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Review

Immune Cells as Central Coordinators of Cardiorenal Crosstalk in Hypertension: A Narrative Review of Mechanisms, Pathways, and Therapeutic Implications

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Abstract

Hypertension remains the leading preventable cause of cardiovascular disease and premature death worldwide. In the hypertensive state, renal and cardiovascular dysfunctions become entrenched in a self-perpetuating feedback loop, with immune cells emerging as central coordinators of this pathological crosstalk. This narrative review examines the mechanisms by which immune cells integrate signals from high salt, the renin–angiotensin–aldosterone system (RAAS), and the sympathetic nervous system (SNS) to drive chronic inflammation and end-organ damage. We highlight the salt-dendritic cell-isolevuglandin (IsoLG)-T cell axis as a critical pathway linking dietary sodium to immune activation and hypertension. We also explore bidirectional interactions between immune cells and RAAS components, as well as neuro-immune crosstalk that amplifies sympathetic outflow. Counter-regulatory mechanisms, including the ACE2/Ang-(1-7)/Mas axis, the kallikrein–kinin system, Urodilatin, Klotho, and renalase, provide endogenous braking signals that limit inflammation. Finally, we discuss emerging immunomodulatory therapeutic strategies and identify key unanswered questions for future research. Understanding immune cells as central coordinators of cardiorenal communication offers new opportunities for precision medicine approaches to hypertension.

Keywords: hypertension; immune cells; cardiorenal crosstalk

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1. Introduction

Hypertension, affecting approximately one-third of adults (more than1.3 billion people) worldwide, is the most common risk factor contributing to the global burden of cardiovascular morbidity and mortality [1]. Effectively managing hypertension significantly could avert millions of cardiovascular disease-related deaths annually [2]. The kidney and heart work together intimately to maintain blood pressure stability and their dysfunctions play inextricable roles in the development of hypertension [3,4].

Cardiovascular dysfunction and renal dysfunction are deeply interconnected. Impairment in one organ quickly creates a cascading negative impact on the other, often referred to as Cardiorenal Syndrome or Cardiovascular–Kidney–Metabolic (CKM) Syndrome [3,5]. Renal dysfunction is highly prevalent in cardiovascular disease (CVD), affecting approximately half of patients with cardiac conditions [6]. Cardiac dysfunction is highly prevalent in patients with kidney disease. About half of all patients with chronic kidney disease (CKD) stage 4/5 experience cardiovascular disease, and cardiovascular complication is the leading cause of death for CKD patients [7,8]. Cardiovascular and renal dysfunctions trigger chronic systemic high blood pressure through a self-perpetuating spiral of damage. Beyond hemodynamic factors, the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system (SNS) play central roles in the cardiorenal connections underlying hypertension.

A large body of evidence demonstrated that hypertension is a state of chronic immune activation and low-grade systemic inflammation [9]. Immune cells interact closely with RAAS and SNS, forming a self-amplifying cycle that drives hypertension, chronic inflammation, tissue fibrosis, and progressive cardiorenal organ damage. Despite extensive research into the complex pathology of hypertension and the development of numerous effective medications, more than half of patients still have poorly controlled blood pressure [10]. Exploring the precise interconnected immune cells pathway in the cardiorenal axis is critically needed for developing better diagnostics and targeted therapies.

In this review we focus on the cardiorenal connections in hypertension and the central coordinator role of immune cells in this process (Figure 1). We provide a comprehensive synthesis of how immune cells sense hypertensive stimuli, integrate signals from RAAS and SNS, and amplify inflammation and tissue injury. We also highlight the emerging concept of neuro-immune circuits that link the brain, kidney, and cardiovascular system. Finally, we discuss the translational potential of immunomodulatory strategies and identify key unresolved questions that should guide future research.

This narrative review was informed by searches of PubMed conducted through January 2026 to August 2026. Search terms included “Inflammation and Cardiorenal Syndrome”. Publications were selected for their relevance to immune mechanisms of hypertension and cardiovascular–renal communication, with attention to mechanistic studies, counter-regulatory pathways, and findings that differed across experimental settings. The literature was synthesized narratively; formal systematic-review screening and risk-of-bias assessment were not performed.

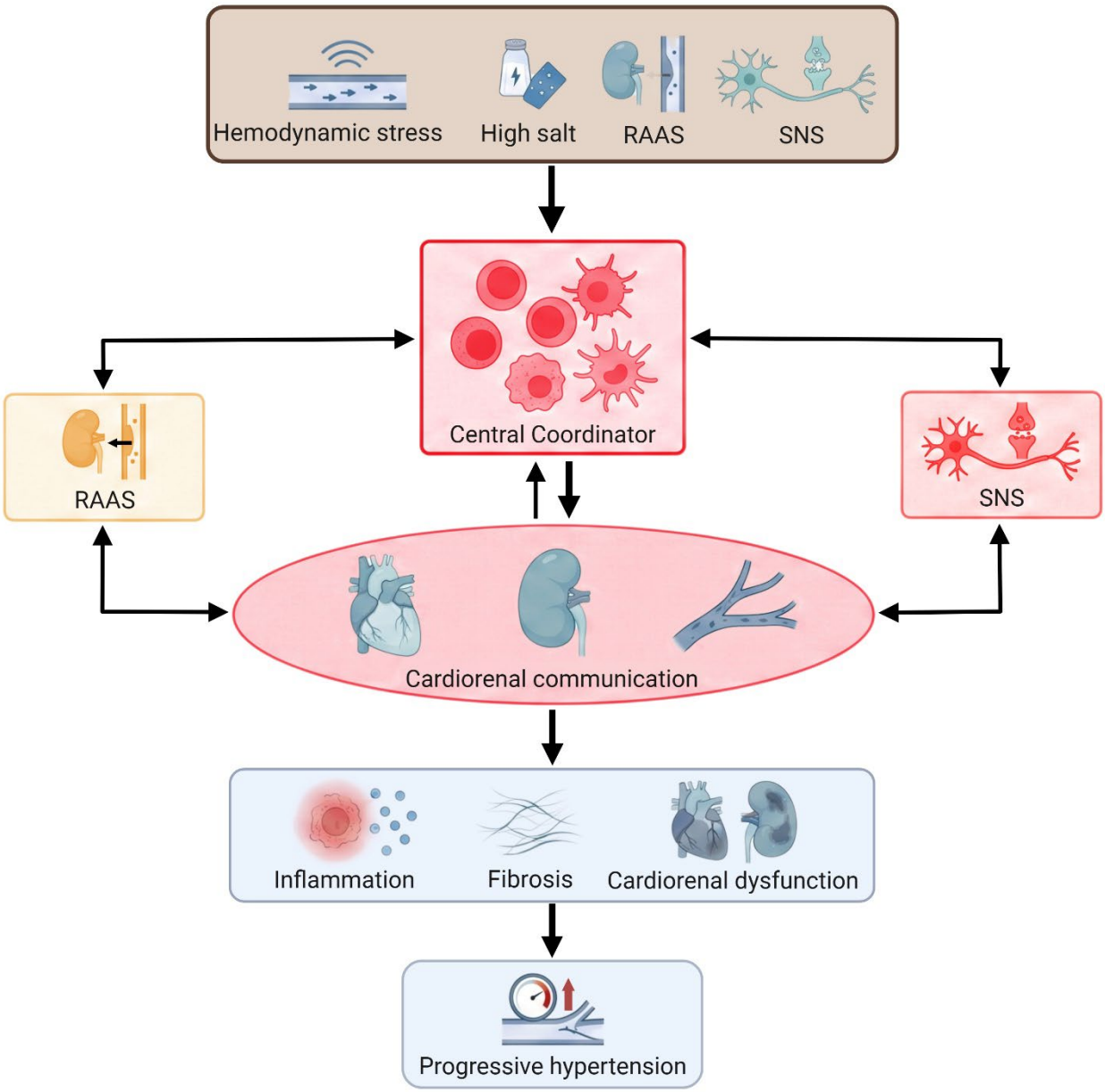


Figure 1. Immune cells act as central coordinators of cardiorenal crosstalk in hypertension. Immune cells integrate signals from hemodynamic stress, high salt, the renin–angiotensin–aldosterone system (RAAS), and the sympathetic nervous system (SNS) to disrupt the normal cardiorenal communication in blood pressure management. The dysregulated cardiorenal communication drives chronic inflammation, fibrosis and end-organ damage in cardiorenal system, causing progressive hypertension.

2. Pathophysiology of Cardiorenal Connections in Hypertension

Blood pressure is fundamentally determined by the product of cardiac output (CO) and systemic vascular resistance (SVR). The kidneys regulate systemic blood pressure by dynamically controlling blood volume and vascular tone, primarily through the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system (SNS) [11–13]. In turn, the heart provides hormonal signals, including atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), as well as neural inputs that regulate blood pressure by modulating vascular tone and renal sodium handling [14,15].

High dietary salt intake is one of the most common factors that directly increases blood volume, thereby elevating CO [16]. Elevated blood pressure increases glomerular hydrostatic pressure, resulting in a transient increase in the glomerular filtration rate (GFR) [17].

Increased renal blood flow suppresses the activity of sodium transporters, including the Na^+/K^+-ATPase and Na^+/H^+ exchangers, along the renal tubules [18]. Under physiological conditions, elevated systemic blood pressure suppresses SNS activity and renin release while stimulating the production of renal vasodilators through multiple counter-regulatory mechanisms [19,20]. In hypertension, however, this finely coordinated feedback system becomes disrupted because of renal and/or cardiovascular dysfunction, resulting in persistent elevation of blood pressure.

Endothelial dysfunction, vascular remodeling, and fibrosis are the major pathological processes responsible for vascular lumen narrowing and increased arterial stiffness, both of which elevate systemic blood pressure [21]. Endothelial dysfunction is characterized by impaired endothelial function, with reduced bioavailability of vasodilators, including nitric oxide, prostaglandins, and kinins, together with increased production of vasoconstrictors such as endothelin-1, vasopressin, and angiotensin II [22]. Nitric oxide is the principal endogenous vasodilator and promotes vascular smooth muscle relaxation through the cyclic guanosine monophosphate (cGMP) signaling pathway [23]. Oxidative stress and inflammatory cytokines are the primary drivers of impaired nitric oxide bioavailability [24]. Endothelin-1 (ET-1), primarily produced by the kidney and vascular endothelial cells, is the most potent endogenous vasoconstrictor. Binding to receptors on vascular smooth muscle cells, ET-1 triggers intracellular calcium influx, producing sustained vasoconstriction and increasing systemic vascular resistance [25,26].

In hypertension, renal and cardiovascular dysfunction establish a self-perpetuating vicious cycle that further increases CO and/or SVR. Prolonged systemic hypertension causes hypertensive nephropathy by damaging the glomerular microvasculature. Impaired renal filtration promotes sodium retention, fluid overload, and chronic inflammation, all of which contribute to sustained elevations in blood pressure [12]. Injured kidneys also release vasoactive mediators that promote vasoconstriction, vascular remodeling, and arterial stiffening, further exacerbating hypertension [27]. Sustained hypertension imposes chronic pressure overload on the heart, ultimately leading to adverse cardiovascular remodeling, including left ventricular hypertrophy (LVH), arterial injury, and eventually heart failure [28,29]. As cardiac function declines, reduced cardiac output diminishes renal perfusion and lowers effective arterial pressure [30]. The resulting renal hypoperfusion activates the RAAS, further increasing blood pressure and accelerating progressive injury to both the heart and kidneys [3,31]. In addition, impaired cardiac function elevates central venous pressure, causing renal venous congestion that further compromises renal function and perpetuates cardiorenal injury [32].

3. The Inflammatory Paradigm in Hypertension

Hypertension is increasingly recognized as a chronic systemic inflammatory condition. Excess sodium accumulation in tissues, hormones like angiotensin II (Ang II) and aldosterone, and overactive SNS are the most common factors that stimulate immune cell activation and infiltration into the heart, blood vessels, and kidneys [9,33]. Circulating monocytes and recruited T cells and macrophages infiltrate into the vessel walls, creating a chronic inflammatory cycle that accelerates arterial stiffening and vascular dysfunction [34,35]. The inflammatory immune cells accumulated in kidney produce pro-inflammatory cytokines and ROS, causing kidney injury, driving sodium retention and blood volume expansion [33,36]. On the other hand, once the blood pressure is elevated, immune cells can sense the mechanical stretch and amplify the inflammatory cycle. Mechanical stretch from high blood pressure triggers the bone marrow to release more inflammatory monocytes into the bloodstream [37]. High blood pressure physically stretches the endothelial cells, triggering the release of pro-inflammatory cytokines and reactive oxygen species, which

recruit immune cells into the walls of blood vessels [38]. Mechanical stretching of high blood pressure triggers neutrophils to release reactive oxygen species (ROS) and neutrophil extracellular traps (NETs) through influx of calcium by activation of TRPV4 and PIEZO1 channels [39,40].

The immune cells integrate signals from high salt, the RAAS, and the SNS to drive chronic inflammation and cardiorenal system end-organ damage. Figure 2 illustrates how immune cells integrate signals from the cardiovascular and renal systems to influence blood pressure regulation. Depending on their phenotype and the physiological context, immune cells may support homeostasis or amplify inflammation and tissue injury. Hypertension can develop when maladaptive immune–cardiorenal interactions overwhelm counter-regulatory mechanisms.

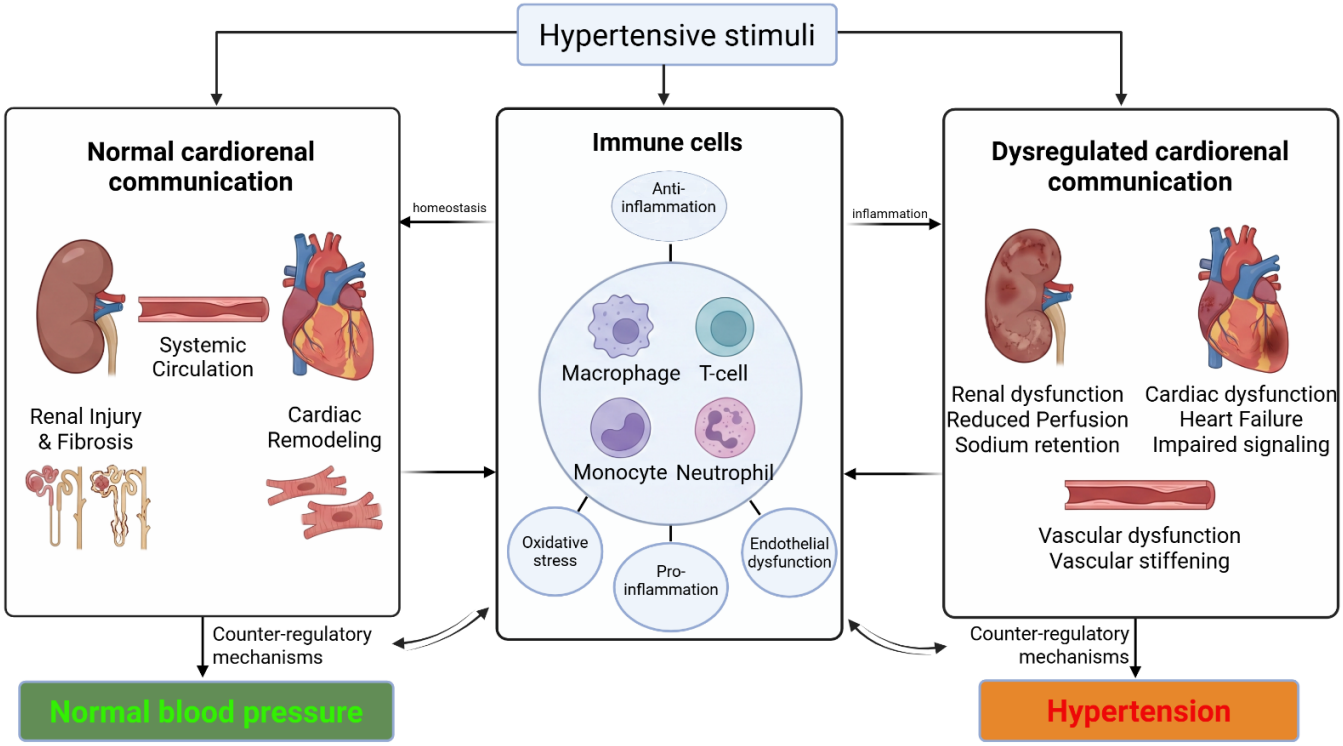


Figure 2. Schematic illustration of the role of immune cells in cardiorenal communication. The balance of pro-inflammatory and anti-inflammatory immune cells determines the blood pressure health status. In healthy bodies, blood pressure is maintained stably through normal cardiorenal communication and multiple counter-regulatory mechanisms. Dysregulated cardiorenal communication disrupts the immune cell balance, promoting renal dysfunction and cardiovascular dysfunction. Sustained sodium retention and vascular stiffening lead to hypertension.

4. Salt-Mediated Immunologic Response as a Link Between Renal Dysfunction and Hypertension

High dietary salt levels have been associated with hypertension. To keep the blood pressure stable, the kidneys actively maintain sodium and water balance through pressure natriuresis [41]. In hypertensive individuals, renal inflammation, ROS, and hyperactive sodium channels impair pressure natriuresis, resulting in sodium retention [42,43]. Continued research has shown that excess Na^+ accumulates in the skin, skeletal muscle and interstitium rather than just circulating in the bloodstream [44–46]. Furthermore, patients that demonstrate limited therapeutic response to hypertension treatment have higher tissue sodium levels [47,48]. The role of tissue sodium storage in causing hypertension is related

to both innate immune cells and adaptive immune cells, like T cells, dendritic cells and macrophages [31,49,50].

4.1. T Lymphocytes in Salt-Sensitive Hypertension

Accumulating evidence suggests that T lymphocytes are important drivers of salt-sensitive hypertension [51,52]. Guzik and colleagues demonstrated that RAG-1-deficient mice, which lack T and B lymphocytes, were protected against DOCA-salt- and Ang II-induced hypertension. However, transfer of T cells, but not B cells, restored the hypertensive response, highlighting the central role of T cells in blood pressure regulation [51]. The role of B cells in hypertension shows contradictory results and requires further investigation [53,54]. Further studies indicate activated pro-inflammatory T cells (including Th17, Th1, CD8+ T cells, γδ T Cells) infiltrate into the kidneys and blood vessels, leading to hypertension. In the kidneys, they release inflammatory substances such as IL-17A and TNF-α, which increase sodium reabsorption, promote inflammation and fibrosis, and impair kidney function [55,56]. In blood vessels, they release IL-17A, IFN-γ, and reactive oxygen species, leading to inflammation, reduced nitric oxide, poor blood vessel relaxation, and increased stiffness [31,57]. Together, these kidney and blood vessel changes increase blood pressure and contribute to salt-sensitive hypertension.

Exposure to high salt environments has been found to suppress Treg and promote Th17 [49,58]. The relationship between high salt intake, immune cell activation, and hypertension is illustrated in Figure 3. Tregs are a specialized subset of CD4+ T cells that express the transcription factor forkhead box protein 3 (FOXP3). Regulatory T cells suppress excessive immune responses and maintain immune tolerance. Their protective effects in experimental hypertension include IL-10-mediated suppression of inflammation, although the effects of IL-10 on blood pressure and renal injury depend on the experimental context [59]. Both the number and function of regulatory Tregs are reduced in people and animal models with hypertension [60,61]. High salt exposure further impairs their suppressive function by activating serum/glucocorticoid-regulated kinase 1 (SGK1), which reduces FOXP3 expression and increases interferon-gamma (IFN-γ) secretion [58]. Reduced IFN-γ may restore some of the immune-suppressive activity of these Tregs [58]. At the same time, high salt promotes differentiation of naïve T cells into Th17 cells through the p38/MAPK pathway involving NFAT5 and SGK1. Inhibiting p38/MAPK, NFAT5, or SGK1 prevents high salt-induced Th17-cell development [49]. This shifts from protective Treg responses to inflammatory Th17 contributes to kidney and vascular injury, sodium retention, and ultimately salt-sensitive hypertension.

4.2. Dendritic Cells and Antigen Presentation in Hypertension

Our work demonstrated that dendritic cells (DCs) play a critical role as professional antigen-presenting cells (APCs) through a specific pathway: ROS lead to lipid peroxidation of arachidonic acid, forming immunogenic IsoLG-protein adducts [62]. ENaC is a constitutively active channel that allows Na^+ influx; in renal epithelium it reabsorbs Na^+, regulating BP and volume [63]. ENaC serves as a direct route for extracellular sodium entry when tissue sodium levels rise. ENaC α- and γ-subunits are present on DCs of mice, while human APCs express ENaC α- and δ-subunits [64,65]. A process regulated by SGK1 increases ENaC α- and γ-subunit expression in mouse APCs [66]. In vivo models with ENaC α-subunit knockout or pharmacological inhibition show decreased salt-induced DC activation, reduced inflammasome signaling, and lowered hypertensive responses [67].

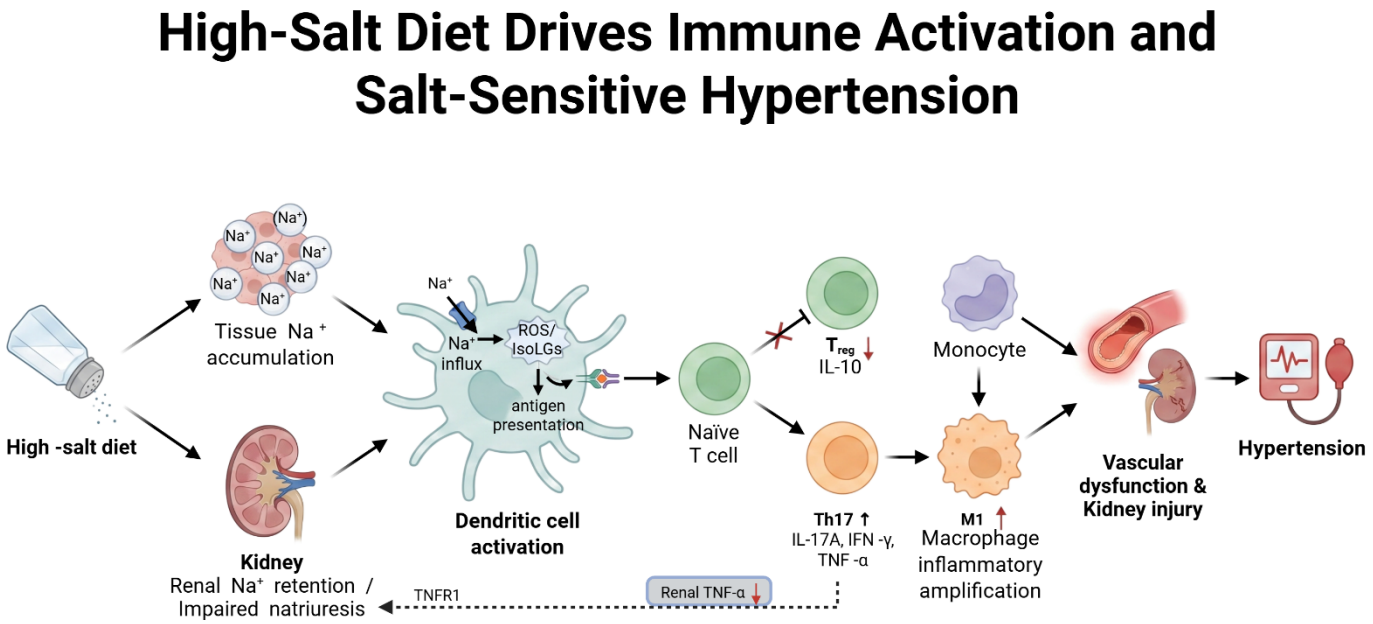


Figure 3. High salt diet drives immune activation and salt-sensitive hypertension. Salt accumulation increases intracellular Na^+ in dendritic cells, leading to ROS production. ROS increases the isolevuglandin (IsoLG)-protein adducts. The IsoLG-protein adducts act as antigens, driving naïve T cells to differentiate into pro-inflammatory T17 cells, producing IL-17A, IFN-γ, and TNF-α. At the same time, high salt suppresses Treg cells, decreasing IL-10 production. High salt concentrations trigger macrophages by shifting them into M1 phenotype while suppressing their M2 phenotype. Pro-inflammatory Th17 cells and M1 macrophages drive vascular dysfunction and kidney dysfunction, leading to the development of SSBP. In some conditions, high salt intake decreases renal TNF-α production, which lowers the natriuretic function of TNF-α in the kidney through TNFR1 activation.

Sodium-hydrogen exchanger 1 (NHE1) exchanges an intracellular H+ for an extracellular Na^+ to maintain cell pH. NHE1 was identified as a part of a dual sodium influx transport system alongside ENaC in dendritic cells. Inhibition of NHE1 with a selective inhibitor or NHE1 siRNA hindered a key step of NADPH oxidase activation that involves the association of p47phox with gp91phox [64]. As a key producer of ROS, NADPH oxidase is directly involved in the activation of dendritic cells and subsequent immune responses that lead to hypertension [64]. It has been demonstrated across multiple studies that excess intracellular sodium in DCs converges onto the activation of NADPH oxidase complexes. This enzyme system is assembled via a Ca^{2+}/protein kinase C (PKC)-mediated phosphorylation of p47phox, which then associates with gp91phox and starts rapidly generating superoxides (O^{2-}), a type of reactive oxygen species [64]. Generation of superoxides leads to superoxide-driven lipid peroxidation, ultimately causing the formation of IsoLGs. These are highly reactive γ-ketoaldehydes that form noncovalent adducts with lysine residues on proteins [68]. The IsoLG-protein adduct is presented to DCs as a neo-antigen that converts DCs into a hyperinflammatory phenotype. Furthermore, the accumulations of IsoLGs promote the secretion of pro-inflammatory cytokines from DCs, such as IL-1β [64]. Upon activation by IsoLGs, NLRP3 assembles with apoptosis-associated speck-like protein (ASC) and caspase-1 in DCs, which results in the cleavage of pro-IL-1β into its active IL-1β form [67]. Through IL-1β release, APCs promote T cell release of cytokines IL-17A and IFN-γ. IL-17A and IFN-γ are the most notorious pro-inflammatory drivers that directly promote vascular damage and renal damage, exacerbating high blood pressure. IL-17A contributes to hypertension by driving vascular oxidative stress and endothelial dysfunction while enhancing the renal sodium retention via SGK1 mediated transport [69]. Experimental models have shown that blocking NADPH oxidase reduces IsoLG-adduct formation,

subsequently decreasing T cell activation and blood pressure elevation [70]. A recent study by our group showed that Janus kinase 2 (JAK2) in $CD11c^+$ cells play critical roles in this progress [71]. Janus kinase 2 (JAK2), signal transducer and activator of transcription 3 (STAT3), and SMAD family member 3 (SMAD3) participate in signaling mechanisms that regulate immune function [71]. Salt loading upregulates the JAK2/STAT3/SMAD3 signaling in APCs from patients with salt-sensitive hypertension, while simultaneously suppressing the suppressor of cytokine signaling (SOCS) proteins that downregulate JAK signaling. This increases immunologic response conditions that lead to hypertension. Additionally, mouse model testing suggests that JAK2 expression in $CD11c^+$ myeloid cells is necessary for salt-induced hypertension, for a conditional knockout of JAK2 protected mice from developing hypertension and they displayed normal renal responses to volume expansion [71].

4.3. Macrophages in Hypertension

In response to hypertensive stimuli, circulating monocytes transmigrate through the blood vessel walls and transform into inflammatory macrophages, releasing damaging cytokines (such as TNF-α, IL-1b and TGF-β) which promote inflammation and fibrosis, increasing peripheral resistance [31,72,73]. De Ciuceis et al. found homozygous osteopetrotic mice, lacking normal macrophage activity due to deficient macrophage colony-stimulating factor (m-CSF), were protected from BP elevation and vascular damage [74]. Infiltration of macrophages into the renal interstitium causes local renal injury and fibrosis, which directly impairs sodium handling [75]. The accumulation of macrophages in the heart promotes pathological cardiac hypertrophy and progressive myocardial dysfunction [76]. In addition, macrophages release cytokines that trigger further recruitment of adaptive immune cells to the cardiorenal system, creating a vicious cycle of inflammation that raises blood pressure [31].

High salt concentrations trigger macrophages by shifting them into M1 phenotype while suppressing their M2 phenotype through p38 MAPK, NFAT5 and SGK1 pathways [50,77,78]. Pro-inflammatory M1 macrophage buildup in the kidney and cardiovascular system releases ROS and pro-inflammatory cytokines, which trigger chronic oxidative stress and inflammation [79]. Conversely, M2 macrophages produce anti-inflammatory cytokines, such as IL-10 and TGF-β. Macrophages with reparative or immunoregulatory phenotypes can suppress inflammation and support tissue repair [72]. However, macrophage functions extend beyond the conventional M1/M2 classification, and their effects on blood pressure depend on the tissue environment and signaling pathways engaged.

4.4. Context-Dependent Roles of Cytokines in Hypertension

The roles of immune cells in blood pressure control are complex. Typically, pro-inflammatory cytokines were believed to drive hypertension via chronic, low-grade inflammation, while anti-inflammatory cytokines act as a counterregulatory mechanism to suppress this damage. However, this classic notion is challenged by some evidence from recent studies. For example, when TNF-α binds to TNF receptor 1 (TNFR1) in the kidney, it triggers a natriuretic and diuretic response to lower blood pressure [80,81]. In some conditions, high salt intake decreases renal TNF-α production, suggesting the natriuretic function of TNF-α in the kidney [82]. A meta-analysis showed anti-TNF agents may increase the risk of developing hypertension in rheumatoid arthritis patients, again suggesting diverse roles of TNF-α in blood pressure control [83]. As a typical anti-inflammatory cytokine, Il-10 may also play a pro-inflammatory role in certain conditions, such as Ang II-induced salt-sensitive hypertension [84].

4.5. Endothelin Signaling in Immune–Cardiorenal Crosstalk

High salt intake increases ET-1 production in the kidney, as well as non-renal tissues such as blood vessels and skin [85,86]. As a well-known potent vasoconstrictor, ET-1 may also act locally in the kidneys or skin to maintain sodium homeostasis [87,88]. ETA receptors and ETB receptors are the two main receptors of ET-1. When ET-1 binds to the ETA receptor on vascular smooth muscle cells, it triggers strong vasoconstriction and inflammation, while activation of ETB receptors in the kidney and skin promotes sodium secretion [87–89]. Disruption of the ETB receptor may cause severe salt-sensitive hypertension [89,90]. Both ETA and ETB receptors are expressed in various immune cells, including T lymphocytes, B lymphocytes, neutrophils, monocytes, macrophages, and dendritic cells [91,92]. Some immune cells produce their own ET-1, such as monocytes, macrophages, and dendritic cells, suggesting the important role of the endothelin system in immune cells communication in the pathogenesis of hypertension [92,93]. Czopek et al. demonstrated that macrophages internalize ET-1 through ETB receptor-mediated endocytosis, providing a clearance mechanism that can limit its hypertensive effects [94]. Our previous study showed that a high-sodium environment stimulates IsoLG formation in DCs, which promotes the production of Endothelin 3 (ET-3). ET-3 interacts with ETB receptors on renal lymphatic endothelial cells, altering their pumping dynamics. This results in renal lymphangiogenesis, immune cell infiltration and activation, kidney injury, and elevated blood pressure [95].

4.6. Gut Microbiota and Hypertension

High dietary salt intake may alter gut microbial composition and host–microbial interactions, potentially contributing to immune dysregulation and elevated blood pressure [96,97]. High dietary salt levels in both humans and mice change the gut microbial composition, specifically increasing Firmicutes, Proteobacteria, and Prevotella, but depleting beneficial bacteria like Lactobacillus. A high salt diet in mice induces systemic inflammation in vascular tissues such as the mesenteric arteries and aorta, enhancing susceptibility to Ang II. When transferring fecal matter, hence microbiota, from high salt-fed mice to germ-free mice, it predisposed them to increased inflammation and hypertension phenotypes [98].

Emerging evidence indicates that microbial metabolites, particularly short-chain fatty acids (SCFAs) like butyrate and propionate, play protective roles by promoting Treg differentiation and reducing inflammation. Conversely, dysbiosis leads to reduced SCFA production and increased levels of pro-inflammatory metabolites [99,100]. Gut-derived signals also influence kidney function, sympathetic outflow and renin release [101]. These findings open the possibility for microbiome-targeted interventions such as probiotics, prebiotics, or dietary fiber supplementation as adjunctive therapies in hypertension.

5. Renin–Angiotensin–Aldosterone System (RAAS) and Immune Cell Interactions

5.1. Overview of RAAS in Hypertension

The renin–angiotensin–aldosterone system (RAAS) is a central hormone system that regulates blood pressure. Chronic activation of the RAAS causes excessive vasoconstriction and sodium retention, which leads to hypertension [102]. Multiple mechanisms are involved in elevating blood pressure in the RAAS. Renin is released by renal juxtaglomerular cells in response to reduced renal perfusion pressure, decreased NaCl delivery to the macula densa, or sympathetic stimulation. Renin acts upon angiotensinogen, converting it into Angiotensin I (Ang I). Angiotensin-converting enzyme (ACE) converts Ang I into Ang II, which is the primary effector peptide acting on the AT1 receptor (AT1R) to constrict arterioles. Ang II triggers the adrenal glands to release aldosterone, which activates ENaC and SGK1,

prompting the kidneys to retain sodium. Ang II signals the pituitary gland to release antidiuretic hormone (ADH), which further increases water reabsorption in the kidneys. In addition to circulating Ang II, locally generated intrarenal Ang II activates AT1 receptors, promoting renal sodium reabsorption and vasoconstriction [13,103]. Furthermore, both Ang II and aldosterone act on the brain to stimulate thirst and salt appetite, driving a subsequent expansion of total blood volume [104].

RAAS is a crucial survival mechanism in evolutionary history and remains functional in specific situations in modern ages, such as severe trauma and dehydration [105]. Chronic hyperactivation of the RAAS is highly prevalent in contemporary populations, primarily driven by environmental and lifestyle stressors. This continuous upregulation establishes a destructive cycle of vasoconstriction, oxidative stress, and inflammation. Bidirectional communication between immune cells and RAAS is shown in Figure 4.

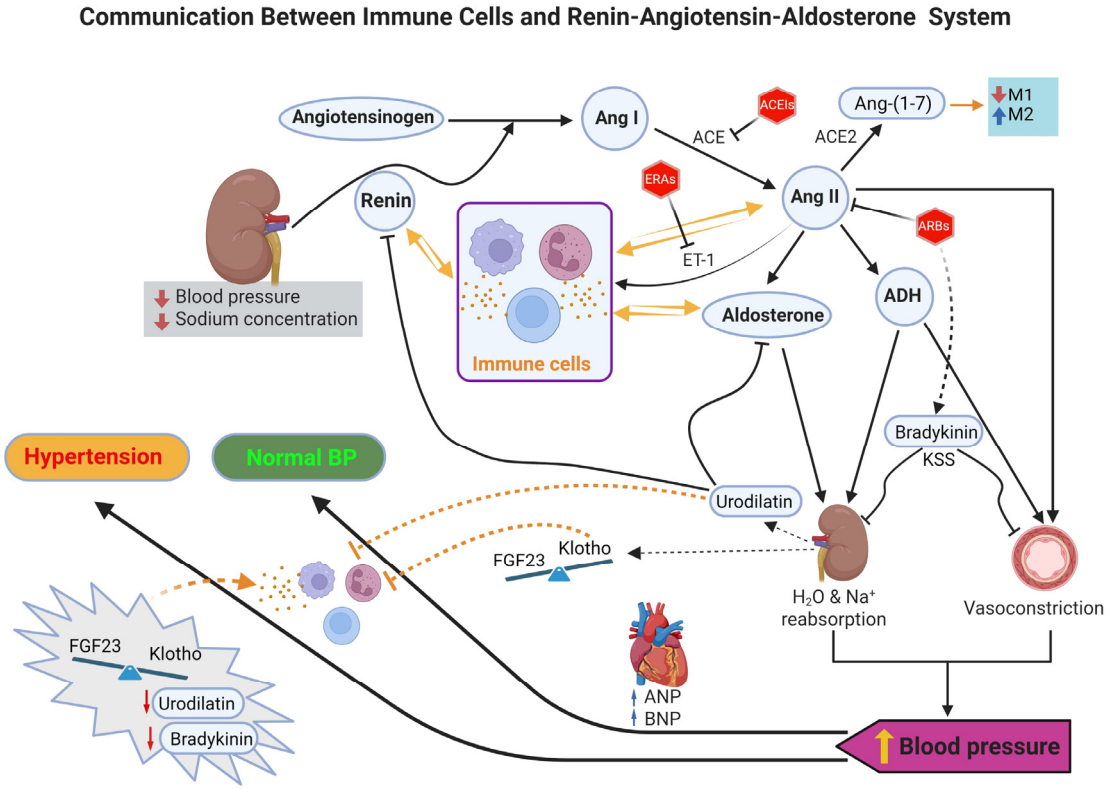


Figure 4. Bidirectional communication between immune cells and renin–angiotensin–aldosterone system (RAAS). The major RAAS components, including renin, Ang II and aldosterone, are bidirectionally communicated with immune cells. They interact with various immune cells to balance the inflammation status and blood pressure. Multiple counter-regulatory mechanisms are involved to provide endogenous braking signals that limit inflammation, including ACE2, kallikrein–kinin system (KSS), and kidney released Urodilatin, Klotho, and endothelin system. Impaired communication between immune cells and RAAS interrupts the balance, leading to hypertension. Pharmacological blockades of this communication, such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and endothelin receptor antagonists (ERAs), are promising immunomodulatory strategies for managing hypertension.

5.2. Bidirectional Communication Between Immune Cells and RAAS

Pro-inflammatory cytokines secreted from immune cells bind to receptors on juxtaglomerular cells, altering intracellular cyclic AMP (cAMP) levels driving renin gene transcription and releasing of stored renin [106,107]. Oh et al. demonstrated that renal macrophages can directly promote juxtaglomerular cells to secrete renin, through their increased release of miR-106b-5p [108]. On the other hand, renin triggers inflammatory

pathways in immune cells. Renin activates (pro)renin receptor expressed in monocytes and T cells, triggering intracellular ERK1/2 phosphorylation, enhancing the secretion of cytokines like IL-6, TNF-α, and inflammatory mediators like cyclooxygenase-2 [109–111].

Pro-inflammatory cytokines stimulate hepatocytes and renal cells to upregulate angiotensinogen (AGT) production, accelerating Ang II formation [112,113]. A study by Lai et al. demonstrated that cytokine IL-6 drives angiotensinogen expression in the liver through activation of JAK/STAT3 and JAK/p38/NF-kB signaling pathways [114]. While systemic AGT is primarily synthesized in the liver, localized renal inflammation triggers intrarenal AGT production, leading to localized Ang II spikes, promoting vasoconstriction, ROS production, and fibrosis [115]. In the kidney, IL-6 acts directly on renal proximal tubules to initiate angiotensinogen (AGT) transcription through the NF-κB and JAK-STAT pathways [116,117].

Ang II functions as an inflammatory mediator by activating the Ang II receptors expressed in immune cells, such as T lymphocytes, dendritic cells, macrophages, and neutrophils [118]. At the same time, inflammatory conditions upregulate the angiotensin receptors (particularly the AT_1R subtype), increasing the immune cell's sensitivity to Ang II [119]. Ang II binds to AT1Rs on native Cd4+ T cells, activating naive CD4+ T cells to pro-inflammatory Th1/Th17 cells while suppressing the master regulator of regulatory T cells (Tregs) [120,121].

Activation of AT1Rs on T cells activates the PKA–proteasome pathway, promoting the degradation of IkBa and MKP-1. Degradation of these inhibitory proteins upregulates NF-kB and STAT1, triggering the production of Th1 cytokines such as IFN-γ and TNF-α, suppressing FoxP3 expression [120–123]. AT1R activation enhances T cell responsiveness to inflammatory cytokines (like IL-6 and IL-12), activating STAT3 and RORgt, driving naïve T cells to differentiate into the Th17 [120,121,124]. With the presence of Ang II, TGF-β signaling acts to disrupt immune tolerance by shifting the differentiation of naïve T cells diverted away from the Treg pathway and into the pro-inflammatory Th17 pathway [121,125]. The accumulation of activated Th1/Th17 T cells in kidneys and blood vessels secretes cytokines that increase inflammation, contributing significantly to high blood pressure and vascular remodeling [51,126,127]. Moreover, Ang II acts as a co-stimulatory molecule binding to AT1R on CD8+ T cells to synergize with the T cell receptor (TCR) and enhance T cell proliferation and differentiation [119]. NK cells are also fully equipped with RAAS elements. They produce and deliver Ang II to localized sites of inflammation, which triggers the maturation of other innate immune cells, like dendritic cells and macrophages [124,128].

Type 1 angiotensin receptors expressed on CD11c+ dendritic cells act as an immune-regulatory brake. They suppress dendritic cell maturation and constrain T cell activation, limiting pro-inflammatory cytokine release and fluid retention [129]. Ang II causes vascular smooth muscle cells, endothelial cells, and macrophages to release Monocyte Chemoattractant Protein-1 (MCP-1) [130–132]. Ang II binds to the AT1R, stimulates NADPH oxidase, resulting in a rapid increase in intracellular ROS. The ROS production and G protein signaling activate several mitogen-activated protein kinase (MAPK) pathways, specifically ERK1/2 and p38 MAPK. The activated MAPKs, alongside calcium signaling, stimulate the translocation of the Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) transcription factor to the nucleus, promoting the MCP-1 gene expression [132–134]. MCP-1 binds to CCR2 on monocytes, drawing them into the arterial wall, heart and kidneys where they turn into macrophages and contribute to hypertension [135]. The activation of NF-κ B also upregulates adhesion molecule gene expression on endothelial cells, such as ICAM-1, VCAM-1, and E-selectin, which promotes the infiltration of immune cells including T cells, macrophages, and neutrophils into vessel walls and kidneys [34,130,136]. Ang II prompts endothelial cells to release inflammatory chemokines (such as IL-8), which rapidly recruit

neutrophils to sites of injury [137]. Similarly, Ang II stimulates neutrophils to produce high amounts of ROS [138]. Ang II triggers neutrophils to release neutrophil extracellular traps (NETs) that can cause blood clots and vascular inflammation [139]. While Ang II stimulates neutrophils, activated neutrophils can also release proteases (such as cathepsin G) that convert Ang I directly into Ang II, sustaining local inflammation [137,140]. Ang II stimulates B cells to differentiate into plasma cells that secrete large amounts of Immunoglobulin G (IgG). These antibodies accumulate in the walls of blood vessels, promoting structural remodeling and stiffness. The deposition of IgG triggers the recruitment of pro-inflammatory macrophages and T cells to the vascular wall, which worsens endothelial dysfunction and increases oxidative stress [54,141]. Recruitment and activation of immune cells, including T cells, macrophages, neutrophils, and B cells, within the kidneys, heart, and vasculature can contribute to renal dysfunction, vascular remodeling, and sustained hypertension. The consequences depend on the recruited cell populations, their activation states, and the affected tissue [111,142]. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) modulate the immune system by blocking pro-inflammatory AT1Rs. This suppresses leukocyte recruitment, reduces the secretion of pro-inflammatory cytokines, and mitigates long-term tissue damage [113,120,142].

In addition, Ang II may interact with immune cells indirectly to regulate blood pressure through other pathways. For example, Ang II stimulates endothelial and smooth muscle cells to express ET-1, which mediates vasoconstriction and immune cell activation, ultimately driving vascular inflammation [143]. It is worth noting that our previous study found that acute dietary salt changes do not alter the expression of RAAS-related genes in human myeloid cells. This result suggests that high salt exposure activates ENaC in APCs not through the RAAS, but relying on alternative pathways [144].

5.3. Aldosterone and Mineralocorticoid Receptor Signaling

Aldosterone drives inflammation by activating mineralocorticoid receptors (MRs) on dendritic cells, T cells, and macrophages. Aldosterone activates dendritic cells, triggering the release of pro-inflammatory cytokines like IL-6 and TGF-β, and downregulates programmed death-ligand 1 (PD-L1) [145,146]. Through dendritic cell interactions, aldosterone polarizes $CD4^+$ T cells toward a Th17 phenotype and activates $CD8^+$ cytotoxic T cells [147]. MR signaling alters the distribution of T cells, reducing circulating naive T cell counts in the blood while upregulating migration markers like CXCR4, causing them to accumulate in the kidneys and aorta [148]. Once MR is activated by aldosterone, T cells are differentiated into subsets Th1 and Th17 phenotypes while suppressing anti-inflammatory regulatory T cells (Tregs) [149]. MR activation regulates $CD8^+$ and $CD4^+$ T cells, driving the secretion of IFN-γ, a cytokine that promotes superoxide generation and inflammation [150,151]. Aldosterone triggers monocytes and macrophages to release inflammatory cytokines like IL-6 and TGF-β1, promoting migration into vascular walls, leading to tissue remodeling, plaque instability, and fibrosis [145,152]. Mineralocorticoid receptor antagonists (MRAs), like spironolactone and finerenon, have been shown to reduce the polarization of inflammatory Th17 cells by monocyte-derived dendritic cells [153,154].

5.4. Counter-Regulatory Mechanisms of RAAS

Multiple intrinsic counter-regulatory pathways are employed to mitigate hyperactivation of RAAS and maintain blood pressure homeostasis (Figure 4). Renin is the initiating and rate-limiting enzyme of RAAS. Live-tissue mapping showed that high Ang II triggers rapid calcium oscillations across neighboring juxtaglomerular cells. This calcium surge acts as a physical biological brake to shut down renin overproduction [155,156]. Urodilatin, synthesized in the distal tubules of the kidney, inhibits renin secretion and blocks

aldosterone releasing [157]. In addition, Urodilatin binds to Natriuretic Peptide Receptor A (NPR-A) receptors in the renal medullary collecting ducts, increasing cyclic GMP (cGMP). Elevated cGMP activates protein kinase G (PKG) and inhibits sodium (Na^+) entry via apical amiloride-sensitive sodium channels and suppresses water reabsorption [157]. Urodilatin also exhibits anti-inflammatory effects by modulating the function of immune cells, including neutrophils and macrophages, and inhibited the generation ROS, suppressing pro-inflammatory cytokines like TNF-α and IL-6 [158,159].

The ACE2/Ang-(1-7)/Mas receptor axis is "counter-regulatory" arm of the RAAS. Angiotensin-converting enzyme 2 (ACE2) breaks down the Ang II into Angiotensin-(1-7) [160]. Ang-(1-7) binds to the Mas G protein-coupled receptor to trigger cellular responses, such as promotion of nitric oxide synthesis, inhibition of pro-inflammatory cytokines, suppression of fibrogenesis, and prevention of oxidative stress and NLRP3 inflammasome [161]. Activation of the Mas receptor in macrophages suppresses the pro-inflammatory M1 state and drives their polarization toward an anti-inflammatory M2 -like phenotype [162].

The kallikrein–kinin system (KKS) is an important hormonal system that counteracts RAAS and lowers blood pressure [163]. The enzyme kallikrein acts on kininogens to generate kinins (mainly bradykinin), which bind to the B_2 receptor on kidneys and blood vessels, promoting sodium excretion and stimulating the release of vasodilators, such as nitric oxide and prostaglandins [164,165]. Bradykinin plays a critical role in immune homeostasis [166]. Bradykinin suppresses the Type I Interferon (IFN) responses by inhibiting the phosphorylation of STAT2, preventing excessive inflammation [167]. Experimental approaches delivering the kallikrein gene were developed to combat hypertension [168]. ACE inhibitors not only reduce the production of the Ang II, but also prevent the breakdown of bradykinin simultaneously [163,165]. Angiotensin receptor blockers (ARBs) block the angiotensin type 1 receptors directly. Blocking AT1, the excess Ang II is diverted to act on AT2 receptors. AT2 receptor stimulation activates the tyrosine phosphatase SHP-1, which subsequently upregulates prolylcarboxypeptidase (PRCP). PRCP acts as a catalyst that converts plasma prekallikrein into active plasma kallikrein, activating KKS [169,170].

5.5. The FGF23–Klotho Axis in Hypertension

The FGF23–Klotho axis is another important hormonal pathway interconnected with RAAS to manage blood pressure [171]. Fibroblast Growth Factor 23 (FGF23) is a hormone secreted primarily by osteocytes in response to rising phosphate levels or active vitamin D (1,25-dihydroxyvitamin D). FGF23 is massively elevated in hypertension patients with CKD. FGF23 suppresses the synthesis of active vitamin D in the kidneys by downregulating the expression of the enzyme 1α-hydroxylase (*CYP27B1*). Simultaneously, it stimulates the enzyme 24-hydroxylase (CYP24A1), which breaks down active vitamin D into inactive metabolites [172]. Vitamin D is a potent inhibitor of renin and its deficiency leads to increased renin biosynthesis, effectively upregulating RAAS [173]. In addition, FGF23 promotes sodium reabsorption by upregulating the sodium/chloride co-transporter (NCC) on the distal convoluted tubule of the kidney through the ERK1/2 and SGK1 pathways [174]. FGF23 promotes sympathetic overactivity by activating FGFR4-calcineurin signaling [175]. Ang II directly stimulates FGF-23 production in osteocytes and FGF-23 suppresses Ace2 in the kidney, preventing the breakdown of Ang II [176,177]. Aldosterone interacts with mineralocorticoid receptors (MRs) in osteoblasts and osteocytes, stimulating the expression of the FGF23 gene [178]. Ang II and aldosterone upregulate FGF23 production but act directly to reduce renal expression of Klotho on renal tubules [171].

Klotho, a crucial anti-aging protein highly expressed in all major tubular segments of kidneys, functions as an obligatory co-receptor of FGF23 to regulate the production of active vitamin D and signal the kidneys to excrete excess phosphate [179]. In CKD patients,

their kidneys lose the ability to produce the Klotho protein. Klotho suppresses RAAS activity through the Wnt/β-catenin signaling pathway [180]. The Wnt/β-catenin pathway positively regulates the transcription of multiple RAS genes [181]. Klotho binds directly to Wnt proteins (such as Wnt1, Wnt4, and Wnt7a), blocking β-catenin activation and its entry into the cell nucleus [180]. Klotho inhibits vascular smooth muscle cells (VSMCs) from transforming into osteoblast-like cells, directly stopping arterial stiffening [182]. Klotho shields cardiomyocytes from structural remodeling, preventing left ventricular hypertrophy (LVH) by reducing systemic oxidative stress and limiting abnormal cellular signaling (such as the p38 and ERK pathways) [183,184].

During periods of severe systemic inflammation, activated macrophages produce FGF23 locally. The locally produced FGF23 interacts with FGFRs to directly stimulate the expression of pro-inflammatory cytokines like TNF-α and inhibit anti-inflammatory-like Arginase-1 [185,186]. High circulating levels of FGF23 bind to FGFR2 on neutrophils, impairing the ability to navigate to sites of inflammation [187]. FGF23 acts to suppress active vitamin D production in the kidneys, which exaggerates inflammatory responses and impaired infection clearance [185,188]. Research suggests that elevated FGF23 could be a novel marker for identifying individuals at higher risk for developing high blood pressure [189].

The Klotho protein acts as a systemic anti-inflammatory factor by suppressing pathways such as NF-kB and the NLRP3 inflammasome, ultimately reducing the production of active inflammatory cytokines [190]. Klotho directly limits the production of pro-inflammatory cytokines like IFN-γ, TNF-α, and IL-6 from T cells, suppressing the differentiation of Th1 and Th17 cells while promoting the activity of Tregs [188,191]. Klotho protects monocytes from DNA damage and stress-induced senescence, reducing the secretion of pro-inflammatory cytokines while boosting anti-inflammatory markers like IL-10 [192]. It actively shifts macrophages away from the pro-inflammatory M1 type and toward the anti-inflammatory M2 type [188]. Preclinical studies indicate that restoring Klotho levels can stop further increases in blood pressure and mitigate end-organ damages in the cardiorenal system [171,184,193].

6. Sympathetic Nervous System (SNS) and Immune Interactions

6.1. SNS Overactivation in Hypertension

Acute sympathetic activation raises blood pressure to support perfusion during physical stress or threat. Sustained sympathetic activation, however, can contribute to hypertension through persistent vascular, renal, and immune effects [194]. Chronic overactivation of SNS continuously releases norepinephrine, which binds to b1 adrenergic receptors in the heart. This accelerates heart rate and increases myocardial contractility. It acts on vascular a1 receptors to constrict blood vessels and increase arterial stiffness, which elevates systemic blood pressure and increases the heart's workload [195]. In the kidney, sympathetic signals constrict the renal arteries, reducing renal blood flow and the Glomerular Filtration Rate (GFR), which limits the kidney's ability to excrete sodium and water properly [196]. Increased SNS releases norepinephrine, which binds to a-adrenergic and b-adrenergic receptors on the basolateral membranes of tubular cells, stimulating Na and K-ATPase activity, directly driving the proximal tubule to absorb more sodium and water [197].

Norepinephrine released from renal sympathetic nerves binds directly to b1-adrenoceptors on juxtaglomerular (JG) granular cells, activating the cAMP pathway. Elevated intracellular cAMP levels activate protein kinase A (PKA), triggering the phosphorylation and exocytosis of renin into the bloodstream [198]. On the other hand, sustained sympathetic overactivity leads to cardiac hypertrophy and renal disfunction, which in turn trigger sensory afferent nerves that signal the brain and central sympathetic outflow [199,200].

6.2. Neuro-Immune Crosstalk

The SNS directly innervates primary and secondary lymphoid organs, including bone marrow, thymus, spleen, and lymph nodes [201]. For example, sympathetic nerve activation significantly drives the mobilization and release of hematopoietic stem and progenitor cells (HSPCs) from the bone marrow into the peripheral circulation, thereby influencing the systemic immune repertoire [202]. As shown in Figure 5, SNS overactivation stimulates immune cells (such as T cells, macrophages, and neutrophils) to release pro-inflammatory cytokines, causing arterial stiffening, endothelial dysfunction, and fluid retention. Research by Marvar et al. demonstrated that noradrenaline can activate T cells and promote their infiltration into blood vessel walls, leading to peripheral vascular inflammation [203]. Increasing evidence showed that elevated norepinephrine from nerve terminals activates adrenergic receptors on T cells, promoting their accumulation in the kidneys and blood vessels and creating a feedforward mechanism that raises blood pressure [204–206]. Catecholamines (noradrenaline and adrenaline) activate α and β adrenergic receptors expressed on macrophages, creating antagonistic effects [207]. When catecholamines bind to α1 adrenergic receptors on macrophages, this massively increases the secretion of proinflammatory mediators, such as IL-1β, by the protein kinase C (PKC) and p38 mitogen-activated protein kinase (p38 MAPK) pathways [208]. β2AR is generally expressed at higher levels than the other subtypes on macrophages. When NE binds to β_2-ARs, it activates adenylate cyclase, increasing intracellular cyclic AMP (cAMP) levels. Elevated cAMP activates PKA, which prevents the pro-inflammatory transcription factor NF-κB from entering the cell nucleus. By blocking NF-κB, NE inhibits the transcription and release of pro-inflammatory cytokines like TNF-α, IL-6, and IL-8, while promoting the production of anti-inflammatory IL-10, which drives fibrosis instead of inflammation [209,210]. NE decreases the expression of the CCR2 chemokine receptor, which reduces the ability of macrophages to migrate out of the bloodstream and into inflamed tissues [211]. Renal nerves contribute to the migration of CD161a+/CD68+ macrophages to the renal medulla, where they contribute to increased renal expression of NKCC2, promoting water and sodium reabsorption [212,213].

SNS directly affects immune cell behaviors. In return, active immune cells release pro-inflammatory cytokines (such as IL-1b, IL-6, and TNF-α) that communicate back to the brain and activate microglia in the hypothalamus and brainstem, further amplifying SNS output (Figure 5) [214]. Sympathetic ganglia contain resident macrophages that directly interact with neuronal cell bodies, modulating neurotransmitter release and neuronal excitability [215]. This neuro-immune crosstalk creates a powerful, self-sustaining bio-loop, amplifying the chronic inflammation condition [216]. Spiral catheter technology disrupts overactive nerves lining the kidney arteries, which effectively reduces blood pressure in experimental models and humans [217]. Renal denervation has been shown to lower inflammation by decreasing the activation of monocytes, dendritic cells, and T cells [204,218,219].

6.3. Purinergic Signaling and Immune Activation

When the SNS is activated in hypertension, it releases ATP alongside norepinephrine from nerve terminals into the kidneys [220,221]. As a sympathetic cotransmitter, ATP binds to P2 receptors (such as P2X1) on vascular smooth muscle cells, triggering an influx of calcium, causing blood vessels to constrict and increasing peripheral vascular resistance [222]. Disruption of some P2 receptors (such as P2Y2, P2X4) can impair sodium excretion, leading to salt-resistant arterial hypertension [223,224]. Recently P2 receptors are increasingly recognized as a vital communication bridge between the immune system and the development of hypertension [225,226]. A recent study by Shokoples et al. demonstrated that elevated extracellular ATP acts as a damage-associated molecular patterns (DAMPs) in hypertension [227]. Excess ATP binds to P2X7 receptors on immune cells, activating the

NLRP3 inflammasome, and amplifies Ca^{2+} influx during T cell activation, which triggers the release of potent pro-inflammatory cytokines like IL-1β and IL-18 [228–230]. Disruption of P2RX7 could reduce the infiltration of activated T cells and blunt Ang II-induced BP elevation [227]. When the P2RX7 receptor is activated by excess ATP on Tregs, it promotes a significant loss of FOXP3 and drives their conversion into pro-inflammatory Th17-like cells [231].

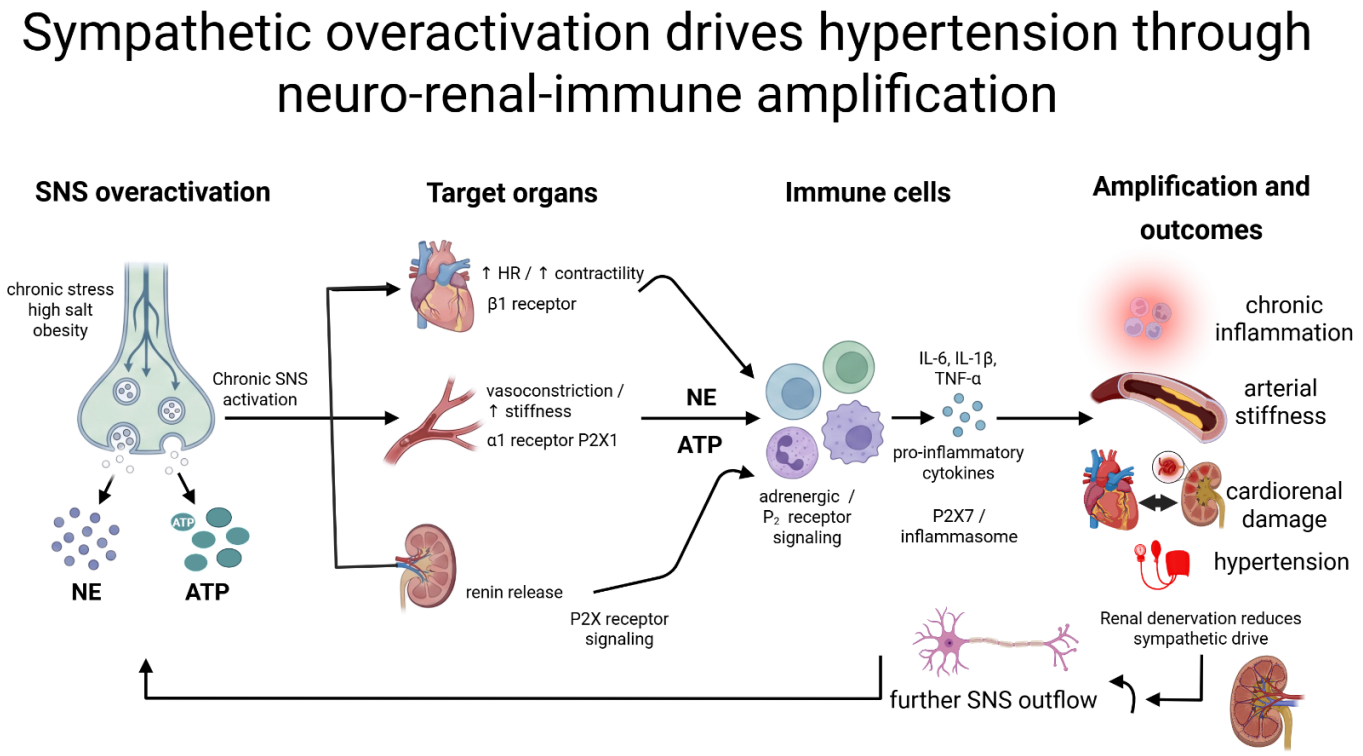


Figure 5. Sympathetic overactivation drives hypertension through neuro-renal-immune amplification. Chronic stress, high salt and obesity cause sympathetic nervous system (SNS) overactivation. SNS nerve terminals release norepinephrine (NE) and ATP. NE stimulates immune cells (such as T cells, macrophages, and neutrophils) to release pro-inflammatory cytokines (such as IL-6, IL-1β, TNF-α), causing inflammation, arterial stiffening, cardiorenal damage, and hypertension. As a sympathetic cotransmitter, ATP binds to P2X7 receptors on immune cells, triggering the release of potent pro-inflammatory cytokines. In return, pro-inflammatory cytokines communicate back to the brain, further amplifying SNS output. Renal denervation is a validated immunomodulatory therapeutic approach to reduce sympathetic drive in patients with hypertension.

6.4. Renalase: A Counter-Regulatory Hormone

Renalase is a kidney-secreted hormone that decreases sympathetic nerve activity by metabolizing circulating adrenaline, noradrenaline and their precursors. Deficiency in renalase, often in CKD patients, is strongly associated with increased sympathetic activity and high blood pressure [232,233]. Renalase deficiency promotes a systemic and local proinflammatory state by triggering a significant upregulation of cytokines like TNF-α and MCP-1 [234]. Renalase functions as a cytokine that activates PI3K/AKT, JAK/STAT, and the MAPK pathways, driving the differentiation of macrophages toward the anti-inflammatory M2 phenotype. Exposure of activated M1 macrophages to renalase blocks inflammasome activation and production of IL6 and IL1β [235]. Proper renalase has been shown to protect the kidney and heart from ischaemic injuries and fibrosis by suppressing oxidative stress [236,237]. Exogenous renalase could potentially be developed as a new treatment for managing hypertension by dampening severe inflammation, especially in CKD patients [234,236,238].

7. Therapeutic Implications and Future Perspectives

7.1. Current Pharmacological Approaches

Because the heart and kidneys operate in a continuous, intertwined loop in hypertension, hypertension should be treated as a disorder of dysregulated cardiorenal communication. Effectively managing hypertension requires a coordinated approach that addresses both organs. In recent years, a combination of SGLT2 inhibitors and GLP-1 receptor agonists has been developed as foundational treatments for cardiovascular-kidney diseases as well as hypertension [239]. SGLT2 inhibitors lower blood sugar and blood pressure by causing the kidneys to excrete excess glucose and sodium, reducing sympathetic tone [240]. GLP-1 receptor agonists significantly reduce appetite and promote substantial weight loss. They reduce systemic inflammation and oxidative stress, protecting kidney function and lowering the risk of major adverse cardiovascular events [241]. When taken together, SGLT2 inhibitors and GLP-1 receptor agonists provide synergistic, complementary benefits [240]. To reduce adverse renal outcomes, ERAs and RAAS inhibitors are increasingly combined with SGLT2 inhibitors to maximally protect kidney function while managing hypertension [242]. Blocking the endothelin system by endothelin receptor antagonist (ERAs), such as Aprocitentan, has emerged as a novel therapeutic approach which significantly lowers blood pressure and protects kidney function in resistant hypertension patients with chronic kidney disease [243,244].

7.2. Emerging Immunomodulatory Strategies

Interventions targeting immune processes show potential in reducing cardiorenal damage and mitigating hypertension [245]. Some studies are looking at the use of anti-inflammatory agents like colchicine and methotrexate to curb hypertension-induced inflammation [245,246]. Drugs have been investigated for their ability to neutralize inflammatory cytokines (IL-17A, IL-1B, TNF-α) that contribute to hypertension [35]. Pre-clinical models showed that specific IsoLG scavengers like 2-hydroxybenzylamine (2-HOBA) intercept and neutralize highly reactive IsoLGs, protecting immune cells from dysfunction and significantly lowering blood pressure [247,248]. NLRP3 inhibitors are being studied for their potential to treat hypertension and its associated organ damage [249,250]. SGK1 inhibitors are an emerging class of experimental therapeutics being investigated for salt-sensitive hypertension and metabolic syndrome [66,251,252]. Regulatory T cells (Tregs) help suppress immune responses and reduce inflammation, acting to protect the vascular system and lower blood pressure [253,254]. Because of this crucial connection, modulating the immune response and balancing T cell subtypes are active areas of clinical research for novel, immune-regulatory treatments for hypertension [255]. For example, Srinivas et al. demonstrated that deletion of the STIM1 gene in Tregs blocks destructive calcium signaling, which restores redox balance and protects against hypertension and its cardiovascular complications [256]. Interventions that shift the balance away from M1 macrophages and toward M2 macrophages may help suppress chronic inflammation and lower blood pressure in hypertension [257].

7.3. Future Directions and Unanswered Questions

Immune cells play a central coordinator role in dysregulated cardiorenal communication in hypertension. Immune cells sense hypertensive stimuli, like high salt, Ang II, aldosterone, and sympathetic neurotransmitters, integrate with signals from the RAAS, SNS, cardiovascular and renal systems, and amplify inflammation and tissue injury, driving persistent hypertension. Although significant work has been done, some questions remain poorly understood. Which immune cell subtypes and pathways are the best targets for hypertension treatment that benefits the whole cardiorenal system? Discrete neuro-immune

circuits that link the brain, kidney, and cardiovascular system in hypertension have been identified. However, the complexity of these circuits and the potential for off-target effects require careful preclinical and clinical evaluation. These interconnected circuits provide multiple nodes for therapeutic intervention. Targeting brain–immune interactions, for example, with drugs that cross the blood–brain barrier or with vagal nerve stimulation, represents a promising frontier in hypertension management. The clinical translation of microbiome-targeted interventions remains in early stages, and the causal relationships between specific microbial taxa and BP regulation require further elucidation. The etiology and pathogenesis of hypertension are highly heterogeneous, especially immune cells. With the unprecedented advances of high-throughput molecular technologies, including single-cell RNA sequencing, spatial transcriptomics, proteomics, and metabolomics, coupled with artificial intelligence, new opportunities are created to develop personalized interventions to better prevent hypertension and improve patient-specific cardiovascular outcomes.

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