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INFLAMMATION AND CARDIOVASCULAR DISEASES (A. KIRABO, SECTION EDITOR)

Innate and Innate-Like Immune System in Hypertension and Vascular Injury

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Abstract

Purpose of Review To describe the important role played by innate and innate-like immunity in the pathophysiology of hypertension and vascular injury.

Recent Findings Innate immune cells, such as neutrophils, dendritic cells, myeloid-derived suppressor cells, and monocytes/macrophages and innate lymphoid cells such as natural killer cells and unconventional T lymphocytes like γδ T cells contribute to hypertensive mechanisms by priming adaptive immune cells, leading to the triggering of vascular inflammation and blood pressure elevation or alternatively protecting against vascular injury. Specifically, monocyte/macrophages and γδ T cells seem to play a crucial role in the initiation of hypertension via regulation of adaptive immunity.

Summary Innate and innate-like immunity play a leading role in the pathophysiology of hypertension. Recent advances in this field provide us clues for future therapeutic approaches.

Keywords Blood pressure · Inflammation · γδ T cells · Natural killer cells · Dendritic cells · Macrophages · Antigen-presenting cells · Cytokines

Abbreviations

B7	Co-stimulatory molecule on antigen-presenting cell surface (CD80 or CD86)
CD28	Cluster of differentiation 28
CNS	Central nervous system
MHC II	Major histocompatibility complex II
TCR	T cell receptor

Introduction

The relationship between high blood pressure (BP) and the immune response has been studied for almost 50 years. Inflammation is the final consequence of the immune response, and accumulating evidence suggests the involvement of both innate and adaptive immunity in the pathophysiology of hypertension and end-organ damage associated with hypertension [1]. The innate and the adaptive immune systems are designed to work cooperatively to combat exogenous invasions of bacteria, viruses, and parasites. However, they can also result in detrimental effects like chronic inflammatory and autoimmune diseases. Infiltration of innate (monocytes/macrophages) and adaptive immune cells (T lymphocytes) in the perivascular adipose tissue, kidneys, and myocardium increased expression of adhesion molecules and chemokines, cytokine production and release, and reactive oxygen species (ROS) generation are consistent features found in tissues of hypertensive animals. Gain- and loss-of-function experiments have shown that innate immune cells such as monocytes/macrophages on the one hand, and adaptive immune cells like B and T lymphocytes on the other, are implicated in hypertension and cardiovascular injury, in a *ying/yang* relationship with anti-inflammatory cells that include anti-inflammatory M2 macrophages, myeloid-derived suppressor cells (MDSC), and T regulatory lymphocytes (Treg).

Recently, the roles of a T cell subset, the γδ T cells, which cannot be included within the conventional adaptive

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classification, have been shown to have an important role in hypertension. These are so-called innate-like immune cells that respond rapidly to pathogens without requiring antigen presentation [2••]. Innate and innate-like immunity are regarded as the first line of defense against pathogens. The present review aims to summarize recent advances in the knowledge of immunity in hypertension pathophysiology, focusing on innate and innate-like immunity.

Role of the Innate Immune System

The innate immune system consists of humoral and cellular components. One of the major humoral components of innate immunity is the complement (C) system [3]. There are three ways in which the complement system is activated to protect against infection. In the classical pathway, the sequential activation of enzymes begins with the formation of the C-1 complex that consists of immunoglobulin, antigen, and C1q. On the other hand, the mannan-binding lectin pathway is initiated by binding of the serum protein mannan-binding lectin to the mannose-containing carbohydrates on bacteria and viruses, whereas the alternative pathway is activated by binding of spontaneously activated complement components to the surface of pathogens. The activation of the three pathways leads to the hydrolysis of C3. C3a and C5a are peptide mediators of inflammation generated in these cascades that will attract macrophages and promote phagocyte ingestion of complement-tagged pathogens via complement receptors expressed on these innate cells. It is noteworthy that complement receptors are also expressed in many other leukocytes, including B cells and Treg [3]. The complement system also plays a critical role among humoral mediators as a contributor to the antibody response, a participant in the lysis of membranes of pathogens, and a stimulator of the production of chemotactic proteins [4].

Neutrophils, monocytes/macrophages, and dendritic cells (DCs) are the main cellular elements that mediate innate immunity. They make use of pattern recognition receptors such as Toll-like receptors (TLRs) to sense pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), or other antigens from injured tissues. Each effector cell participates in the immune response in different ways. Phagocytes such as macrophages and DCs perform phagocytosis and can become antigen-presenting cells (APCs). They can also release pro-inflammatory cytokines to activate other cells including lymphocytes. Neutrophils are not professional APCs as DCs and macrophages, but act as front-line host defenders against infectious diseases. They are rapidly recruited to the site of injury and eliminate microbes via phagocytosis, degranulation, and/or through release of their own nuclear material, forming NETs (neutrophil extracellular traps) to confine pathogens within these. This mechanism of neutrophil death is called NETosis [5].

Macrophages possess functional and phenotypic differentiation plasticity, polarizing into pro-inflammatory M1 or anti-inflammatory M2 subtypes. M1 macrophages are induced by interferon-γ (IFNγ), tumor necrosis factor-α (TNF-α), or bacterial components like lipopolysaccharide (LPS) or peptidoglycan stimulation, leading to an inflammatory response. On the other hand, M2 macrophages are mainly induced by interleukin (IL)-4 or IL-13 and exhibit an anti-inflammatory and reparative phenotype.

Role of the Innate Immune System in Hypertension

The Complement System in Hypertension

There is some evidence suggesting that the complement system plays a role in the initiation and/or maintenance of hypertension [4]. It has been shown that serum C3 levels are elevated in a pre-hypertensive population [6] and in hypertensive patients [6–8]. As well, renal interstitial C3 expression was associated with interstitial macrophage infiltration in the kidney in patients with hypertensive nephropathy [9]. C3a and C5a serum levels were increased in mice after the first day of angiotensin (Ang) II infusion [10]. More recently, Chen et al. reported that Ang II infusion raised the expression of C3a and C5a receptors in Treg and that C3a and C5a receptor double knockout reduced Ang II-induced BP elevation and prevented aortic and renal injury. The latter could be abolished by depletion of Treg with CD25 antibodies [11•]. These authors also demonstrated that adoptive transfer of Treg from C3a and C5a receptor double knockout was more effective in protecting against Ang II-induced hypertension than adoptive transfer of Treg from wild-type mice. Furthermore, Cui et al. [9] and Chen et al. [11•] showed that C3a receptor expression was increased in Treg of hypertensive patients.

Neutrophils in Hypertension

As mentioned above, neutrophils represent an essential part of the innate immune system, and the neutrophil-to-lymphocyte ratio (NLR) has been used as a systemic inflammatory marker in many clinical studies. NLR could serve as a predictor of hypertension in large scale epidemiological studies [12]. Recently, it was reported that elevated blood neutrophil activity (superoxide anion generation and myeloperoxidase activity) was significantly associated with high BP in the spontaneously hypertensive rat [13]. These findings do not necessarily mean that neutrophils are the primary cause of hypertension, but could imply that they have a role to play in the low-grade inflammation observed in hypertensive patients. Neutrophils can also possibly act on the adaptive immune system, as they are capable of regulating adaptive immunity in various ways

such as through cytokine secretion, antigen presentation, and direct cell contact [14].

Monocytes/Macrophages in Hypertension

Monocytes and macrophages belong to the myeloid lineage but have different functions than neutrophils. The role of monocyte/macrophages was initially demonstrated using osteopetrotic (op/op) mice that are deficient in monocyte/macrophage function due to a mutation in the colony-stimulating factor 1 (*Csf1*) gene. *Csf1*$^{Op/Op}$ mice were resistant to Ang II-induced and deoxycorticosterone acetate plus salt-induced BP elevation and vascular injury [15, 16]. This finding was extended by Wenzel et al. using selective ablation of lysozyme M-positive (LysM$^+$) myelomonocytic cells by low-dose diphtheria toxin (DT) in mice with inducible expression of the DT receptor [17]. Ang II-induced BP elevation and vascular injury were blunted in mice deficient in LysM$^+$ myelomonocytic cells, which was reversed by adoptive transfer of monocytes but not neutrophils. It has been reported that C–C motif chemokine receptor type 2 (CCR2)$^+$ monocytes can infiltrate the surrounding vessels and participate in hypertensive vascular and renal injury but not in BP elevation [18–20]. On the other hand, some evidence suggests that cardiac and arterial resident macrophages, which express MerTK (myeloid-epithelial-reproductive tyrosine kinase) and that are also CCR2$^-$, play a protective role by removing apoptotic cells (efferocytosis) in myocardial infarction and atherosclerosis [21, 22]. However, the role of vascular resident macrophages is unknown in hypertension. It has been pointed out in a review of Harwani S.C. [23] that both pro-inflammatory M1 or anti-inflammatory M2 macrophages play a role in hypertension and the M1-to-M2 ratio is closely associated with development and maintenance of hypertension.

The central nervous system (CNS) plays a pivotal role in BP elevation via sympathetic or parasympathetic outflow [24] and is associated with activation of the immune system [1]. Renal denervation (RDN) reduced Ang II-induced BP elevation and peri-aortic and myocardial macrophage infiltration in Ang II-induced hypertension in mice [25, 26]. Similarly, RDN reduced monocyte activation in patients with resistant hypertension [27]. These findings support the hypothesis that neural regulation plays a role in activation of the immune system in hypertension. Nevertheless, it is unclear whether in the course of RDN the adjacent renal lymph nodes were also denervated. The denervation of lymph nodes or spleen echoes studies by Carnevale et al. on the role of the CNS through direct activation of the immune system in hypertension via the spleen. These authors observed than a cholinergic-sympathetic pathway primes immunity and favors T cell activation and egression from the spleen in Ang II-infused mice [28•]. A similar observation was also reported by Harwani et al. showing that nicotinic cholinergic activation mediated CD161a$^+$ renal macrophage infiltration and induced premature hypertension in spontaneously hypertensive rats [29].

Regarding immune cells in the brain, it has been reported that intracerebroventricular (ICV) or subcutaneous Ang II infusion induces the activation of microglia, which are brain resident macrophages, in the paraventricular nucleus (PVN) of the hypothalamus. This effect of Ang II was attenuated by ICV infusion of minocycline, an anti-inflammatory antibiotic, or with mitoTEMPO, a scavenger of mitochondrial superoxide [30, 31]. As well, Shen et al. [32] reported that targeted depletion of microglia using the diphteria toxin technique to ablate brain CD11b-positive cells significantly attenuated inflammation in the brain, plasma vasopressin and kidney norepinephrine concentration, and BP. Furthermore, adoptive transfer of Ang II- or LPS-primed microglia prolonged acute pressor responses to central application of Ang II, suggesting the key role of these cells in neurogenic hypertension.

High-salt intake is associated with higher BP and increased risk of cardiovascular disease. Although a large number of basic and clinical studies have confirmed that excess salt intake can elevate BP, the detailed mechanism of salt sensitivity in hypertension is not well understood. Salt intake has influence not only on hemodynamics but also on immune responses. Machnik A. et al. reported that macrophages play a role in the regulation of dermal interstitial sodium concentrations. Tonicity-enhancer binding protein (TonEBP, also called NFAT5) is a transcription factor that regulates vascular endothelial growth factor (VEGF)-C expression. The activation of TonEBP due to high-salt diet promoted VEGF-C secretion from macrophages, which induces dermal lymphangiogenesis as a buffering system for hypertension [33]. Interestingly, TonEBP is also known as an activator of M1 macrophages and suppresses the M2 phenotype via downregulation of IL-10 production [34]. As well, a high-salt diet suppressed M2 macrophages via reduction of glycolysis and mitochondrial metabolic output. The adaptive immune system is also affected by high-salt intake via effects on the gut microbiome [35] that induce T helper 17 cells (TH17) and reduce Treg numbers [36].

BP-induced endothelial cell mechanical stress could play a role in immune cell activation in hypertension. Using co-culture of human cells, it was shown that endothelial cells undergoing cyclical stretch increased the conversion of monocytes into CD14^{++}CD16$^+$ intermediate monocytes and CD14^{++}CD209$^+$ monocytes that are pro-inflammatory [37]. The activation and differentiation of monocytes is associated with activated signal transducer and activator of transcription 3 (STAT3) activation, increased IL-6 production, and impaired nitric oxide (NO) signaling [37].

Chemokines play an important role in attracting immune cells to injury sites [38]. Many chemokine ligands

(L) and chemokine receptors (R) have been identified and are divided into 4 subgroups based on the spacing of conserved cysteine residues: CC, CXC, C, and CX3C. Recently, Wang et al. demonstrated an important role for the CXCL1/CXCR2 axis in hypertension and vascular injury in Ang II-infused mice [39]. *Cxcl1* was the most highly expressed chemokine in aorta among 13 studied after 1 day of Ang II infusion. Furthermore, increased infiltration of leukocytes expressing the CXCL1 receptor CXCR2 was observed in the aorta of Ang II-infused mice. Ang II-induced BP elevation, aortic injury, and macrophage and T cell infiltration were blunted by genetic ablation or pharmacologic inhibition of CXCR2. The role of CXCR2 expressed on immune cells in hypertension and vascular injury was demonstrated by bone marrow transplantation experiments. Wang et al. extended the role of CXCL1/CXCR2 axis to hypertension and cardiac hypertrophy and remodeling using the same experimental design [40]. CXCR2 may be an interesting therapeutic target since these authors observed that numbers of monocytes and neutrophils expressing CXCR2 were increased in the blood of hypertensive patients compared to normotensive subjects.

Dendritic Cells in Hypertension

DCs are characterized by their highly specialized capability of antigen presentation. There is evidence that DCs participate in hypertension via their role in T cell activation. Barbaro et al. [41••] have described the mechanism whereby DCs activate T cells under the influence of excess salt intake. Extracellular sodium enters DCs through amiloride-sensitive channels leading to subsequent calcium influx via the sodium calcium exchanger. Calcium overload in DCs activates NADPH oxidase that produces superoxide. Reactive oxygen species (ROS) induces the formation of isolevuglandins (IsoLG), which form highly immunogenic protein adducts that are processed and presented to T cells as neoantigens. DCs with accumulated IsoLGs produce large amounts of cytokines such as IL-6 and IL-1β that promote T cells to produce pressor cytokines such as IL-17A. These are important findings that explain possible links between excessive salt intake, inflammation, and high BP.

More recently, Hevia et al. reported a role of DCs in hypertension with regard to renal function [42]. These authors showed that genetic ablation of $CD11c^{high}$ APCs, that were referred to as DCs, prevented the effect of Ang II plus high-salt treatment to induce the intrarenal renin-angiotensin system (RAS) and enhance renal sodium reabsorption and trigger BP elevation [42]. Although the mechanism of intrarenal RAS upregulation was not assessed in detail, a multifactorial role of DCs in hypertension is suggested by this study.

Myeloid-Derived Suppressor Cells (MDSC) in Hypertension

MDSCs are anti-inflammatory immune cells characterized by expression of CD11b and Gr-1 [14, 43]. Anti-Gr-1 antibodies bind to two different epitopes, Ly6G and Ly6C. This particularity has permitted the identification of two subsets of MDSCs, granulocytic (G-MDSCs, $CD11b^{+}Ly6G^{+}Ly6C^{low}$) and monocytic (Mo-MDSCs, $CD11b^{+}Ly6G^{-}Ly6C^{hi}$). G-MDSCs resemble neutrophils and may represent a neutrophil subset with immunosuppressive capacity [14]. These innate cells have a regulatory action in hypertension. MDSCs are considered as a self-restraint immune system to prevent excessive inflammatory injury. They mainly suppress T cell activation by producing hydrogen peroxide. MDSCs can counteract the development of hypertension [44]. MDSCs from hypertensive mice demonstrated increased capacity to suppress T cells in vitro and $CD8^{+}$ T cells in vivo. Gemcitabine- or an anti-Gr-1 antibody-induced MDSC depletion exaggerated Ang II-induced BP elevation and preferentially increased $CD8^{+}$ T cells expressing IL-17A or both IL-17A and IFNγ. Adoptive transfer of MDSCs from hypertensive but not normotensive mice reduced or reversed Ang II-induced BP elevation. Interestingly, an increase of $CD11b^{+}Gr\text{-}1^{+}$ cells was found in the blood, spleen, and kidneys of Ang II-infused mice.

Innate Lymphoid and Unconventional T Cells

The distinctive features of innate immunity refer commonly to the capacity of myeloid and lymphoid cells to exert rapid effector function without previous education. In contrast, T and B lymphocytes which could be considered as leaders of the immune response, orientating pro- or anti-inflammatory processes [3], belong to the adaptive immune system, and are characterized by a large repertoire of antigen receptors, the T cell receptor (TCR), and antibody/B cell receptor (BCR), as a result of site-specific somatic recombination by recombination activation gene (Rag) − 1 and − 2 genes. Basically, TCR heterodimer rearrangement generates two different subsets of T cells. One is the αβ T cells bearing α and β subunits of TCR that comprise the majority of T cells, which are accordingly considered conventional T lymphocytes. A very small proportion of circulating T cells comprises the unconventional T lymphocytes that are not major histocompatibility class (MHC)-restricted and includes those bearing a TCR composed of γ and δ subunits, the $\gamma\delta$ T lymphocytes. Innate lymphoid cells (ILCs), which include natural killer (NK) cells, have the same profile of cytokine production as adaptive immunity conventional lymphocytes, but not the same pathway of activation because they do not need to be educated by APCs.

ILCs in Hypertension

ILCs have been shown to play a role in the initiation, regulation, and resolution of inflammation [45]. ILCs are innate lymphocytes lacking rearranged antigen receptors because they do not express *Rag* genes. ILCs can be grouped according to surface markers, transcription factors, and effector cytokines into 3 groups (ILC1, 2, and 3) following, in part, the T helper (Th) nomenclature. As is the case for Th cells, ILC cytokine secretion is induced by the same stimulators, e.g., after exposure to IL-12 or IL-18 for IFNγ production. IFNγ producers belong to ILC1. IL-4-, IL-5-, IL-9-, and IL-13-positive cells belong to the ILC2 group, and ILC3 secretes IL-17A and/or IL-22. NK cells belong to the ILC1 group and are the only ILCs for which a role has been described in hypertension. One of the first evidences of a possible role of NK cells in hypertension was the in vitro induction of proliferation and migration of NK cells after Ang II exposure [46]. Kossmann and co-authors observed a role of NK cells in vascular injury in hypertension [47]. Ang II caused NK cell recruitment to the aortic wall, which was blunted in mice lacking T-Box 21 (*Tbx21*) or *IFNγ*. NK cell depletion using anti-NK1.1 antibody reduced aortic endothelium-dependent and independent dysfunction induced by Ang II infusion. However, BP was unaffected in mice lacking *Tbx21*, which is highly expressed in NK cells and controls the expression of IFNγ.

Unconventional T Cells in Hypertension

Unconventional T cells include $\alpha\beta$ T lymphocytes such as CD1-restricted T cells, MHC-I-related (MR1)-restricted mucosal-associated invariant T (MAIT) cells and MHC class Ib-reactive T cells and NK T cells, and $\gamma\delta$ T cells [48, 49]. These cells have a tendency to reside in non-lymphoid tissues and have, compared to MHC-restricted T cells, a faster response after activation, including proliferation or cytokine release, and a faster response after a recall stimulation with an antigen. Unconventional T cells recognize non-polymorphic antigen-presenting molecules, some of which are encoded by genes outside of the MHC locus (CD1a, CD1b, CD1c, CD1d in humans, and CD1d only in mice, and MR1) or within the MHC locus (MHC-I-E, homeostatic iron regulator [HFE], H2-M3, and H2-Q). NK T cells are activated by lipid antigens presented by CD1d. They can be divided into two subsets based on differences in their TCR characteristics. Type I NK T cells (also known as invariant NK T cells) express an invariant TCRα chain and type II NK T cells express diverse TCRs [49]. Kirabo et al. [50] have shown that NK T cells do not seem to play a role in hypertension. They observed that *Jα18* null mice lacking the TCR Jα18 invariant chain that are deficient in type I NK T cells, and CD1d knockout mice, which are devoid of both type I and II NK T cells, present similar BP elevation in response to Ang II compared to wild-type mice. These results also indicated that CD1d does not play a role in hypertension. No role has been established so far for the other unconventional $\alpha\beta$ TCR T cells in hypertension.

In the circulation, $\gamma\delta$ T cells represent ~ 0.5–10% of lymphocytes in humans and mice. They are activated by non-protein phosphoantigens, isoprenoid pyrophosphates, alkylamines, non-classical MHC class I molecules, MHC class I chain-related proteins A and B, as well as heat shock protein-derived peptides, without antigen processing and MHC presentation. $\gamma\delta$ T cells are sequestered in many peripheral tissues, with specific homing and retention [48, 51–54]. $\gamma\delta$ T cells are unique because, in addition to effector functions shared with $\alpha\beta$ T cells, they are "innate-like" T lymphocytes with functions that span across the biology of innate and adaptive immune cells. $\gamma\delta$ T cells can produce IL-17A in response to the pro-inflammatory cytokines IL-1β and IL-23 and express CCR6 like T helper 17 cells. $\gamma\delta$ T cells may produce IFNγ, in which case they typically express CD27. Recently, we demonstrated that $\gamma\delta$ T cells play a critical role in hypertension and vascular injury [2••]. Ang II caused an increase in number and activation of $\gamma\delta$ T cells after 7 days of Ang II infusion. Deficiency in $\gamma\delta$ T cells due to *Tcrδ* knockout or injection of $\gamma\delta$ T cell-depleting antibodies, prevented Ang II-induced BP elevation, small artery endothelial dysfunction, and spleen and mesenteric artery perivascular adipose tissue $CD4^+$ and $CD8^+$ T cell activation. This suggests that $\gamma\delta$ T cells participate in the initiation of inflammatory responses involved in the development of hypertension. Moreover, using multiple linear regression, we found a correlation between whole blood expression of the TCR gamma chain constant regions 1 and 2 that were used as an estimate of the frequency of blood $\gamma\delta$ T cells, and systolic BP in a human cohort with and without coronary artery disease and a full range of BPs, from low to high. $\gamma\delta$ T cells are a major source of IL-17A in the aorta, kidneys, and the heart of Ang II-infused mice [55, 56]. Li et al. demonstrated that depletion of $\gamma\delta$ T cells using anti-$\gamma\delta$ TCR antibodies did not affect 7-day Ang II infusion-induced BP elevation but markedly reduced ventricular fibrosis induced by 7-day and 4-week Ang II infusion [56]. The lack of effect on BP elevation could be due to the high dose of Ang II (1500 ng/kg/min) used in this study. Thus, $\gamma\delta$ T cells could play a key pathophysiological role in hypertension and end-organ damage.

Conclusion

Innate and innate-like immune cells play an important role in hypertension. Depleting some of them blunts the inflammatory process, vascular injury, and BP elevation in hypertensive

mouse models. Inflammatory processes may be visualized in terms of an inflammatory vicious cycle (Fig. 1). Genetic predisposition, a high-salt diet, or hypertensive stimuli such as Ang II, aldosterone, and endothelin-1 may increase BP acting directly on the vasculature and the kidneys or by increasing the sympathetic nervous activity and decreasing parasympathetic nervous activity. Over time, high BP and/or hypertensive stimuli induce vascular injury that causes production of DAMPs, which will activate via the TLRs the innate and innate-like immune cells. In addition, vascular injury, together with increased ROS generation induced by vasoactive peptides such as Ang II, induces protein oxidation and favors the production

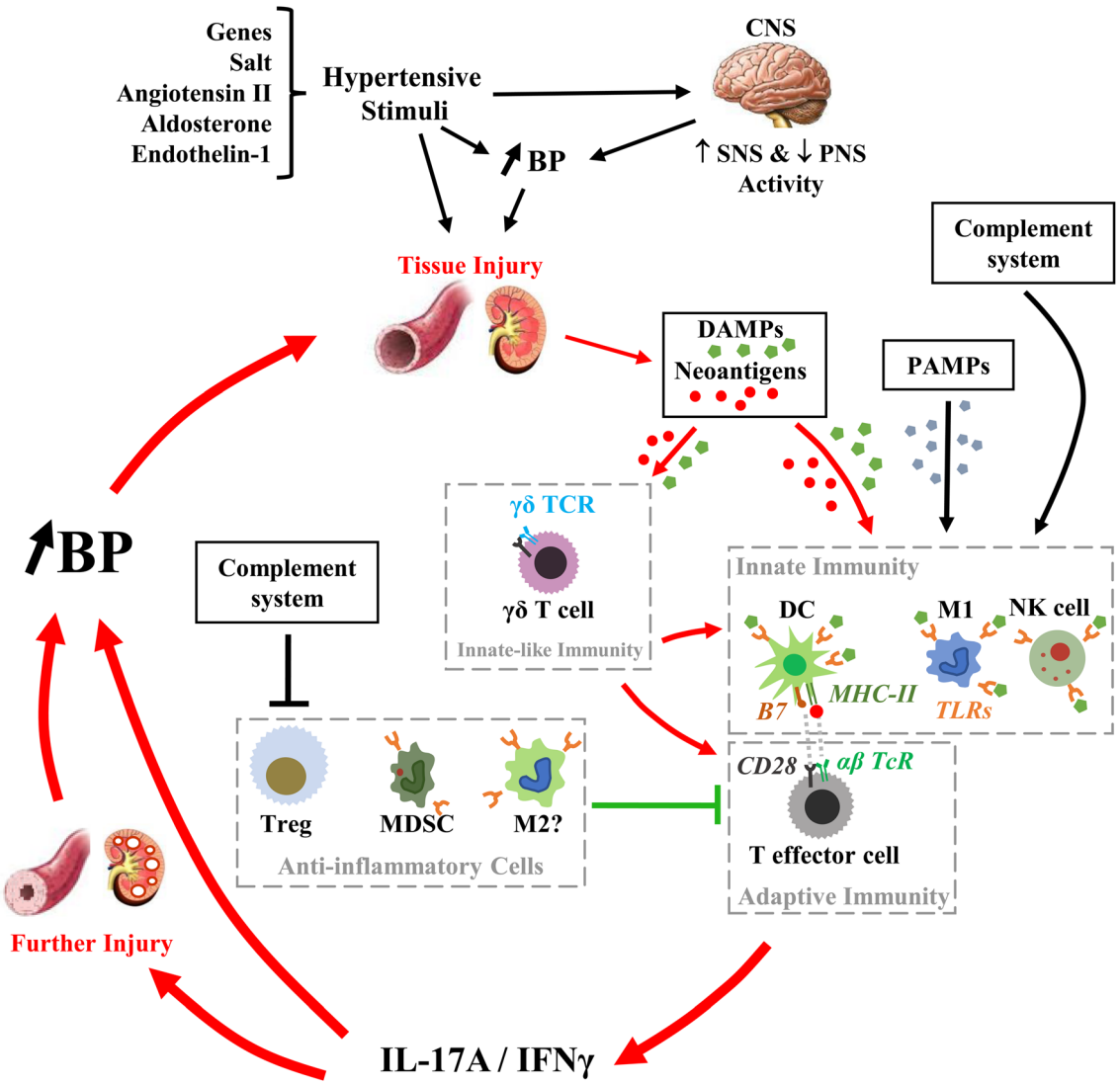

Fig. 1 Role of innate and innate-like immune cells in inflammation in hypertension. Different stimuli such as a high-salt diet, in the presence of genetic susceptibility, may lead to small rises of blood pressure (BP) in part by triggering the activation of the sympathetic nervous system (SNS) and inhibition of the parasympathetic nervous system (PNS) alone or together with other pro-hypertensive factors such as endothelin-1, angiotensin II, and aldosterone. Over time, high BP and/or the pro-hypertensive stimuli induce tissue injury, which together with an increase in oxidative stress caused by vasoactive peptides as well as a release of chemokines and an activated complement system, create favorable conditions for the development of damage-associated molecular patterns (DAMPs) and neoantigens, such as isoketal protein adducts. DAMPs activate innate immunity via Toll-like receptors (TLRs) on type 1 macrophages (M1), type 1 dendritic cells (DC), whereas neoantigens enhance DC immunogenicity and promote DC release of IL-6, IL-1β, and IL-23, causing proliferation of T effector cells and production of IL-17A and IFNγ. DAMPS and neoantigens could also activate unconventional lymphocytes such as innate-like $\gamma\delta$ T cells, which will activate T effector lymphocytes bearing $\alpha\beta$ TCR subunits. Innate lymphoid cells and innate-like immune cell such as natural killer (NK) cells and $\gamma\delta$ T cells contribute to inflammation, both directly or via the activation of adaptive immunity, inducing pro-inflammatory cytokines like IL-17A, and IFNγ, leading to vascular and kidney injury, which closes the pro-hypertensive circle that is a feed-forward process resulting in progressive BP elevation. Throughout this process, anti-inflammatory cells such as T regulatory cells (Treg), myeloid-derived suppressor cells (MDSCs), and type 2 macrophages (M2) could provide homeostatic fine-tuning of the inflammatory process in blood vessels and the kidney

of neoantigens, such as those resulting from isoketal-induced protein modification, which enhances DC immunogenicity and promotes DC release of IL-6, IL-1β, and IL-23, causing proliferation of T cells and production of IL-17A and IFNγ. The first part of the loop could correspond to the production of pro-inflammatory cytokines by APCs. This step would appear to be critical in the development of hypertension. In parallel, activation of DCs and γδ T cells, the latter stimulated by generic "public" antigens, could directly activate the immune system bypassing canonical immune pathways. Activation of the innate immune system could also be exacerbated by opportunistic diseases such as periodontitis or other chronic inflammatory diseases such as rheumatoid arthritis, psoriasis, and Crohn's disease, through PAMPs binding to TLRs and also by activation of the complement system via complement receptors. Once T effector cells are activated, the inflammatory cascade has been triggered and the immune-mediated vascular and renal injury closes the pro-hypertensive circle that is a feed-forward process, resulting in progressive BP elevation. Some anti-inflammatory immune cells could temper the inflammatory process in blood vessels and the kidney. However, this anti-inflammatory mechanism could be rendered unable to counteract the development of hypertension by factors such as Ang II that can cause a decrease in number and function of Treg and by activation of the complement system that decreases the Treg function. The identification of subsets of different immune cell types, and their differential effects and mediators, could allow the development of immune-based therapies with minimal adverse side effects, that can contribute to the healing of vascular injury in hypertension and cardiovascular disease, leading to improved patient outcomes.

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Compliance with Ethical Standards

Conflict of Interest Dr. Schiffrin reports grants from Canadian Institutes of Health Research and Servier France, personal fees from Novartis USA, and Servier Canada, outside the submitted work. The other authors declare no conflicts of interest relevant to this manuscript.

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References

Papers of particular interest, published recently, have been highlighted as:
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1. Norlander AE, Madhur MS, Harrison DG. The immunology of hypertension. J Exp Med. 2018;215(1):21–33. https://doi.org/10.1084/jem.20171773.
2.•• Caillon A, Mian MOR, Fraulob-Aquino JC, Huo KG, Barhoumi T, Ouerd S, et al. Gammadelta T cells mediate angiotensin II-induced hypertension and vascular injury. Circulation. 2017;135(22):2155–62. https://doi.org/10.1161/CIRCULATIONAHA.116.027058 **This study is the first to point out the role of γδ T cells during hypertension. In this study, a crucial role of γδ T cells on the vascular injury associated with hypertension was observed. Other T cells were not activated in absence of γδ T cells, suggesting that γδ T cells play a role in triggering inflammation in the initiation of hypertension.**
3. Janeway CAJ, Travers P, Walport M, Shlomchik MJ. Immunobiology. 5th ed. New York and London: Garland Science; 2001.
4. Dunkelberger JR, Song WC. Complement and its role in innate and adaptive immune responses. Cell Res. 2010;20(1):34–50. https://doi.org/10.1038/cr.2009.139.
5. Papayannopoulos V. Neutrophil extracellular traps in immunity and disease. Nat Rev Immunol. 2018;18(2):134–47. https://doi.org/10.1038/nri.2017.105.
6. Bao X, Meng G, Zhang Q, Liu L, Wu H, Du H, et al. Elevated serum complement C3 levels are associated with prehypertension in an adult population. Clin Exp Hypertens. 2017;39(1):42–9. https://doi.org/10.1080/10641963.2016.1210622.
7. Engstrom G, Hedblad B, Berglund G, Janzon L, Lindgarde F. Plasma levels of complement C3 is associated with development of hypertension: a longitudinal cohort study. J Hum Hypertens. 2007;21(4):276–82. https://doi.org/10.1038/sj.jhh.1002129.
8. Martin-Lorenzo M, Gonzalez-Calero L, Martinez PJ, Baldan-Martin M, Lopez JA, Ruiz-Hurtado G, et al. Immune system deregulation in hypertensive patients chronically RAS suppressed developing albuminuria. Sci Rep. 2017;7(1):8894. https://doi.org/10.1038/s41598-017-09042-2.
9. Cui J, Wan J, You D, Zou Z, Chen Y, Li Z, et al. Interstitial complement C3 activation and macrophage infiltration in patients with hypertensive nephropathy. Clin Nephrol. 2017;88(12):328–37. https://doi.org/10.5414/CN109154.
10. Zhang C, Li Y, Wang C, Wu Y, Cui W, Miwa T, et al. Complement 5a receptor mediates angiotensin II-induced cardiac inflammation and remodeling. Arterioscler Thromb Vasc Biol. 2014;34(6):1240–8. https://doi.org/10.1161/ATVBAHA.113.303120.
11.• Chen XH, Ruan CC, Ge Q, Ma Y, Xu JZ, Zhang ZB, et al. Deficiency of complement C3a and C5a receptors orevents angiotensin II-induced hypertension via regulatory T cells. Circ Res. 2018;122(7):970–83. https://doi.org/10.1161/CIRCRESAHA.117.312153 **This study suggests an interesting role of complement components in hypertension leading to inhibition of anti-inflammatory cell such as Tregs. This paper was the first to describe the effect of complement depletion on Tregs in the pathophysiology of hypertension. The authors reported that the depletion of both C3aR (complement c3a receptor) and C5aR stimulated Foxp3 expression in vitro and in vivo and prevented the BP elevation induced by Ang II. Their study is noteworthy because it may show an alternative novel approach for hypertension treatment.**

12. Liu X, Zhang Q, Wu H, Du H, Liu L, Shi H, et al. Blood neutrophil to lymphocyte ratio as a predictor of hypertension. Am J Hypertens. 2015;28(11):1339–46. https://doi.org/10.1093/ajh/hpv034.
13. Zhang R, Inagawa H, Kazumura K, Tsuchiya H, Miwa T, Morishita N, et al. Evaluation of a hypertensive rat model using peripheral blood neutrophil activity, phagocytic activity and oxidized LDL evaluation. Anticancer Res. 2018;38(7):4289–94. https://doi.org/10.21873/anticanres.12726.
14. Rosales C. Neutrophil: a cell with many roles in inflammation or several cell types? Front Physiol. 2018;9:113. https://doi.org/10.3389/fphys.2018.00113.
15. De Ciuceis C, Amiri F, Brassard P, Endemann DH, Touyz RM, Schiffrin EL. Reduced vascular remodeling, endothelial dysfunction, and oxidative stress in resistance arteries of angiotensin II-infused macrophage colony-stimulating factor-deficient mice: evidence for a role in inflammation in angiotensin-induced vascular injury. Arterioscler Thromb Vasc Biol. 2005;25(10):2106–13. https://doi.org/10.1161/01.ATV.0000181743.28028.57.
16. Ko EA, Amiri F, Pandey NR, Javeshghani D, Leibovitz E, Touyz RM, et al. Resistance artery remodeling in deoxycorticosterone acetate-salt hypertension is dependent on vascular inflammation: evidence from m-CSF-deficient mice. Am J Physiol Heart Circ Physiol. 2007;292(4):H1789–95. https://doi.org/10.1152/ajpheart.01118.2006.
17. Wenzel P, Knorr M, Kossmann S, Stratmann J, Hausding M, Schuhmacher S, et al. Lysozyme M-positive monocytes mediate angiotensin II-induced arterial hypertension and vascular dysfunction. Circulation. 2011;124(12):1370–81. https://doi.org/10.1161/CIRCULATIONAHA.111.034470.
18. Ishibashi M, Hiasa K, Zhao Q, Inoue S, Ohtani K, Kitamoto S, et al. Critical role of monocyte chemoattractant protein-1 receptor CCR2 on monocytes in hypertension-induced vascular inflammation and remodeling. Circ Res. 2004;94(9):1203–10. https://doi.org/10.1161/01.RES.0000126924.23467.A3.
19. Bush E, Maeda N, Kuziel WA, Dawson TC, Wilcox JN, DeLeon H, et al. CC chemokine receptor 2 is required for macrophage infiltration and vascular hypertrophy in angiotensin II-induced hypertension. Hypertension. 2000;36(3):360–3.
20. Liao TD, Yang XP, Liu YH, Shesely EG, Cavasin MA, Kuziel WA, et al. Role of inflammation in the development of renal damage and dysfunction in angiotensin II-induced hypertension. Hypertension. 2008;52(2):256–63. https://doi.org/10.1161/HYPERTENSIONAHA.108.112706.
21. Cai B, Thorp EB, Doran AC, Sansbury BE, Daemen MJ, Dorweiler B, et al. MerTK receptor cleavage promotes plaque necrosis and defective resolution in atherosclerosis. J Clin Invest. 2017;127(2):564–8. https://doi.org/10.1172/JCI90520.
22. DeBerge M, Yeap XY, Dehn S, Zhang S, Grigoryeva L, Misener S, et al. MerTK cleavage on resident cardiac macrophages compromises repair after myocardial ischemia reperfusion injury. Circ Res. 2017;121(8):930–40. https://doi.org/10.1161/CIRCRESAHA.117.311327.
23. Harwani SC. Macrophages under pressure: the role of macrophage polarization in hypertension. Transl Res. 2018;191:45–63. https://doi.org/10.1016/j.trsl.2017.10.011.
24. Kishi T. Regulation of the sympathetic nervous system by nitric oxide and oxidative stress in the rostral ventrolateral medulla: 2012 Academic Conference Award from the Japanese Society of Hypertension. Hypertens Res. 2013;36(10):845–51. https://doi.org/10.1038/hr.2013.73.
25. Hong MN, Li XD, Chen DR, Ruan CC, Xu JZ, Chen J, et al. Renal denervation attenuates aldosterone expression and associated cardiovascular pathophysiology in angiotensin II-induced hypertension. Oncotarget. 2016;7(42):67828–40. https://doi.org/10.18632/oncotarget.12182.
26. Xiao L, Kirabo A, Wu J, Saleh MA, Zhu L, Wang F, et al. Renal denervation prevents immune cell activation and renal inflammation in angiotensin II-induced hypertension. Circ Res. 2015;117(6):547–57. https://doi.org/10.1161/CIRCRESAHA.115.306010.
27. Zaldivia MT, Rivera J, Hering D, Marusic P, Sata Y, Lim B, et al. Renal denervation reduces monocyte activation and monocyte-platelet aggregate formation: an anti-inflammatory effect relevant for cardiovascular risk. Hypertension. 2017;69(2):323–31. https://doi.org/10.1161/HYPERTENSIONAHA.116.08373.
28.• Carnevale D, Perrotta M, Pallante F, Fardella V, Iacobucci R, Fardella S, et al. A cholinergic-sympathetic pathway primes immunity in hypertension and mediates brain-to-spleen communication. Nat Commun. 2016;7:13035. https://doi.org/10.1038/ncomms13035 **This study is one of the first describing how the CNS affects egression of immune cells from lymphatic organs. This observation suggests an interesting role of the sympathetic system in the inflammatory process in hypertension.**
29. Harwani SC, Ratcliff J, Sutterwala FS, Ballas ZK, Meyerholz DK, Chapleau MW, et al. Nicotine mediates CD161a+ renal macrophage infiltration and premature hypertension in the spontaneously hypertensive rat. Circ Res. 2016;119(10):1101–15. https://doi.org/10.1161/CIRCRESAHA.116.309402.
30. Jun JY, Zubcevic J, Qi Y, Afzal A, Carvajal JM, Thinschmidt JS, et al. Brain-mediated dysregulation of the bone marrow activity in angiotensin II-induced hypertension. Hypertension. 2012;60(5):1316–23. https://doi.org/10.1161/HYPERTENSIONAHA.112.199547.
31. Shi P, Diez-Freire C, Jun JY, Qi Y, Katovich MJ, Li Q, et al. Brain microglial cytokines in neurogenic hypertension. Hypertension. 2010;56(2):297–303. https://doi.org/10.1161/HYPERTENSIONAHA.110.150409.
32. Shen XZ, Li Y, Li L, Shah KH, Bernstein KE, Lyden P, et al. Microglia participate in neurogenic regulation of hypertension. Hypertension. 2015;66(2):309–16. https://doi.org/10.1161/HYPERTENSIONAHA.115.05333.
33. Machnik A, Neuhofer W, Jantsch J, Dahlmann A, Tammela T, Machura K, et al. Macrophages regulate salt-dependent volume and blood pressure by a vascular endothelial growth factor-C-dependent buffering mechanism. Nat Med. 2009;15(5):545–52. https://doi.org/10.1038/nm.1960.
34. Choi SY, Lee HH, Lee JH, Ye BJ, Yoo EJ, Kang HJ, et al. TonEBP suppresses IL-10-mediated immunomodulation. Sci Rep. 2016;6:25726. https://doi.org/10.1038/srep25726.
35. Wilck N, Matus MG, Kearney SM, Olesen SW, Forslund K, Bartolomaeus H, et al. Salt-responsive gut commensal modulates TH17 axis and disease. Nature. 2017;551(7682):585–9. https://doi.org/10.1038/nature24628.
36. Afsar B, Kuwabara M, Ortiz A, Yerlikaya A, Siriopol D, Covic A, et al. Salt intake and immunity. Hypertension. 2018;72(1):19–23. https://doi.org/10.1161/HYPERTENSIONAHA.118.11128.
37. Loperena R, Van Beusecum JP, Itani HA, Engel N, Laroumanie F, Xiao L, et al. Hypertension and increased endothelial mechanical stretch promote monocyte differentiation and activation: roles of STAT3, interleukin 6 and hydrogen peroxide. Cardiovasc Res. 2018;114(11):1547–63. https://doi.org/10.1093/cvr/cvy112.
38. Paradis P, Schiffrin EL. CXCL1-CXCR2 lead monocytes to the heart of the matter. Eur Heart J. 2018;39(20):1832–4. https://doi.org/10.1093/eurheartj/ehy114.
39. Wang L, Zhao XC, Cui W, Ma YQ, Ren HL, Zhou X, et al. Genetic and pharmacologic inhibition of the chemokine receptor CXCR2 prevents experimental hypertension and vascular dysfunction. Circulation. 2016;134(18):1353–68. https://doi.org/10.1161/CIRCULATIONAHA.115.020754.
40. Wang L, Zhang YL, Lin QY, Liu Y, Guan XM, Ma XL, et al. CXCL1-CXCR2 axis mediates angiotensin II-induced cardiac hypertrophy and remodelling through regulation of monocyte

infiltration. Eur Heart J. 2018;39(20):1818–31. https://doi.org/10.1093/eurheartj/ehy085.

41.•• Barbaro NR, Foss JD, Kryshtal DO, Tsyba N, Kumaresan S, Xiao L, et al. Dendritic cell amiloride-sensitive channels mediate sodium-induced inflammation and hypertension. Cell Rep. 2017;21(4):1009–20. https://doi.org/10.1016/j.celrep.2017.10.002 **This paper describes a mechanism of antigen presentation by dendritic cells (DC) to T cells in salt-induced hypertension in mice. The authors demonstrated the role of salt that stimulates an amiloride-sensitive channel expressed on the surface of DCs, leading to enhanced activity of NADPH, increased ROS and generation of immunogenic isolevuglandins that form adducts with proteins and could be mediators of the interplay between innate and adaptive immunity in the pathophysiology of salt-sensitive hypertension.**

42. Hevia D, Araos P, Prado C, Fuentes Luppichini E, Rojas M, Alzamora R, et al. Myeloid CD11c(+) antigen-presenting cells ablation prevents hypertension in response to angiotensin II plus high-salt diet. Hypertension. 2018;71(4):709–18. https://doi.org/10.1161/HYPERTENSIONAHA.117.10145.

43. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol. 2009;9(3):162–74. https://doi.org/10.1038/nri2506.

44. Shah KH, Shi P, Giani JF, Janjulia T, Bernstein EA, Li Y, et al. Myeloid suppressor cells accumulate and regulate blood pressure in hypertension. Circ Res. 2015;117(10):858–69. https://doi.org/10.1161/CIRCRESAHA.115.306539.

45. Juelke K, Romagnani C. Differentiation of human innate lymphoid cells (ILCs). Curr Opin Immunol. 2016;38:75–85. https://doi.org/10.1016/j.coi.2015.11.005.

46. Jurewicz M, McDermott DH, Sechler JM, Tinckam K, Takakura A, Carpenter CB, et al. Human T and natural killer cells possess a functional renin-angiotensin system: further mechanisms of angiotensin II-induced inflammation. J Am Soc Nephrol. 2007;18(4):1093–102. https://doi.org/10.1681/ASN.2006070707.

47. Kossmann S, Schwenk M, Hausding M, Karbach SH, Schmidgen MI, Brandt M, et al. Angiotensin II-induced vascular dysfunction depends on interferon-gamma-driven immune cell recruitment and mutual activation of monocytes and NK-cells. Arterioscler Thromb Vasc Biol. 2013;33(6):1313–9. https://doi.org/10.1161/ATVBAHA.113.301437.

48. Godfrey DI, Uldrich AP, McCluskey J, Rossjohn J, Moody DB. The burgeoning family of unconventional T cells. Nat Immunol. 2015;16(11):1114–23. https://doi.org/10.1038/ni.3298.

49. Singh AK, Tripathi P, Cardell SL. Type II NKT cells: an elusive population with immunoregulatory properties. Front Immunol. 2018;9:1969. https://doi.org/10.3389/fimmu.2018.01969.

50. Kirabo A, Fontana V, de Faria AP, Loperena R, Galindo CL, Wu J, et al. DC isoketal-modified proteins activate T cells and promote hypertension. J Clin Invest. 2014;124(10):4642–56. https://doi.org/10.1172/JCI74084.

51. Chien YH, Meyer C, Bonneville M. gammadelta T cells: first line of defense and beyond. Annu Rev Immunol. 2014;32:121–55. https://doi.org/10.1146/annurev-immunol-032713-120216.

52. Krebs CF, Lange S, Niemann G, Rosendahl A, Lehners A, Meyer-Schwesinger C, et al. Deficiency of the interleukin 17/23 axis accelerates renal injury in mice with deoxycorticosterone acetate+angiotensin II-induced hypertension. Hypertension. 2014;63(3):565–71. https://doi.org/10.1161/HYPERTENSIONAHA.113.02620.

53. Paul S, Shilpi LG. Role of gamma-delta (gammadelta) T cells in autoimmunity. J Leukoc Biol. 2015;97(2):259–71. https://doi.org/10.1189/jlb.3RU0914-443R.

54. Vantourout P, Hayday A. Six-of-the-best: unique contributions of gammadelta T cells to immunology. Nat Rev Immunol. 2013;13(2):88–100. https://doi.org/10.1038/nri3384.

55. Saleh MA, Norlander AE, Madhur MS. Inhibition of interleukin 17-A but not interleukin-17F signaling lowers blood pressure and reduces end-organ inflammation in angiotensin II-induced hypertension. JACC Basic Transl Sci. 2016;1(7):606–16. https://doi.org/10.1016/j.jacbts.2016.07.009.

56. Li Y, Wu Y, Zhang C, Li P, Cui W, Hao J, et al. gammadelta T cell-derived interleukin-17A via an interleukin-1beta-dependent mechanism mediates cardiac injury and fibrosis in hypertension. Hypertension. 2014;64(2):305–14. https://doi.org/10.1161/HYPERTENSIONAHA.113.02604.