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Renal effects of cytokines in hypertension

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Abstract

Purpose of review—Inflammatory cytokines contribute to the pathogenesis of hypertension through effects on renal blood flow and sodium handling. This review will update recent advances that explore the renal actions of immune cells and cytokines in the pathogenesis of hypertension.

Recent findings—Populations of cells from both the innate and adaptive immune systems contribute to hypertension by modulating functions of the vasculature and epithelial cells in the kidney. Macrophages and T lymphocytes can directly regulate the hypertensive response and consequent target organ damage. Dendritic cells and B lymphocytes can alter blood pressure (BP) indirectly by facilitating T-cell activation. Proinflammatory cytokines, including tumor necrosis factor- α , interleukin 17, interleukin 1, and interferon- γ augment BP and/or renal injury when produced by T helper 1 cells, T helper 17 cells, and macrophages. In contrast, interleukin 10 improves vascular and renal functions in preclinical hypertension studies. The effects of transforming growth factor- β are complex because of its profibrotic and immunosuppressive functions that also depend on the localization and concentration of this pleiotropic cytokine.

Summary—Preclinical studies point to a key role for cytokines in hypertension via their actions in the kidney. Consistent with this notion, anti-inflammatory therapies can attenuate BP elevation in human patients with rheumatologic disease. Conversely, impaired natriuresis may further polarize both T lymphocytes and macrophages toward a proinflammatory state, in a pathogenic, feed-forward loop of immune activation and BP elevation. Understanding the precise renal actions of cytokines in hypertension will be necessary to inhibit cytokine-dependent hypertensive responses while preserving systemic immunity and tumor surveillance.

Keywords

cytokine; hypertension; immune system; kidney

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Conflicts of interest

There are no conflicts of interest.

INTRODUCTION

Hypertension afflicts more than 1 billion people worldwide and is a prominent risk factor for cardiovascular complications [1]. Kidney and cardiovascular dysfunction are causes and also consequences of persistent hypertension, culminating in a high risk of mortality [2]. Despite an armamentarium of pharmacologic therapies that target renal sodium handling, systemic vascular responses, cardiac output, and sympathetic outflow, blood pressure (BP) remains uncontrolled in up to 50% of hypertensive patients [2,3]. Recent studies have revealed that cells of the immune system contribute to the pathogenesis of hypertension via their actions in the kidney, the vasculature, and the brain, such that immunomodulation may represent a novel approach to reduce BP and limit target organ damage in hypertension [4–6]. However, to mitigate the immune system's contribution to hypertension without subjecting patients to unacceptable risks of immunosuppression, the precise mechanisms through which innate and adaptive immunity regulate BP require elucidation. Hematopoietic cells could modulate the functions of cardiovascular control centers, including the kidney by instigating cellular injury or repair, by altering local levels of oxidant stress, and by elaborating vasoactive cytokines that have downstream effects on renal blood flow and sodium transport. The current review summarizes a set of preclinical experiments that describe the effects of inflammatory cytokines to modulate the hypertensive response through direct actions in the kidney.

IMMUNE CELLS IN HYPERTENSION

Inflammatory cells are present in the kidneys of patients with severe hypertension as demonstrated in autopsy studies [7], and animal models have demonstrated that myeloid cells from the innate immune system and lymphocytes from the adaptive immune system make distinct contributions to the pathogenesis of hypertension. Among the myeloid cell populations, circulating monocytes and tissue macrophages exacerbate both BP elevation and target organ damage in hypertension. Accordingly, deleting LysM-expressing macrophages attenuates endothelial dysfunction and hypertension during chronic infusion of angiotensin (Ang) II [8]. Such actions of macrophages to disrupt vascular function can provoke sodium retention in the kidney by disrupting renal blood flow. In multiple models, expression of the chemokine receptor CCR2 on monocytes facilitates their recruitment into the kidney with consequent exacerbations in hypertensive renal injury [9,10], whereas the mononuclear cell chemokine CCL5 paradoxically protects the kidney from damage and fibrosis in hypertension by tempering CCR2-dependent infiltration of Ly6C^{hi} inflammatory macrophages into the renal interstitium [11]. In contrast to the detrimental actions of proinflammatory macrophages in the kidney and vasculature during hypertension, VEGF-C-expressing macrophages in the skin stimulate lymphatic drainage of sodium from interstitial reservoirs back into the circulation to allow natriuresis and thereby limit BP elevation. Thus, macrophages can have diverse effects on intravascular volume and renal function, depending on their differentiation and tissue distribution [12,13]

Another myeloid cell subset, the dendritic cell, serves as a bridge between innate and adaptive immunity by processing and presenting specific antigens to T lymphocytes that in turn proliferate, differentiate, and secrete both reactive oxygen species and vasoactive

cytokines that could play a role in BP elevation. Dendritic cells in the kidney invite renal infiltration of T cells [14], and the presentation of antigen by dendritic cells to T cells in the context of appropriate costimulatory signals is required for the full manifestation of hypertension in multiple models [15]. Moreover, activated dendritic cells can transfer the susceptibility to hypertension but only the presence of responder T lymphocytes that can undergo activation [16].

Once activated, the adaptive immune system plays a major role in the pathogenesis of sustained hypertension [17]. In a landmark study, Guzik *et al.* [18] established through adoptive transfer that T but not B lymphocytes are essential for the induction of hypertension and associated vascular dysfunction. Our group found that lymphocytes impair natriuresis during hypertension, possibly through the suppression in the kidney of NOS3 and COX-2 [19]. Among the T-cell subsets, CD8+ rather than CD4+ T cells appear to mediate prominent prohypertensive actions of the adaptive immune system, including sodium retention and endothelial dysfunction. Although B lymphocytes in isolation do not drive BP elevation [18], they may exacerbate hypertension by facilitating T-cell activation and consequent cytokine generation [20,21]. Thus, cells in both the innate and adaptive immune systems contribute to hypertension via actions in the vasculature and the kidney. Next, we focus on the specific actions of individual cytokines produced by these cells to drive renovascular dysfunction and/or renal sodium retention.

RENAL EFFECTS OF CYTOKINES IN HYPERTENSION

Tumor necrosis factor- α

A prototypical macrophage cytokine, tumor necrosis factor (TNF) is also produced by T cells and resident kidney cells, including renal epithelial cells, mesangial cells, and vascular endothelial cells [22]. Ramseyer *et al.* [23] recently provided a comprehensive summary of TNF's actions in the kidney. Although infused, TNF exerts a natriuretic effect via ligation of TNF receptor 1 [24,25], the net effect of endogenous TNF is to augment the hypertensive response and associated renal injury in rodent models. For example, TNF deficiency or blockade in mice blunts the chronic hypertensive response to Ang II [18,26,27]. TNF suppresses NOS3-dependent sodium transport in the thick ascending limb [28], and cross-transplant studies established that these actions of TNF in the kidney exaggerate hypertension *in vivo* [26]. TNF is directly toxic to glomerular epithelial cells [29,30]. In rats, TNF inhibition attenuates glomerular and tubular injury accruing from hypertension of several causes [31–33], and infusion of a TNF blocker directly into the renal interstitium can protect against salt-induced BP elevation [34]. Thus, preclinical studies substantiate a role for TNF to promote sodium retention during hypertension, possibly via stimulation of TNF receptor 2 rather than TNF receptor 1 [35], but the local distribution and concentration of TNF within the compartments of the kidney are critical determinants of TNF-dependent BP modulation.

In humans, the effects of TNF on BP have been mixed. In patients with congestive heart failure, TNF inhibition did not reduce BP [36,37]. However, the antihypertensive effects of TNF antagonism may be more easily demonstrated among patients with frank immune activation. Accordingly, in small numbers of hypertensive patients with psoriatic or

rheumatoid arthritis, urinary levels of TNF correlated with BP [38], and TNF blockade with infliximab reduced 24-h ambulatory BP in a crossover study design [39]. Future studies will need to investigate how to vigorously disrupt the actions of TNF that promote sodium retention in the kidney without engendering off-target immunosuppression and loss of tumor surveillance.

Interleukin-1

Interleukin 1 is an inflammatory cytokine and produced by hematopoietic cells and several resident kidney cell lineages [40]. The two active isoforms of interleukin 1, interleukin 1 α , and interleukin 1 β , both ligate the same receptor for interleukin 1. An innate signaling complex called the NLRP3 inflammasome cleaves prointerleukin 1 β to its active form. Ligation of interleukin 1R1 in turn drives its recruitment of Myd88 and several interleukin 1 receptor-associated kinases that together facilitate translocation of NF- κ B's p65 component to the nucleus where it drives the transcription of genes encoding inflammatory proteins, including TNF. A role for interleukin 1 in BP regulation is suggested by the capacity of the NLRP3 components to exacerbate the hypertensive response to several stimuli. For example, deficiency of these components mitigates BP elevation and/or renal injury following Ang II or mineralocorticoid infusion [41–43]. Although infusion of exogenous interleukin 1 promotes a natriuresis [44–46], endogenous interleukin 1 appears to potentiate hypertension through several actions that could indirectly or directly impact renal function. In the brain, intracisternal injection of interleukin 1 enhances sympathetic outflow causing systemic vasoconstriction, which could impair renal sodium excretion [46]. Interleukin 1 in the systemic or pulmonary vasculature similarly augments pressor responses [47,48]. We found that interleukin 1R1 deficiency or blockade limits NKCC-dependent sodium retention in the thick ascending limb of the nephron and thereby affords partial protection from Ang II-dependent hypertension. In our system, interleukin 1R1 activation promotes the maturation of myeloid cells that in their immature state preserve natriuresis via the elaboration of nitric oxide [49]. Whether activation of the interleukin 1R1 directly on myeloid cells mediates this phenotypic change is unclear from our experiments, particularly as interleukin 1R1 activation of macrophages favors nitric oxide generation in the setting of infection [50]. Dissecting kidney-specific mechanisms through which interleukin 1 aggravates hypertension will be critical as global interleukin 1 blockade ameliorates cardiovascular disease in humans but increases the susceptibility to fatal infection [51].

Interferon- γ

Interferon (IFN) is an inflammatory cytokine, produced by T lymphocytes and macrophages, that drives and marks T-cell differentiation toward a proinflammatory T helper 1 cells subtype and stimulates both macrophages and B cells. IFN enhances sodium transport via the NHE3 transporter in the proximal tubule and via NKCC2 and NCC in the distal nephron [52]. Accordingly, IFN deficiency attenuates the chronic hypertensive response to Ang II [53]. However, abrogating signals via one component of the heterodimeric receptor for IFN (IFNR1) did not impact Ang II-induced BP elevation [54], suggesting that signaling via the other component of the heterodimer (IFNR2) may be sufficient to preserve IFN-dependent sodium retention. Nevertheless, signaling via IFNR1 appears to be critical for propagating tubulointerstitial inflammation in the kidney during hypertension [54].

Transforming growth factor- β

Transforming growth factor- β (TGF- β) is a key driver of fibrosis in the kidney, particularly during activation of the renin–Ang system (RAS), a prime instigator of hypertension [45,55]. TGF- β triggers renal fibrogenesis by increasing the deposition of extracellular matrix proteins and inhibiting the activity of matrix metalloproteinases [56–58]. Accordingly, chronic administration of recombinant TGF- β 1 or TGF- β 2 causes renal fibrosis, proteinuria, and elevated BP, presumably because of loss of vascular elasticity and/or impaired natriuresis [59]. Circulating TGF- β levels are increased in Ang II-dependent hypertension [60]. Moreover, in salt-sensitive hypertension, dietary sodium intake may stimulate the renal production of TGF- β [61,62]. Inversely, anti-TGF- β therapy significantly reduces BP, proteinuria, and renal fibrosis in Dahl SS rats [63,64]. Although these studies point to a monolithic, prohypertensive effect of TGF- β in the kidney, TGF- β produced by T regulatory cells (Tregs) may act in concert with interleukin 10, discussed below, to temper BP elevation via the suppression of neighboring T effector lymphocytes [65]. Thus, as with other cytokines, the effects of TGF- β on kidney function in hypertension likely depend on compartmental localization and concentration. Parsing these effects will require incisive experiments, particularly given the complexity and redundancy of the fibrotic signaling pathways downstream of TGF- β [66].

Interleukin-17

Interleukin-17A, the founding member of the interleukin 17 family, plays a significant role in infection and autoimmune diseases [67]. Interleukin 17-producing ROR γ t and CD4 $^{+}$ T cells are the primary source of interleukin 17A, which augments cell-mediated immune responses by stimulating the production of proinflammatory cytokines and chemokines [68,69]. Interleukin 17A induces damage to vascular smooth muscle cells by driving the local generation of ROS, CCL2, interleukin 8, and interleukin 6 [70,71]. Madhur *et al* [72] reported that serum interleukin 17 levels are increased more than three-fold in hypertensive patients compared with healthy controls. In mice, systemic RAS activation augments the elaboration of interleukin 17 by T lymphocytes and triggers the accumulation of interleukin 17 protein in the medial layer of the vessel wall [72]. Accordingly, interleukin 17 administration stimulates endothelial dysfunction and BP elevation via a p kinase-dependent pathway [73]. Inversely, interleukin 17A deletion or inhibition, but not blockade of the alternative interleukin 17 isoform, interleukin 17F, inhibits renal and vascular inflammation and BP elevation during chronic Ang II infusion [72,74]. Similarly, deletion of γ - δ T cells, a key source of interleukin 17A, yields protection from experimental hypertension [75[■]]. Within the kidney, interleukin 17A drives sodium reabsorption via the NHE3 exchanger in the proximal tubule and the NCC sodium transporter in the distal convoluted tubule [76[■]]. Thus, the effects of interleukin 17A on vascular remodeling renal sodium handling may synergistically contribute to hypertension. Nevertheless, the tissue and isoform-specific actions of interleukin 17 will require additional clarification as the broad disruption of interleukin 17's effects has had neutral or even detrimental effects on renal damage in some hypertension models [77,54].

Interleukin-10

Interleukin 10 is an anti-inflammatory cytokine produced by T helper 2 cells, Tregs, monocytes, and mast cells. Interleukin 10 inhibits activation of NF- κ B and limits the production of proinflammatory cytokines and chemokines during hypertension [78,79]. Interleukin 10 administration reduces urinary protein levels, endothelial dysfunction, and BP in rats with pregnancy-induced hypertension [80–82]. Inversely, interleukin 10 deficiency exacerbates endothelial dysfunction and hypertension in TLR3-induced preeclampsia, an effect that is reversed by interleukin 10 supplementation [83]. Following RAS activation, interleukin 10-deficient mice exhibit augmented NADPH oxidase activity and microvascular endothelial dysfunction with variable effects on the hypertensive response [84–86]. Thus, the effects of interleukin 10 to protect the vasculature in preclinical hypertension studies are consistent, but interleukin 10's capacity to modulate BP may depend on whether these vascular effects are sufficient to alter systemic vascular resistance and/or renal sodium handling. Thus, additional studies addressing the precise actions of interleukin 10 in the kidney during hypertension would be informative.

CONCLUSION AND FUTURE DIRECTIONS

In the Guytonian view of renal physiology, only impaired clearance of salt and water by the kidney permits sustained elevations in BP [87]. Even in the context of more recent models in which excess sodium is stored nonosmotically in the dermis [12,13], the kidney still regulates BP through careful titration of intravascular volume. Thus, understanding how inflammatory mediators secreted by hematopoietic cells regulate kidney function is paramount to understanding the immune system's contribution to the pathogenesis of hypertension (Fig. 1). Cytokines can modulate salt and water balance by altering sympathetic tone and renal nerve activity, by provoking endothelial dysfunction with secondary effects on renal blood flow, and/or by augmenting sodium transport along the nephron [49[■]]. TGF- β likely has complex actions in the hypertensive kidney because of its dual pro-fibrotic and immunosuppressive functions. On balance, however, the effects of individual cytokines on salt retention and hypertension mirror the inflammatory polarization of the cells from which they are secreted. Thus, proinflammatory T helper 1 and T helper 17 cells and M1 macrophages produce TNF, interleukin 17A, interleukin 1, and IFN, all of which seem to favor BP elevation and/or renal injury when produced endogenously. By contrast, interleukin 10, produced by Tregs, limits the severity of hypertension. VEGF-C and nitric oxide, inasmuch as they facilitate the removal of sodium from the organism, warrant consideration as antihypertensive macrophage 'cytokines' [12,49[■]]. Depending on the dose, distribution, and isoform of the specific cytokines, the preclinical experiments cited above certainly include exceptions to the paradigm in which inflammation begets hypertension. Nevertheless, the general propensity of inflammation to foster BP elevation may represent an evolutionary consequence of the immune system's preventing circulatory collapse in the face of overwhelming infection.

The relevance of cytokines to human hypertension will require further evaluation. Circulating levels of certain cytokines correlate with BP in some hypertensive patients [88], and blocking inflammation and cytokine actions can reduce BP among selected hypertensive

patients with rheumatologic disease [38,39]. However, the risk of infection when using immunomodulatory agents in patients with cardiovascular disease is nontrivial [51]. Understanding the precise renal actions of cytokines in hypertension may, therefore, permit us to inhibit cytokine-dependent sodium retention while largely preserving systemic immunity and tumor surveillance. In the meantime, given recent findings that retained salt can reciprocally polarize both T lymphocytes and macrophages toward a heightened inflammatory state [89–90,91[■],92], treatment regimens that include diuretics to promote salt excretion together with an anti-inflammatory agent warrant testing in selected patients with hypertension that is sufficiently severe to provoke renal and cardiovascular damage.

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KEY POINTS

- Cytokines produced by the innate and adaptive immune systems contribute to the pathogenesis of hypertension by modulating renal function.
- Macrophages and T lymphocytes directly regulate BP and target organ damage. Dendritic cells and B cells can influence hypertensive responses by facilitating T-cell activation.
- Proinflammatory cytokines aggravate hypertensive responses and kidney damage, whereas anti-inflammatory cytokines inhibit BP elevation and end-organ injury.

FIGURE 1.

Renal effects of cytokines in hypertension. Both B cells and DCs participate in the pathogenesis of hypertension through facilitating activation of inflammatory cells. Proinflammatory cytokines including TNF- α , IL-1, IFN- γ , TGF- β , and IL-17 are produced by macrophages and T cells and augment renal function decline and the hypertensive response. By contrast, IL-10 is generated by Th2 cells and Treg and attenuates renal injury and blood pressure elevation. DC, dendritic cells; IFN, interferon; IL, interleukin; TGF, transforming growth factor; TNF, tumor necrosis factor; Treg, T regulatory cells.