypertension and progression of end-organ damage. T regulatory lymphocytes counteract hypertension and associated injury by producing IL-10 or by other mechanisms, and suppression of innate and adaptive immune responses. CD, cluster of differentiation; CNS, central nervous system; MHC-II, major histocompatibility complex-II; PAMPs, pathogen-associated molecular patterns; TCR, T-cell receptor.

## Clinical perspectives

Elevated circulating levels of immunoglobulins, C-reactive protein, and cytokines, and increased incidence of autoreactive antibodies to arterial wall antigens have been reported in hypertensive patients, suggesting that low-grade inflammation is present in hypertension.[72,73] However, evidence of involvement of adaptive immunity in human hypertension is still preliminary. Early studies demonstrated that antihypertensive treatment in humans modified the distribution of T lymphocytes.[74] A Multicenter AIDS Cohort Study indicated that untreated HIV-positive patients, i.e. severely lacking $CD4^+$ T lymphocytes, were significantly less likely than HIV-negative patients to have systolic hypertension.[75] Antiretroviral therapy increased the hypertension prevalence in HIV-positive patients. In another study, mycophenolate mofetil immunosuppressive treatment of hypertensive patients with psoriasis and rheumatoid arthritis was associated with decreased blood pressure.[76] T effector memory cell levels have been reported to be increased in coronary heart disease patients and correlate with media-intima thickness.[77] Furthermore, circulating levels of $T_h17$ are increased in subjects with coronary artery disease.[2] Youn *et al.*[78] first demonstrated a role for C-X-C chemokine receptor type 3 (CXCR3) chemokines, which are well-known tissue-homing chemokines for T cells, in human hypertension. Their study showed an increased fraction of immunosenescent ($CD28^-$ and $CD57^+$), pro-inflammatory, cytotoxic $CD8^+$ T cells, which secrete perforin, granzyme B, IFN-γ and TNF-α, and increased circulating levels of CXCR3 chemokines in hypertensive patients. Finally, Tregs were decreased in women suffering from preeclampsia compared with those with normal pregnancies.[79] These studies demonstrate that various subsets of T lymphocytes may indeed participate in the pathophysiology of human hypertension.

## Conclusion

Experimental and clinical evidence discussed in this review strongly suggests that adaptive immunity, represented by T effector and regulatory lymphocyte subsets, plays a dual role in hypertension (*Figure 2*).

Increased sympathetic outflow as a consequence of stimulation of the CNS by hypertensive stimuli may result in mild blood pressure elevation, causing tissue injury and formation of neoantigens[2] and/or damage-associated molecular patterns (DAMPs).[80] Activation of innate APCs by DAMPs, or by pathogen-associated molecular patterns (PAMPs) generated in response to low-grade infection,[80,81] and direct stimulation by CNS, may be the cause of activation of $CD4^+$, and perhaps $CD8^+$, T effector lymphocytes, and differentiation of $CD4^+$ T cells towards pro-inflammatory $T_h1/T_h17$ phenotypes.[41] $T_h1/T_h17$ effector lymphocytes contribute to the progression of hypertension by producing pro-inflammatory mediators, including ROS, IFN-γ, TNF-α, and IL-17, to promote low-grade inflammation.[24,41,42,51,52] T regulatory lymphocytes, on the other hand, counteract hypertensive abnormalities by suppressing innate and adaptive immune responses, perhaps by secreting IL-10.[65–71] As such, circulating levels of Tregs or their immune-suppressive activity may be affected in hypertension.

To conclude, studies showing the role of adaptive T lymphocytes in hypertension have identified novel targets for further investigation into their therapeutic potential for the treatment of hypertension. It is hoped that such studies will help develop new therapies or improve existing ones that will result in better cardiovascular outcomes for hypertensive patients.

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