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Targeting cytokine signaling in salt-sensitive hypertension

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Crowley SD, Jeffs AD. Targeting cytokine signaling in salt-sensitive hypertension. *Am J Physiol Renal Physiol* 311: F1153–F1158, 2016. First published August 24, 2016; doi:10.1152/ajprenal.00273.2016.—Activated immune cell populations contribute to hypertension in part through inciting damage to the kidney and by provoking inappropriate sodium reabsorption in the nephron. Inflammatory mediators called cytokines produced by T lymphocytes and macrophages act on specific sodium transporters in the kidney, augmenting their activity or expression, with consequent expansion of intravascular fluid volume and cardiac output. The overlapping functions of these cytokines, each of which may activate multiple receptors, present challenges in precisely targeting inflammatory signaling cascades in hypertension. Moreover, broad immune suppression could expose the hypertensive patient to disproportional risks of infection or malignancy. Nevertheless, the possibility that incisive immunomodulatory therapies could provide cardiovascular and renal protection through both blood pressure-dependent and -independent mechanisms justifies comprehensive investigation into the relevant signaling pathways and tissue sites in which inflammatory cytokines function to exaggerate blood pressure elevation and target organ damage in hypertension.

hypertension; cytokine signaling; organ damage

HYPERTENSION IMPACTS A BILLION people worldwide and leads to severe kidney and cardiovascular disease (34). Despite the availability of several classes of anti-hypertensive medications, blood pressure remains poorly controlled in up to half of patients with hypertension (17), highlighting the need to reduce barriers to compliance with existing treatments and to develop novel anti-hypertensive therapies. Blood pressure homeostasis is maintained by coordinated inputs from the kidney, heart, vasculature, nervous system, and even the immune system (9). While dysfunction in any one of these cardiovascular control centers has been shown to enhance the susceptibility to experimental hypertension, Guyton (22) suggested that sustained elevations in blood pressure reflect inappropriate reabsorption of sodium in the kidney nephron. Otherwise, in response to blood pressure elevation, the kidney should excrete salt and water in sufficient amounts to lower intravascular volume and return blood pressure back toward normal. In recent years, several laboratories including our own have sought to understand how perturbations in immune responses can provoke renal sodium retention leading to hypertension and consequent target organ damage.

Preclinical studies have implicated both the innate and adaptive immune systems in the pathogenesis of hypertension. Among myeloid cell populations of the innate immune system,

LysM-expressing inflammatory monocytes, CD39-responsive neutrophils, and CD11c⁺ dendritic cells (DCs) bearing oxidized isoketals can all potentiate blood pressure elevation (19, 28, 66). These DCs transfer susceptibility to hypertension only in the presence of circulating lymphocytes, suggesting that DCs provoke increases in blood pressure by presenting antigens to the T cell receptor with concomitant provision of a costimulatory signal (28, 63). Although the actions of myeloid cells in the vasculature and kidney to regulate blood pressure have historically received the most attention, an emerging literature indicates that macrophages resident in the dermis can also modulate salt sensitivity through effects on nonosmotic sodium storage outside the vasculature (38, 67, 73).

Within the adaptive immune system, both B and T lymphocytes contribute to the chronic hypertensive response (6, 23). However, B cells appear to regulate blood pressure by modulating T cell function, as transfer of B cells does not recapitulate hypertension in the absence of T cells (23). We observed that animals lacking functional T cells had preserved natriuresis, blunted oxidative stress in the kidney, enhanced renal generation of nitric oxide, and blunted hypertension in response to activation of the renin-angiotensin system (RAS) (11). T cell inhibition yielded similar protective effects in other rodent models of hypertension (13, 14), suggesting that activated T cells promote hypertension by augmenting oxidative stress and sodium reabsorption in the kidney. Individual T cell subpopulations can have varying effects on renal sodium transport by modulating the function of neighboring mononuclear cells, elaborating vasoactive cytokines, and altering levels of reactive oxygen species (ROS) within the vasculature and kidney. The potential role of T lymphocytes, and those with a memory phenotype in particular, has been elegantly summarized earlier in this Perspective series (25). Below, we will consider the contribution to hypertension of several inflammatory cytokines typically produced by T and myeloid cell populations.

Inflammatory Cytokines in Hypertension

A host of inflammatory cytokines shape the hypertensive response, typically by regulating oxidant stress and/or levels of nitric oxide in the vasculature or kidney. IL-17A, a cytokine produced by Th17 cells that figure prominently in autoimmunity, provokes generation of ROS in the blood vessel wall and augments sodium transport in the proximal tubule of the nephron with consequent blood pressure elevation (26, 27, 39). IL-6 helps to sustain Th17 cell differentiation and potentiates hypertension probably by promoting renal sodium reabsorption both directly in the collecting tubule epithelium and indirectly by facilitating RAS-induced renal vasoconstriction (4, 36, 51).

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Moreover, IL-17A directly promotes renal sodium retention by enhancing expression and activity of sodium-hydrogen exchanger 3 in the proximal tubule and activity of the sodium chloride cotransporter in the distal nephron (43). Studies such as these that uncover the precise functions of individual IL-17 isoforms to regulate blood pressure will be critical to the successful targeting of IL-17 in hypertension. To this point, globally interrupting IL-17's downstream signaling pathways did not impact blood pressure and worsened kidney damage in more severe hypertension, and a broad IL-17 blocking antibody had no effect (31, 41). Thus, future interventions will need to selectively disrupt the prohypertensive functions of IL-17A while preserving IL-17's protective actions in the kidney.

Interferon- γ (IFN) is the prototypical inflammatory cytokine produced by cytotoxic CD8⁺ T cells. While CD8⁺ and not CD4⁺ T cells appear to mediate T cell-dependent hypertension during RAS activation (60, 72), and IFN facilitates sodium transport in the proximal and distal nephron (26), interpreting the actions of IFN in hypertension presents the same challenges as those of IL-17. IFN deficiency has provided either robust or no protection from RAS-dependent hypertension (49, 70), and deficiency of the receptor for IFN afforded only compartment-specific protection for the kidney through a blood pressure-independent mechanism (41). While discrepancies in the results from these studies can be ascribed to differences in study design, rodent strain, and even epigenetic factors such as gut microbiota, collectively these experiments would indicate that blood pressure is exquisitely sensitive to a cytokine's precise localization and dose.

Studies of two prototypical macrophage cytokines, tumor necrosis factor- α (TNF) and IL-1, corroborate this hypothesis. Circulating levels of TNF and IL-1 are dramatically increased in the hypotensive state of sepsis (21). Moreover, intravenous infusion of these cytokines causes natriuresis (29, 52, 53, 61). Nevertheless, genetic deficiency of TNF or the receptor for IL-1 affords significant protection from hypertension, suggesting that on balance these cytokines are prohypertensive in the intact animal (23, 58, 71). To resolve these paradoxes, others and we began to examine the actions of these cytokines in cardiovascular control centers.

Prohypertensive Actions of TNF and IL-1

TNF is a pleiotropic cytokine produced in several cardiovascular control centers with complex physiologic effects on renal function that have been comprehensively summarized in this journal (45). TNF enhances the appetite for salt, so TNF acting in the central nervous system (CNS) may contribute to hypertension (58). In our hands, TNF secreted by proinflammatory Th1 lymphocytes did not contribute to hypertension but did impact injury within the kidney glomerulus (72), consistent with the known effects of TNF to injure the glomerular endothelium (3). We also found that the presence of TNF in the blood vessel wall did not augment RAS-dependent vasoconstriction (70). By contrast, TNF suppresses nitric oxide synthase (NOS)3 expression in the thick ascending limb of the nephron such that deleting TNF selectively from the kidney via a cross-transplantation strategy attenuates the chronic hypertensive response (46, 70). These data would suggest that targeting TNF's actions

within the kidney should ameliorate hypertension (Fig. 1). However, even within the kidney, activating the two receptors for TNF, TNFR1 and TNFR2, has divergent effects on blood pressure (5, 7, 57), which could confound attempts to target signaling pathways downstream of TNF in hypertensive patients.

The inducible form of IL-1, IL-1 β , is cleaved to its active form by the NLRP3 inflammasome. Blood pressure elevation induces components of this inflammasome, whereas deficiency of these components blunts the hypertensive response (32, 55). Once activated, IL-1 could promote hypertension through actions in several tissue beds. IL-1 injected into the CNS provokes catecholamine release and blood pressure elevation (44, 54, 59). IL-1 triggers constriction of the pulmonary vasculature and aorta (16, 64), but we did not find that IL-1 receptor (IL-1R1) activation potentiates RAS-induced vasoconstriction in the systemic circulation (71). Rather, our experiments revealed that IL-1R1 expression on intrarenal myeloid cells constrains their elaboration of nitric oxide (NO), releasing the NKCC2 sodium cotransporter from tonic NO-dependent inhibition with consequent renal sodium retention during angiotensin II-dependent hypertension (71) (Fig. 1). By contrast, IL-1R1 activation on macrophages recruited to combat parasitic infection enhances NO production (37), so further studies are warranted to understand whether IL-1's actions in myeloid cells are context-specific or whether IL-1R1 activation on kidney parenchymal cells modulates the phenotype of infiltrating myeloid cells. Such an interaction in which the kidney epithelium regulates hematopoietic cell differentiation has been appreciated during the pathogenesis of acute kidney injury (35).

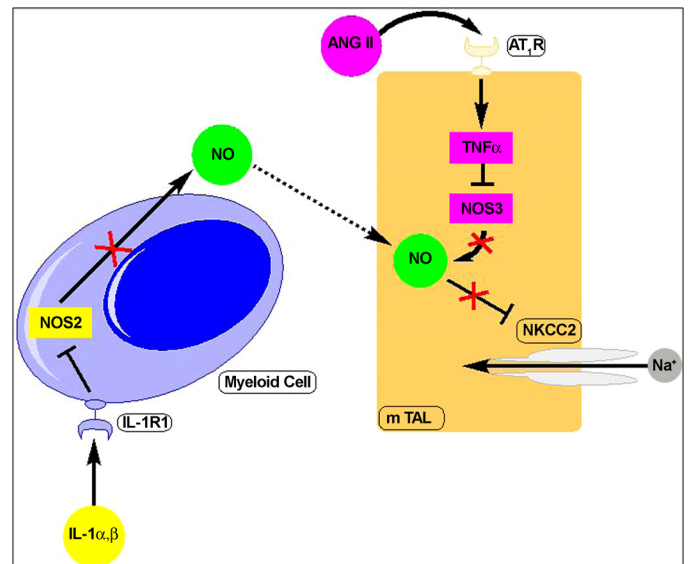


Fig. 1. Ligation of the IL-1R1 receptor on intrarenal myeloid cells inhibits nitric oxide synthase (NOS)2 expression, leading to reduced nitric oxide (NO) production. Binding of ANG II to the type 1 angiotensin receptor (AT₁R) on the medullary thick ascending limb (mTAL) epithelial cell in the kidney enhances TNF- α production, which inhibits NOS3 expression and thereby reduces NO production. In each case, the blunted NO generation permits augmented activity of the NKCC2 sodium cotransporter and exaggerated sodium reabsorption.

Prospects for Targeting the TNF or IL-1 Pathways in Human Hypertension

When considering the use of any immunomodulatory drug, weighing the benefits of cardiovascular protection against the risks of infection and compromised tumor surveillance is paramount. Broad immunosuppression appears to blunt the hypertensive response in human patients (24). However, more targeted approaches might reduce blood pressure and/or attenuate end-organ damage in hypertension without markedly enhancing infection risk. Even individual cytokine blockade is not without risk as TNF antagonism, for example, has been associated with enhanced susceptibility to tuberculosis reactivation (20).

In light of these risks, pursuing additional preclinical studies to more precisely target intracellular signaling pathways downstream of TNF and IL-1 in hypertension might be prudent. On the other hand, these intracellular mediators may receive signals via multiple receptors leading to inconsistent effects on blood pressure. For example, IL-1R1 forms a signaling complex with several IL-1 receptor-associated kinase (IRAK) isoforms and Myd88 that together liberate the p65 subunit of NF- κ B to allow its nuclear translocation (65), but Myd88 deletion has been reported to have pro- and anti-hypertensive effects in the same model of RAS activation (30, 56). An alternative to blocking signaling pathways downstream of TNF or IL-1 would be to globally target TNF or IL-1 signals with a tissue-specific strategy. Such a biomedical engineering approach has proved elusive to date, but harnessing the body's endogenous "tissue address" machinery with SNARE technology, piggyback transposons, or antibody conjugates represents three creative strategies in this direction (33, 50, 68).

A promising feature of the preclinical data that encourages translation to the hypertension clinic is the congruent effect of cytokine deficiency vs. blockade on blood pressure. Accordingly, TNF blockade blunted the hypertensive response in the rat subjected to RAS activation and in a mouse model of systemic lupus erythematosus (SLE) (18, 62). Similarly, we saw that IL-1R1 blockade with anakinra afforded protection from hypertension on par with that seen in IL-1R1 deficiency (71). As noted above with pharmacologic infusion models, the therapeutic benefit of TNF or IL-1 antagonists may depend on their dose and the tissues they reach, particularly given the discrepant functions of the two TNF receptors and the divergent expression profiles and induction patterns of the two IL-1 isoforms, IL-1 α and IL-1 β .

Studies examining the roles of TNF and IL-1 in human hypertension are inconclusive but point to the need for mechanistic studies in larger hypertensive cohorts. Levels of both TNF and IL-1 β are elevated in the monocytes and circulation of some hypertensive populations (2, 12, 15), suggesting they may play a role in blood pressure elevation, but it is conversely possible that the enhanced cytokine expression is the result rather than the cause of blood pressure elevation in these patients. TNF or IL-1 blockade was not reported to reduce blood pressure in clinical studies of these therapies for normotensive patients with rheumatologic disease, and in studies of patients with heart failure, TNF antagonism only rarely yielded a reportable hypotensive response (8, 40). Nevertheless, blood pressure reductions accruing from blockade of lymphocyte proliferation correlated with lower urinary TNF levels (24),

and TNF blockade in one small study of hypertensive patients reduced continuous ambulatory blood pressure (69). Regarding blockade of the IL-1 signaling pathways, large, ongoing studies with the IL-1 β inhibitor canakinumab and the IL-1R1 antagonist anakinra in patients with atherosclerosis should reveal whether targeting the IL-1 signaling pathway can ameliorate cardiovascular damage and may also lend clues to the effects of IL-1 receptor activation on human blood pressure (1, 47, 48).

Concluding Remarks

Immune activation clearly promotes renal sodium retention in experimental models of salt-sensitive hypertension. Nevertheless, the employment of small rodents to study the mechanisms that link inflammatory cytokines to enhanced sodium transport in the nephron poses considerable challenges. Although we have seen clear links between natriuresis, aquaresis, and acute reductions in total body weight (as a measure of changes in intravascular volume) with genetic manipulations that fully prevent hypertension (10, 11), typically we are not able to link natriuresis to acute changes in total body weight in our experiments with cytokine-deficient mice that are only partially protected from hypertension. Admittedly, our experimental systems may not be sufficiently sensitive to detect small changes in intravascular volume. However, an alternative possibility is that alterations in total body sodium attributable solely to kidney function do not fully capture the full complexity of sodium homeostasis as it relates to blood pressure regulation. In this regard, as tonicity-sensing macrophages regulate the storage of sodium bound to proteoglycans in the dermis (38), targeting functions of inflammatory cells and the cytokines they produce has the capacity to reduce morbidity in hypertension both by directly limiting end-organ injury and by improving sodium homeostasis throughout the body.

Despite the compelling evidence for the role of inflammatory cytokines in the pathogenesis of hypertension, the risks of immune suppression in hypertensive patients compel us to pursue carefully targeted disruptions of the immune response and to reserve such interventions for patients who clearly have biologically resistant hypertension. Evaluating inflammatory biomarkers may further allow us to reserve testing of immunomodulatory therapies for hypertensive patients with evidence of underlying immune activation. One motivation for exploring new immunomodulatory therapies for hypertension despite their inherent risks is that these novel approaches may have the capacity to attenuate injury to the brain, heart, and kidney even when they fail to reduce blood pressure (42). We therefore submit that future studies should continue to define *in vivo* both the signaling pathways through which cytokines regulate sodium homeostasis and the key cardiovascular control tissues in which cytokines act to modulate blood pressure.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

S.D.C. conception and design of research; S.D.C. performed experiments; S.D.C. analyzed data; S.D.C. interpreted results of experiments; S.D.C. and A.D.J. prepared figures; S.D.C. drafted manuscript; S.D.C. and A.D.J. edited and revised manuscript; S.D.C. and A.D.J. approved final version of manuscript.

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