Kidney360

IFN-γ Contributes to the Immune Mechanisms of Hypertension

Lance N. Benson, Yunmeng Liu, Katherine Deck, Christoph Mora, and Shengyu Mu

Abstract

Hypertension is the leading cause of cardiovascular disease and the primary risk factor for mortality worldwide. For more than half a century, researchers have demonstrated that immunity plays an important role in the development of hypertension; however, the precise mechanisms are still under investigation. The current body of knowledge indicates that proinflammatory cytokines may play an important role in contributing to immune-related pathogenesis of hypertension. Interferon gamma (IFN-γ), in particular, as an important cytokine that modulates immune responses, has been recently identified as a critical regulator of blood pressure by several groups, including us. In this review, we focus on exploring the role of IFN-γ in contributing to the pathogenesis of hypertension, outlining the various immune producers of this cytokine and described signaling mechanisms involved. We demonstrate a key role for IFN-γ in hypertension through global knockout studies and related downstream signaling pathways that IFN-γ production from $CD8^+$ T cell (CD8T) in the kidney promoting CD8T-stimulated salt retention *via* renal tubule cells, thereby exacerbating hypertension. We discuss potential activators of these T cells described by the current literature and relay a novel hypothesis for activation.

KIDNEY360 3: 2164–2173, 2022. doi: https://doi.org/10.34067/KID.0001292022

Hypertension, a major cause of premature death, affects roughly half of the US population and 1.3 billion people worldwide (1,2). This condition has been subjected to intensive study for more than half a century leading to the development of a variety of classes of pharmaceutical options to lower BP; however, fewer than 50% of patients achieve good BP control (3). Further confounding clinical treatment of hypertension is the multifactorial dysfunctional aspect of this disease, wherein an estimated 90%–95% of treated patients present with unclear origin (essential hypertension) (4), and an estimated 20%–30% of cases are resistant to currently available treatment (resistant hypertension) (5). Thus, it is important to investigate unknown mechanisms causing essential hypertension and develop new therapeutic strategies against hypertension (6). Years of intense research have confirmed that the kidney plays a critical role in regulating BP (7), for example transplanting kidneys from hypertensive donors to normotensive recipients transfers hypertension (8). Guyton and others proposed that a physiologic defect in the kidney impairs its salt handling, which contributes to the development of hypertension (9,10). However, the exact identity of this kidney defect is still under investigation. One potential suspect being investigated recently is disorder of immunity, in particular adaptive immune cells, which contribute to hypertension through several possible mechanisms (11), including dysregulation of natriuresis and driving renal injury (12).

Published in the 1970s, Svendsen first demonstrated the role of the immune system in the classic deoxycorticosterone acetate (DOCA)+salt murine model of hypertension (13). In this experiment, nude mice (lacking thymus, immunodeficient) exhibited blunted BP increase compared with haired wild-type (WT) mice, along with fewer round cell infiltrations. When these nude mice received a thymus graft—thereby restoring mature immune cell production—the BP increase to DOCA+salt was restored to normal levels. This study identified a thymus-independent phase of BP elevation followed by a thymus-dependent phase (13). The particular immune cells driving the thymus-dependent phase of BP elevation had not been identified and became of interest to researchers. In 2007, Harrison and colleagues not only corroborated blunted BP elevation due to immunodeficiency through the use of $RAG1^{-/-}$ mice (immunodeficient mice that produce no mature T or B cells) but also found that the adoptive transfer of T cells—but not B cells—would restore the hypertensive response to angiotensin II (AngII) (14). This landmark study was limited, wherein other labs found $RAG1^{-/-}$ mice no longer showed blunted hypertensive response to AngII in later studies (15,16), and a discussion of this change and potential explanations were provided in an excellent editorial from Madhur *et al.* (17). Many other preclinical studies indicating the role of the immune system have been published in the last 20 years. A few highlights include the use of the immunosuppressant

Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, Little Rock, Arkansas

Correspondence: Dr. Shengyu Mu or Dr. Lance N. Benson, Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, 4301 W Markham St., Little Rock, AR 72205. Email: SMu@uams.edu or LNBenson@uams.edu

tacrolimus to ameliorate BP elevation in Dahl salt-sensitive rats fed a high salt diet (12) and the use of the immunosuppressants dexamethasone and etanercept to reduce renal fibrosis, albuminuria, T-cell infiltration, and NF-κB activation accompanying AngII-infused double-transgenic rats (18). As researchers began to characterize particular immune players involved, Kamat *et al*. demonstrated the critical roles of IFN-γ in AngII-mediated hypertension, wherein global knockout (KO) of the cytokine blunted BP elevation to this pressor (19). Known producers of IFN-γ include T cells, natural killer (NK) cells, monocytes/macrophages, neutrophils, and dendritic cells (DCs), and each of these immune cells have been implied as participating in the process of hypertension (11,20–25). Certain T cells (Th17) and macrophages have been specifically implicated to play a role through sodium-driven proinflammatory responses as described here (26); however, the purpose of this review is to highlight current research describing the proposed immune cells contributing to this "thymus-dependent" phase of BP elevation and outline the elucidated mechanisms, and provide insight into the particular role of IFN-γ in the immune cell-mediated stage of hypertensive development. For a comprehensive network of IFN-γ JAK/STAT signaling pathways, we refer the reader to this 2018 review by Bhat *et al*. (27), and these reviews for a discussion of IFN-γ transcription regulation (28,29).

T Cells

The specific role of the T cell, and not B cell, in contributing to hypertension was first outlined by Guzik *et al*. in 2007, wherein adoptive transfer of T cells but not B cells to RAG-$1^{-/-}$ immunodeficient mice restored the blunted BP elevation of this model to AngII treatment. In that study, the authors also determined that NADPH oxidase contributed to complete development of hypertension *via* affecting T-cell infiltration (14). NAPDH oxidases (NOX)—particularly NOX2—mediate release of reactive oxygen species (ROS) alongside cellular mitochondria in a process termed "oxidative burst" to aid in elimination of invading microorganisms (30,31). The role of NADPH oxidases and T cell–aggravated hypertension has been connected to the central nervous system in an AngII model of hypertension (32,33). Of interest, IFN-γ has been linked to upregulation of NAPDH oxidase in exposed epithelial cells (34,35) to concomitant upregulation of NADPH and IFN-γ in leukocytes in sickle cell disease (36), and to $CD8^+$ enhanced ROS signaling through an NADPH oxidase-dependent CD39 expression mechanism (37,38). From these studies, and others, NAPDH oxidase activity within the immune cell has been tied to IFN-γ production and plays a role in cellular response to IFN-γ.

$CD4^+$ Th1 T cells may play a role in the development of kidney damage in hypertension but not necessarily elevated BP itself as indicated by T-bet KO mice showing reduced renal damage but similarly elevated BP to WT mice in the AngII model of hypertension (39,40), Sun *et al*. further indicated the MR receptor on $CD4^+$ T cells contributes to hypertension through regulation of IFN-γ (41). Our laboratory has found that $CD8^+$ T cells (CD8Ts) play a direct role in the development of hypertension. After induction of hypertension in the DOCA+salt model (Cat. M-121, 50 mg/pellet in 21-day release formula and 1% NaCl drinking water) for 14–18 days, adoptive transfer of 1×10^7 splenocyte-derived CD8Ts from these mice into uninephrectomized C57BL/6J male mice results in salt-sensitive hypertension in the recipient mice that can be alleviated through treatment with a thiazide diuretic (42). We found that these T cells remain within the kidney, directly interacting with the distal tubule and continuing to promote NCC expression and activity despite treatment with the diuretic (42). More recently, we found that this mechanism of hypertensive-derived CD8Ts interacting with the distal tubule thereby generating salt-sensitivity in the recipient mice is *via* the IFN-γ-programmed cell death ligand 1 (PDL1) pathway (43). IFN-γ KO mice demonstrate blunted BP in either the AngII model of hypertension (19) or DOCA+salt model (43). In performing adoptive transfer of DOCA+salt-induced hypertensive CD8Ts from WT or IFN-γ KO mice to the alternative strain (methods according to previously described laboratory protocols) (42,43), only the WT CD8Ts were able to generate salt-sensitive hypertension in the recipient mouse (Figure 1), indicating that IFN-γ from the CD8T itself is sufficient to drive salt-sensitive hypertension.

Activation of T cells—characterized by elevated expression of IFN-γ and TNF-α among other cytokines—has been linked to the development of salt-sensitive hypertension (44). In agreement with clinical data finding increased human hypertensive CD8T IFN-γ production compared with normotensive CD8Ts (45), we found that hypertensive murine CD8Ts demonstrated enhanced capacity of producing IFN-γ—but not TNF-α—compared with sham mouse–derived CD8Ts (43). This evidence, the ability of immunosuppressants to reduce BP in animal models of hypertension, and our co-culture model showing activated CD8Ts promoted greater NCC upregulation, sodium retention, and PDL1 expression through IFN-γ and the IFN-γ receptor in mouse distal convoluted tubular cells compared with naïve CD8Ts further supports the hypothesis that activated CD8Ts contribute to the development of hypertension. When we knocked down PDL1 within the renal tubule, BP elevation was blunted in both the DOCA+salt and CD8T adoptive transfer models of hypertension (43). Renal specific targeting of PDL1 may prove a promising clinical target in treating resistant hypertension.

During full activation of naïve CD8Ts, clonal expansion takes place after presentation of antigen, co-stimulatory factor, and a third signal (such as IL-12) wherein T-cell clones that are specific for individual antigens proliferate (46–48). Trott *et al*. performed a clonotype analysis of kidney $CD8^+$ T-cell receptor sequences and found 3522 ± 1049 unique T-cell receptor sequences in mice treated with AngII with three shared specific clonotypes in Vβ3, 8.1, and 17 families from four of the five mice that were not present in multiple sham mice; however, these clonal subtypes were not observed in other organs (48). The conclusion of this study suggested that rather than a single clonal population, an oligoclonal population of CD8Ts accumulate in the kidney and contribute to hypertension and sodium retention (48). The presence of more than one clonal population of CD8Ts presents at least two potential explanations: either (*1*) multiple unique antigens are being presented simultaneously leading to CD8T accumulation in the kidney through a IFN-γ-dependent mechanism or (*2*) activation of these CD8Ts is

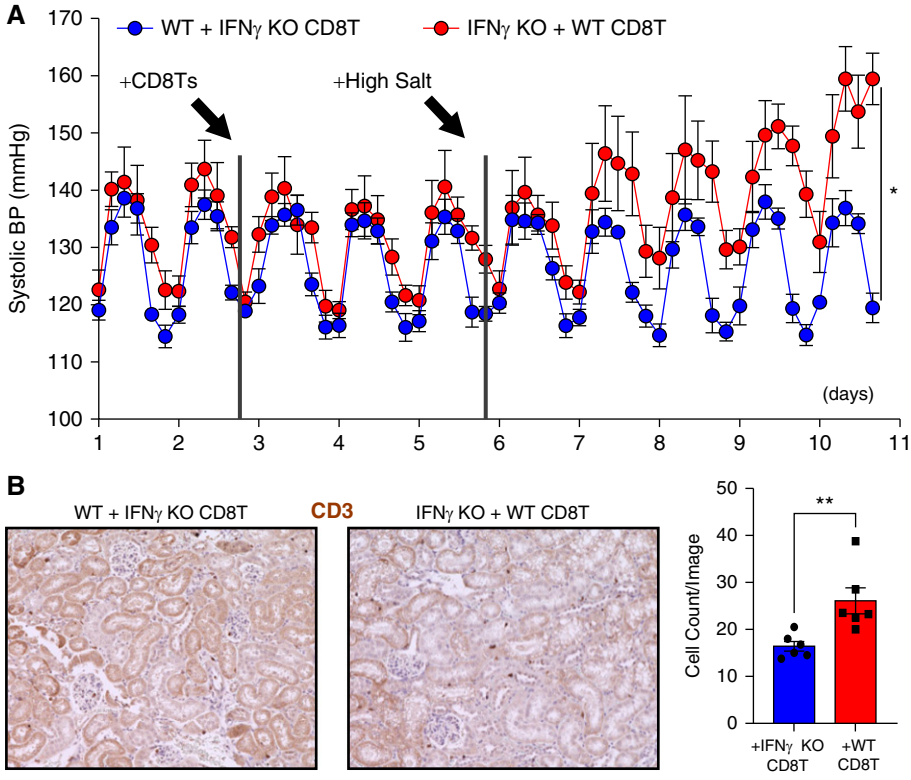

Figure 1. | **Interferon -γ contributes to CD8T-mediated salt-sensitive hypertension.** (A) Radiotelemetry recording of systolic BP in recipient wild-type (C57/B6) mice (blue) and IFN-γ knockout (B6 background) mice (red) after adoptive transfer of 1×10^7 CD8Ts freshly isolated from deoxycorticosterone acetate+salt-treated IFN-γ knockout or wild-type mice. All mice were purchased from the Jackson Laboratory. Data were recorded every 15 minutes and averaged to six time points a day; $n=5$–6 mice per group. Statistical analysis was performed by two-way ANOVA. Significance for interaction effect: $P<0.001$; time effect: $P<0.001$; and strain recipient: $P=0.02$. (B) At the end point of BP recording in (A), immunohistochemistry staining (DAB) of kidney sections was performed using CD3 specific monoclonal antibody after the protocol we have published previously (42,43). In the quantification bar graph, each dot shown is the mean of four images taken per sectioned kidney. $^{**}P<0.05$.

occurring *via* nonantigen-specific mechanisms, leading to IFN-γ production.

Some antigen-specific activation evidence includes this study by Rudemiller *et al.*, wherein knocking down CD247 (responsible for coupling antigen recognition to intracellular transduction) (49,50) in Dahl salt-sensitive rats led to reduced T-cell infiltration into the kidneys and reduced BP (51). Blocking antigen presentation by DCs resulted in blunted BP elevation in two murine models of hypertension (52). The study by Hevia *et al.* found that ablation of $CD11c^+$ antigen presenting cells prevented hypertension in an AngII+ high salt diet murine model (53). A few proposed antigens include isolevuglandin protein adducts (54,55), heat shock protein 70 (56,57), and Toll-like receptor (TLR) 4 or 2 activators such as C-reactive protein (58), uric acid (59), and others (60).

Experimental evidence suggests that such molecules may individually or collectively contribute to the role of T cells in hypertension; however, the presence of more than 3000 unique T-cell receptor sequences in AngII-induced hypertensive mice indicates that clonal expansion may not be occurring due to antigen presentation and recognition. Under certain conditions such as lymphopenia (61) or exposure to both IL-6 or IL-21 and IL-17 or IL-15 (62–65), CD8Ts can be activated without direct antigen presentation (66). IL-7 has also been implicated in the activation of autoimmune CD8Ts (62). In like manner, stimulation of T cells with phorbol myristate acetate (PMA) and the calcium ionophore ionomycin can bypass the T-cell membrane receptor complex and activate the T cell, leading to elevated expression of TNF-α and IFN-γ (67,68). Further research is needed to identify alternative pathways that may contribute to the activation of CD8Ts resulting in their infiltration within the kidney and stimulation of sodium retention.

NK Cells

Group 1 innate lymphocytes, NK cells arise from the same family as T and B cells (69) and have been implicated in both AngII-mediated hypertension and pulmonary hypertension. Depleting NK1.1 cells in WT C57BL/6 mice before AngII treatment resulted in blunted vascular dysfunction. Through a mechanism involving IFN-γ and T-bet, Kossmann *et al.* described a mutual activation pathway involving IL-12-secreting monocytes stimulating NK cells, leading to increased IFN-γ production and AngII-mediated hypertension (70). This relationship between monocyte and NK cell differentiation has been elucidated to involve TXb21 and IL-15R in a tumor environment (71). IL-12 driving NK production of IFN-γ has been described for some time (72).

In a rat model of pulmonary hypertension, NK cells have been proposed to play a protective role rather than pathologic (73); as such, the role of NK cells likely involves environment-specific driven regulation. Such tissue specific regulation has not yet been fully elucidated.

Monocytes and Macrophages

In addition to their role in promoting NK differentiation, monocytes (in particular macrophages) have been described as contributing to the pathogenesis of hypertension. An excellent review was provided by Rucker and Crowley; as such, we refer the reader to this publication for a thorough description of the contribution of macrophages to hypertension (74). Macrophages have been discovered to infiltrate and remain within the renal interstitium in the AngII model of hypertension, correlating with elevated TGF-β and monocyte chemotactic protein (MCP), even after cessation of AngII (75). LysM$^+$ monocytes have been described to contribute to—and be increased by—AngII-driven arterial hypertension through an experiment wherein depletion of LysM$^+$ myelomonocytic cells reduced AngII-induced BP elevation and blunted vascular dysfunction, nitric oxide bioactivity, and vascular oxidative stress. Reconstitution with WT monocytes but not neutrophils restored the AngII-mediated disease phenotype (76).

Due to the ability of immunosuppressants to, at minimum, reduce renal damage elicited in several animal models of hypertension and the correlation between macrophage infiltration and inflammation in models of hypertension (77,78), it would follow that at least a connection can be established between proinflammatory macrophages and tissue inflammation and damage in hypertension. Such a relationship was discussed in the excellent review by Rodriguez-Iturbe *et al*. (79) in reference to the studies by Bravo *et al*. (80) and Quiroz *et al*. (81), wherein macrophage numbers and oxidative stress were correlated in two different animal models of hypertension. The excellent review provided by Rucker and Crowley described the elucidated role of TNF-α from macrophages driving renal inflammation (74); as such, we will focus on the relationship between IFN-γ and macrophages in hypertension.

In addition to aiding in the transition from innate immunity to adaptive immunity, IFN-γ can influence its surroundings directly through actions such as local dilation of blood vessels allowing for immune cells to localize at sites of inflammation (21). However, of particular note is the effect of IFN-γ on macrophages. After release by other immune cells such as NK cells or T cells, IFN-γ stimulates macrophages and primes them for response by inducing a proinflammatory activation and stimulating the release of other cytokines causing the M1 phenotype seen in macrophages (82,83). The M1 phenotype name was derived to match Th1 release of IFN-γ; however, various cytokines and stimuli can affect the activation state of macrophages. Because stimulation with a combination of factors or high salt can shift the activation spectrum of macrophages, the classification of M1 and M2 phenotypes may become insufficient to distinguish the activation status (82,83). Generally, this classic activation by T cells through IFN-γ leads to macrophage production of inflammatory response genes and cytokines such as IL-12, IL-23, and NO generating the proinflammatory macrophage type (82,84). Macrophages also have the ability to secrete IFN-γ to the same extent as T cells *via* stimulation with certain cytokines such as through simultaneous activation by IL-12 and IL-18 (24), leading to the potential of generating IFN-γ in an autocrine manner (24,85). Accordingly, macrophage activation by IFN-γ is multifaceted in the source and the activation state on the basis of other factors and cytokines present.

Serum IFN-γ levels have been clinically shown to be a predictor of high systolic BP (86). With diastolic BP, there was not only significance with IFN-γ but also MCP-1 levels—after corrections for variables such as age and sex (86). Within models of hypertension with IFN-γ knocked out, such as AngII mini osmotic pump implantation, some labs have demonstrated a reduction in monocyte infiltration within the aorta and a reduction in MCP-1 and other cytokines such as macrophage inflammatory protein 1α, and P-selectin ligand (75,87). Due to MCP-1's role in recruiting macrophages to tissues, this suggests a potential interaction between hypertension, the renin-angiotensin system, and macrophage activation and recruitment to tissue.

Within the kidney, macrophage infiltration with hypertension has been noted by several research groups (75,88,89). Infiltration not only occurs during high levels of AngII but can also persist after AngII and systolic BP return to the normal range with lingering MCP-1 and TGF-β (75). Macrophages within the kidneys have been suggested to be involved in kidney injury seen with hypertension. For instance, depletion of macrophages with liposome-encapsulated clodronate has been demonstrated to reduce the kidney injury seen in Ang II-induced hypertension (88), and a similar observation was also found in Dahl salt-sensitive rats (88). Continuing to elucidate the ties between hypertension and macrophages remains, including the forms of activation macrophages may experience from IFN-γ release whether by other immune cells or other cytokines. Additionally, further research to expand on the role of infiltrating macrophages in the kidney and the damage induced through inflammation during hypertension is also needed.

Neutrophils

In the innate response to bacterial infection (such as *Salmonella*-induced colitis), neutrophils—phagocytic cells from the innate immune system (90)—function as a critical source of IFN-γ production, and depletion of these cells results in relief of many IFN-γ-induced disease symptoms (91,92). In contrast, depletion of neutrophils by administration of RB6–8C5 resulted in hypotension in WT C57BL/6 mice but not in IFN-γ or iNOS deficient mice, indicating neutrophils may also maintain physiologic BP *via* suppression of IFN-γ-dependent iNOS expression (93). Neutrophils play a role in the maintenance of homeostasis (93), and disruption could lead to elevated inflammation and BP dysregulation as evidenced by neutrophil/lymphocyte ratios functioning as predictors of hypertension (94–96); however, the specific relationship between neutrophil-derived IFN-γ and hypertension in an inflammatory situation is still unclear. Additionally, WT monocytes, not neutrophils, restored the AngII-mediated disease phenotype in LysM+-depleted mice (76). This excellent review by Araos *et al*. further describes

the role of neutrophils in hypertension, and we refer the reader here for further information (97).

Myeloid-Derived Suppressor Cells

Immature and heterogeneous myeloid cells have been recently demonstrated to regulate the immune system (77,98). Myeloid-derived suppressor cells (MDSCs) can be identified by expression of CD11B and Gr-1 surface antigens (99). In addition to playing a role in amino acid metabolism and ROS production, it is known that MDSCs are capable of downregulating immune-system facilitated T-cell response *in vivo* and *in vitro* (99). This alludes to a possible role of MSDCs in regulating BP. It had been previously observed in tumor models that the T-cell suppression acts by a mechanism that is independent of traditional MHC complex function—meaning there is no classic antigen presentation by these cells (100). In a recent study utilizing AngII-induced hypertension, it was discovered that MSDCs undergo a phenotypic change after the onset of hypertension; MDSCs harvested from hypertensive mice lost the expression of their surface CD80 and MHC-II (77). Concomitantly, these same cells exhibited increased expression of the IFN-γ receptor, IFN-γR1 (77). Hypertension results in an increase of $CD8^+$T-cells that express IFN-γ (43,45). This increase of T cells was attenuated by the presence of MDSCs (77). Further, antibody-mediated depletion of MDSCs resulted in a great increase of IFN-γ-expressing CD4T and CD8T cells (77). Although the complete mechanism of action of MDSCs remains unknown, there is evidence to support that MDSCs might induce development of regulatory T cells. These cells suppress immune response by inhibiting T-cell proliferation and cytokine expression (101). Although MDSCs may have other activities that have still not been discovered, these promising results point to the possibility that MDSCs are capable of inducing regulatory T-cell differentiation to suppress inappropriate T-cell proliferation and attenuate its effects.

DCs

$CD11c^+$ DCs have been demonstrated to play an important role in hypertension, wherein blocking antigen presentation by DCs *via* antagonizing CD80 and CD86 with CTLA4-Ig or B7 deficient mice blunted BP elevation in both the AngII and DOCA+salt models of hypertension (52). Depleting DCs in the mice prevented the development of hypertension in the AngII model, which could be restored by adoptive transfer of WT $CD11c^+$ antigen presenting cells (53). DCs are found activated in hypertensive animals to stimulate T-cell production of IFN-γ and IL-17A (102–104). However, the mechanisms regulating of DCs in hypertension is still under investigation. For example, sodium has been suggested to play a role in DC activation through amiloride-sensitive channels and the serum/glucocorticoid kinase 1 (105). Other evidence suggest that isoketal-modified proteins (proteins oxidatively modified by highly reactive γ-ketoaldehydes that accumulate in DCs during hypertension) are responsible for DC activation and subsequent T-cell activation in hypertension (102), and more recently, using DC-specific KO of AT1R, Lu *et al*. demonstrated a protective role of AT1 receptor on DCs against hypertension and T-cell activation (106). Nevertheless, how DCs are regulated in hypertension and what are the antigen(s) they present to activate T cells to exacerbate hypertension are critical questions that need to be further studied.

Limitations

The relationship between IFN-γ and tissue damage and fibrosis appears to be somewhat contextual, wherein blocking IFN-γ signaling in AngII-infused mice can reduce cardiac remodeling and immune cell infiltration (107,108), but alternative models propose a protective role for IFN-γ (109,110). Further exploration is needed for delineation of these effects. In addition, environmental exposure and subsequent gut microbiota alterations play a role directing the development of murine immune systems and host response to various challenges; as such, laboratory mice do not necessarily model clinical situations (111,112). The microbiota, in particular, has become increasingly implicated in regulating the murine response to hypertension in many experimental models (113,114) and may contribute to cardiovascular phenotypes in some immune-deficient mice. To this end, the preclinical established link between the immune cell activation and hypertension may involve gut microbiome alterations that regulate immune responses in such a way that are not inherently translatable to the clinic; however, such gut microbiome dysregulations have been described in clinical studies (115). We refer the reader to this excellent review by Avery *et al*. for further discussion of the gut microbiome and hypertension (116).

Clinical Translation

Clinical immunosuppression and hypertension have a rather complicated relationship due to adverse drug effects. In renal transplants, immunosuppressant calcineurin inhibitors have been linked to exacerbated BP (117), but BP post renal transplant has been ameliorated through non-nephrotoxic immunosuppression with mycophenolate mofetil with or without rapamycin (118). Immunosuppression (excluding calcineurin inhibitors) has been shown to be favorable in a clinical trial for patients with CKD (119). In agreement, several proinflammatory factors have been found to be upregulated in patients with treatment-resistant hypertension cases of CKD (120). Further clinical studies are needed to verify the efficacy of targeting key immune players in hypertension (121).

In Summary

IFN-γ plays a key role in the development and maintenance of hypertension. Global KO of IFN-γ results in blunted BP elevation in both the AngII and DOCA+salt models of hypertension. Potential mechanistic relationships between IFN-γ production and hypertension have been noted with NK cells, neutrophils, macrophages, DCs, and T cells (Figure 2). The source(s) of activation—particularly for CD8Ts—driving elevated IFN-γ production are still being researched; nonetheless, a potential novel mechanism

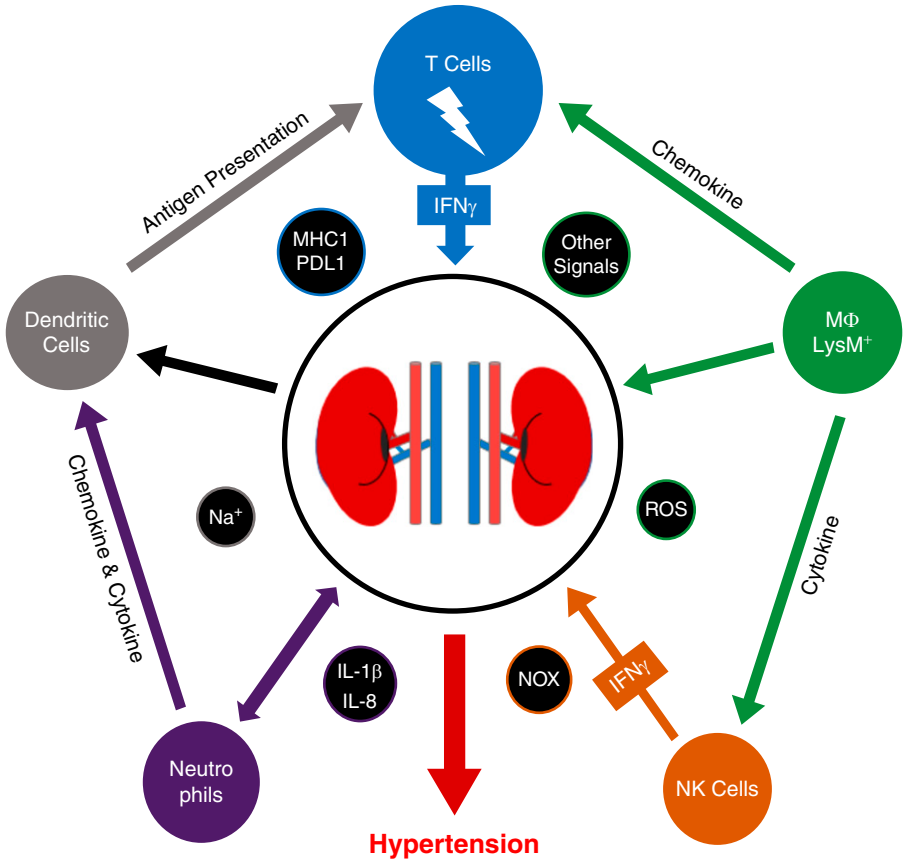

Figure 2. | **Graphical representation of proposed mechanisms by which immune cells contribute to the development of hypertension through enhanced immune cell infiltration, inflammation, and sodium retention**.

involving activators appears promising in light of the identification of an oligoclonal population of CD8Ts in the kidneys of hypertensive mice.

Disclosures

All authors have nothing to disclose.

Funding

This study was supported by NIH/NHLBI (Grant R01-HL146713) to S. Mu, AHA (Grant 15BGIA25730047) to S. Mu, UAMS Medical Research Endowment Awards to S. Mu, and the Systems Pharmacology and Toxicology Training Program (Grant T32-GM106999) to L. Benson.

Author Contributions

L.N. Benson and Y. Liu were responsible for the investigation; L.N. Benson, K.S. Deck, and C. Mora wrote the original draft of the manuscript; S. Mu, L.N. Benson, and Y. Liu were responsible for the methodology; and S. Mu was responsible for the conceptualization, funding acquisition, supervision, and validation, and reviewed and edited the manuscript.

References

1. Centers for Disease Control and Prevention: High Blood Pressure Symptoms and Causes. Available at: https://www.cdc.gov/bloodpressure/about.htm. Accessed January 17, 2022
2. World Health Organization: Hypertension. Available at: https://www.who.int/news-room/fact-sheets/detail/hypertension. Accessed January 17, 2022
3. Muntner P, Miles MA, Jaeger BC, Hannon Iii L, Hardy ST, Ostchega Y, Wozniak G, Schwartz JE: Blood pressure control among US adults, 2009 to 2012 through 2017 to 2020. *Hypertension* 79: 1971–1980, 2022 https://doi.org/10.1161/HYPERTENSIONAHA.122.19222
4. Ferdinand KC, Nasser SA: Management of essential hypertension. *Cardiol Clin* 35: 231–246, 2017 https://doi.org/10.1016/j.ccl.2016.12.005
5. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, White A, Cushman WC, White W, Sica D, Ferdinand K, Giles TD, Falkner B, Carey RM; American Heart Association Professional Education Committee: Resistant hypertension: Diagnosis, evaluation, and treatment: A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation* 117: e510–e526, 2008 https://doi.org/10.1161/CIRCULATIONAHA.108.189141
6. Saklayen MG, Deshpande NV: Timeline of history of hypertension treatment. *Front Cardiovasc Med* 3: 3, 2016 https://doi.org/10.3389/fcvm.2016.00003
7. Coffman TM: The inextricable role of the kidney in hypertension. *J Clin Invest* 124: 2341–2347, 2014 https://doi.org/10.1172/JCI72274
8. Rettig R: Does the kidney play a role in the aetiology of primary hypertension? Evidence from renal transplantation studies in rats and humans. *J Hum Hypertens* 7: 177–180, 1993
9. Guyton AC, Coleman TG, Cowley Jr AV, Scheel KW, Manning Jr RD, Norman Jr RA: Arterial pressure regulation. Overriding dominance of the kidneys in long-term regulation and in hypertension. *Am J Med* 52: 584–594, 1972 https://doi.org/10.1016/0002-9343(72)90050-2

10. Guyton AC: Blood pressure control—Special role of the kidneys and body fluids. *Science* 252: 1813–1816, 1991 https://doi.org/10.1126/science.2063193
11. Caillon A, Paradis P, Schiffrin EL: Role of immune cells in hypertension. *Br J Pharmacol* 176: 1818–1828, 2019 https://doi.org/10.1111/bph.14427
12. De Miguel C, Guo C, Lund H, Feng D, Mattson DL: Infiltrating T lymphocytes in the kidney increase oxidative stress and participate in the development of hypertension and renal disease. *Am J Physiol Renal Physiol* 300: F734–F742, 2011 https://doi.org/10.1152/ajprenal.00454.2010
13. Svendsen UG: Evidence for an initial, thymus independent and a chronic, thymus dependent phase of DOCA and salt hypertension in mice. *Acta Pathol Microbiol Scand A* 84: 523–528, 1976 https://doi.org/10.1111/j.1699-0463.1976.tb00150.x
14. Guzik TJ, Hoch NE, Brown KA, McCann LA, Rahman A, Dikalov S, Goronzy J, Weyand C, Harrison DG: Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. *J Exp Med* 204: 2449–2460, 2007 https://doi.org/10.1084/jem.20070657
15. Seniuk A, Thiele JL, Stubbe A, Oser P, Rosendahl A, Bode M, Meyer-Schwesinger C, Wenzel UO, Ehmke H: B6.Rag1 knockout mice generated at the Jackson Laboratory in 2009 show a robust wild-type hypertensive phenotype in response to Ang II (angiotensin II). *Hypertension* 75: 1110–1116, 2020 https://doi.org/10.1161/HYPERTENSIONAHA.119.13773
16. Ji H, Pai AV, West CA, Wu X, Speth RC, Sandberg K: Loss of resistance to angiotensin II-induced hypertension in the Jackson Laboratory recombination-activating gene null mouse on the C57BL/6J background. *Hypertension* 69: 1121–1127, 2017 https://doi.org/10.1161/HYPERTENSIONAHA.117.09063
17. Madhur MS, Kirabo A, Guzik TJ, Harrison DG: From rags to riches: Moving beyond Rag1 in studies of hypertension. *Hypertension* 75: 930–934, 2020 https://doi.org/10.1161/HYPERTENSIONAHA.119.14612PMC7067673
18. Muller DN, Shagdarsuren E, Park JK, Dechend R, Mervaala E, Hampich F, Fiebeler A, Ju X, Finckenberg P, Theuer J, Viedt C, Kreuzer J, Heidecke H, Haller H, Zenke M, Luft FC: Immunosuppressive treatment protects against angiotensin II-induced renal damage. *Am J Pathol* 161: 1679–1693, 2002 https://doi.org/10.1016/S0002-9440(10)64445-8
19. Kamat NV, Thabet SR, Xiao L, Saleh MA, Kirabo A, Madhur MS, Delpire E, Harrison DG, McDonough AA: Renal transporter activation during angiotensin-II hypertension is blunted in interferon-γ–/– and interleukin-17A–/– mice. *Hypertension* 65: 569–576, 2015 https://doi.org/10.1161/HYPERTENSIONAHA.114.04975
20. Fukao T, Matsuda S, Koyasu S: Synergistic effects of IL-4 and IL-18 on IL-12-dependent IFN-gamma production by dendritic cells. *J Immunol* 164: 64–71, 2000 https://doi.org/10.4049/jimmunol.164.1.64
21. Schroder K, Hertzog PJ, Ravasi T, Hume DA: Interferon-γ: An overview of signals, mechanisms and functions. *J Leukoc Biol* 75: 163–189, 2004 https://doi.org/10.1189/jlb.0603252
22. Frucht DM, Fukao T, Bogdan C, Schindler H, O'Shea JJ, Koyasu S: IFN-gamma production by antigen-presenting cells: Mechanisms emerge. *Trends Immunol* 22: 556–560, 2001 https://doi.org/10.1016/S1471-4906(01)02005-1
23. Flaishon L, Hershkoviz R, Lantner F, Lider O, Alon R, Levo Y, Flavell RA, Shachar I: Autocrine secretion of interferon γ negatively regulates homing of immature B cells. *J Exp Med* 192: 1381–1388, 2000 https://doi.org/10.1084/jem.192.9.1381
24. Munder M, Mallo M, Eichmann K, Modolell M: Murine macrophages secrete interferon gamma upon combined stimulation with interleukin (IL)-12 and IL-18: A novel pathway of autocrine macrophage activation. *J Exp Med* 187: 2103–2108, 1998 https://doi.org/10.1084/jem.187.12.2103
25. Shtrichman R, Samuel CE: The role of gamma interferon in antimicrobial immunity. *Curr Opin Microbiol* 4: 251–259, 2001 https://doi.org/10.1016/S1369-5274(00)00199-5
26. Wilck N, Balogh A, Markó L, Bartolomaeus H, Müller DN: The role of sodium in modulating immune cell function. *Nat Rev Nephrol* 15: 546–558, 2019 https://doi.org/10.1038/s41581-019-0167-y
27. Bhat MY, Solanki HS, Advani J, Khan AA, Keshava Prasad TS, Gowda H, Thiyagarajan S, Chatterjee A: Comprehensive network map of interferon gamma signaling. *J Cell Commun Signal* 12: 745–751, 2018 https://doi.org/10.1007/s12079-018-0486-y
28. Schoenborn JR, Wilson CB: Regulation of interferon-γ during innate and adaptive immune responses. *Adv Immunol* 96: 41–101, 2007 https://doi.org/10.1016/S0065-2776(07)96002-2
29. Jorgovanovic D, Song M, Wang L, Zhang Y: Roles of IFN-γ in tumor progression and regression: A review. *Biomark Res* 8: 49, 2020 https://doi.org/10.1186/s40364-020-00228-x
30. Panday A, Sahoo MK, Osorio D, Batra S: NADPH oxidases: An overview from structure to innate immunity-associated pathologies. *Cell Mol Immunol* 12: 5–23, 2015 https://doi.org/10.1038/cmi.2014.89
31. Nazarewicz RR, Dikalov SI: Mitochondrial ROS in the prohypertensive immune response. *Am J Physiol Regul Integr Comp Physiol* 305: R98–R100, 2013 https://doi.org/10.1152/ajpregu.00208.2013
32. Marvar PJ, Thabet SR, Guzik TJ, Lob HE, McCann LA, Weyand C, Gordon FJ, Harrison DG: Central and peripheral mechanisms of T-lymphocyte activation and vascular inflammation produced by angiotensin II-induced hypertension. *Circ Res* 107: 263–270, 2010 https://doi.org/10.1161/CIRCRESAHA.110.217299
33. Harrison DG, Marvar PJ, Titze JM: Vascular inflammatory cells in hypertension. *Front Physiol* 3: 128, 2012 https://doi.org/10.3389/fphys.2012.00128
34. Kuwano Y, Kawahara T, Yamamoto H, Teshima-Kondo S, Tominaga K, Masuda K, Kishi K, Morita K, Rokutan K: Interferon-gamma activates transcription of NADPH oxidase 1 gene and upregulates production of superoxide anion by human large intestinal epithelial cells. *Am J Physiol Cell Physiol* 290: C433–C443, 2006 https://doi.org/10.1152/ajpcell.00135.2005
35. Kamizato M, Nishida K, Masuda K, Takeo K, Yamamoto Y, Kawai T, Teshima-Kondo S, Tanahashi T, Rokutan K: Interleukin 10 inhibits interferon gamma- and tumor necrosis factor alpha-stimulated activation of NADPH oxidase 1 in human colonic epithelial cells and the mouse colon. *J Gastroenterol* 44: 1172–1184, 2009 https://doi.org/10.1007/s00535-009-0119-6
36. Marçal LE, Dias-da-Motta PM, Rehder J, Mamoni RL, Blotta MHSL, Whitney CB, Newburger PE, Costa FF, Saad STO, Condino-Neto A: Up-regulation of NADPH oxidase components and increased production of interferon-gamma by leukocytes from sickle cell disease patients. *Am J Hematol* 83: 41–45, 2008 https://doi.org/10.1002/ajh.20991
37. Bai A, Moss A, Rothweiler S, Longhi MS, Wu Y, Junger WG, Robson SC: Author correction: NADH oxidase-dependent CD39 expression by CD8+ T cells modulates interferon gamma responses via generation of adenosine. *Nat Commun* 11: 3036, 2020 https://doi.org/10.1038/s41467-020-16314-5
38. Bai A, Moss A, Rothweiler S, Serena Longhi M, Wu Y, Junger WG, Robson SC: NADH oxidase-dependent CD39 expression by CD8(+) T cells modulates interferon gamma responses *via* generation of adenosine [published correction appears in *Nat Commun* 11: 3036, 2020 10.1038/s41467-020-16314-5]. *Nat Commun* 6: 8819, 2015 https://doi.org/10.1038/ncomms9819
39. Kanhere A, Hertweck A, Bhatia U, Gökmen MR, Perucha E, Jackson I, Lord GM, Jenner RG: T-bet and GATA3 orchestrate Th1 and Th2 differentiation through lineage-specific targeting of distal regulatory elements. *Nat Commun* 3: 1268, 2012 https://doi.org/10.1038/ncomms2260
40. Zhang J, Patel MB, Griffths R, Mao A, Song YS, Karlovich NS, Sparks MA, Jin H, Wu M, Lin EE, Crowley SD: Tumor necrosis factor-α produced in the kidney contributes to angiotensin II-dependent hypertension. *Hypertension* 64: 1275–1281, 2014 https://doi.org/10.1161/HYPERTENSIONAHA.114.03863
41. Sun XN, Li C, Liu Y, Du LJ, Zeng MR, Zheng XJ, Zhang WC, Liu Y, Zhu M, Kong D, Zhou L, Lu L, Shen ZX, Yi Y, Du L, Qin M, Liu X, Hua Z, Sun S, Yin H, Zhou B, Yu Y, Zhang Z, Duan SZ: T-cell mineralocorticoid receptor controls blood pressure by regulating interferon-gamma. *Circ Res* 120: 1584–1597, 2017 https://doi.org/10.1161/CIRCRESAHA.116.310480

42. Liu Y, Rafferty TM, Rhee SW, Webber JS, Song L, Ko B, Hoover RS, He B, Mu S: $CD8^+$ T cells stimulate Na-Cl co-transporter NCC in distal convoluted tubules leading to salt-sensitive hypertension. *Nat Commun* 8: 14037, 2017 https://doi.org/10.1038/ncomms14037
43. Benson LN, Liu Y, Wang X, Xiong Y, Rhee SW, Guo Y, Deck KS, Mora CJ, Li LX, Huang L, Andrews JT, Qin Z, Hoover RS, Ko B, Williams RM, Heller DA, Jaimes EA, Mu S: The IFNγ-PDL1 pathway enhances CD8T-DCT interaction to promote hypertension. *Circ Res* 130: 1550–1564, 2022 https://doi.org/10.1161/CIRCRESAHA.121.320373
44. Ren J, Crowley SD: Role of T-cell activation in salt-sensitive hypertension. *Am J Physiol Heart Circ Physiol* 316: H1345–H1353, 2019 https://doi.org/10.1152/ajpheart.00096.2019
45. Itani HA, McMaster Jr WG, Saleh MA, Nazarewicz RR, Mikolajczyk TP, Kaszuba AM, Konior A, Prejbisz A, Januszewicz A, Norlander AE, Chen W, Bonami RH, Marshall AF, Poffenberger G, Weyand CM, Madhur MS, Moore DJ, Harrison DG, Guzik TJ: Activation of human T cells in hypertension: Studies of humanized mice and hypertensive humans. *Hypertension* 68: 123–132, 2016 https://doi.org/10.1161/HYPERTENSIONAHA.116.07237
46. Zhu J, Yamane H, Paul WE: Differentiation of effector CD4 T cell populations (*). *Annu Rev Immunol* 28: 445–489, 2010 https://doi.org/10.1146/annurev-immunol-030409-101212
47. Zhu J, Paul WE: CD4 T cells: Fates, functions, and faults. *Blood* 112: 1557–1569, 2008 https://doi.org/10.1182/blood-2008-05-078154
48. Trott DW, Thabet SR, Kirabo A, Saleh MA, Itani H, Norlander AE, Wu J, Goldstein A, Arendshorst WJ, Madhur MS, Chen W, Li CI, Shyr Y, Harrison DG: Oligoclonal CD8+ T cells play a critical role in the development of hypertension. *Hypertension* 64: 1108–1115, 2014 https://doi.org/10.1161/HYPERTENSIONAHA.114.04147
49. Irving BA, Chan AC, Weiss A: Functional characterization of a signal transducing motif present in the T cell antigen receptor zeta chain. *J Exp Med* 177: 1093–1103, 1993 https://doi.org/10.1084/jem.177.4.1093
50. Sussman JJ, Bonifacino JS, Lippincott-Schwartz J, Weissman AM, Saito T, Klausner RD, Ashwell JD: Failure to synthesize the T cell CD3-zeta chain: Structure and function of a partial T cell receptor complex. *Cell* 52: 85–95, 1988 https://doi.org/10.1016/0092-8674(88)90533-8
51. Rudemiller N, Lund H, Jacob HJ, Geurts AM, Mattson DL: CD247 modulates blood pressure by altering T-lymphocyte infiltration in the kidney. *Hypertension* 63: 559–564, 2014 https://doi.org/10.1161/HYPERTENSIONAHA.113.02191
52. Vinh A, Chen W, Blinder Y, Weiss D, Taylor WR, Goronzy JJ, Weyand CM, Harrison DG, Guzik TJ: Inhibition and genetic ablation of the B7/CD28 T-cell costimulation axis prevents experimental hypertension. *Circulation* 122: 2529–2537, 2010 https://doi.org/10.1161/CIRCULATIONAHA.109.930446
53. Hevia D, Araos P, Prado C, Fuentes Luppichini E, Rojas M, Alzamora R, Cifuentes-Araneda F, Gonzalez AA, Amador CA, Pacheco R, Michea L: Myeloid CD11c+ antigen-presenting cells ablation prevents hypertension in response to angiotensin II plus high-salt diet. *Hypertension* 71: 709–718, 2018 https://doi.org/10.1161/HYPERTENSIONAHA.117.10145
54. Xiao L, Patrick DM, Aden LA, Kirabo A: Mechanisms of isolevuglandin-protein adduct formation in inflammation and hypertension. *Prostaglandins Other Lipid Mediat* 139: 48–53, 2018 https://doi.org/10.1016/j.prostaglandins.2018.09.008
55. Aschner M, Nguyen TT, Sinitskii AI, Santamaría A, Bornhorst J, Ajsuvakova OP, da Rocha JBT, Skalny AV, Tinkov AA: Isolevuglandins (isoLGs) as toxic lipid peroxidation byproducts and their pathogenetic role in human diseases. *Free Radic Biol Med* 162: 266–273, 2021 https://doi.org/10.1016/j.freeradbiomed.2020.10.024
56. Pons H, Ferrebuz A, Quiroz Y, Romero-Vasquez F, Parra G, Johnson RJ, Rodriguez-Iturbe B: Immune reactivity to heat shock protein 70 expressed in the kidney is cause of salt-sensitive hypertension. *Am J Physiol Renal Physiol* 304: F289–F299, 2013 https://doi.org/10.1152/ajprenal.00517.2012
57. Rodriguez-Iturbe B, Lanaspa MA, Johnson RJ: The role of autoimmune reactivity induced by heat shock protein 70 in the pathogenesis of essential hypertension. *Br J Pharmacol* 176: 1829–1838, 2019 https://doi.org/10.1111/bph.14334
58. Liu N, Liu J, Ji Y, Lu P: Toll-like receptor 4 signaling mediates inflammatory activation induced by C-reactive protein in vascular smooth muscle cells. *Cell Physiol Biochem* 25: 467–476, 2010 https://doi.org/10.1159/000303052
59. Liu-Bryan R, Scott P, Sydlaske A, Rose DM, Terkeltaub R: Innate immunity conferred by Toll-like receptors 2 and 4 and myeloid differentiation factor 88 expression is pivotal to monosodium urate monohydrate crystal-induced inflammation. *Arthritis Rheum* 52: 2936–2946, 2005 https://doi.org/10.1002/art.21238
60. Rodríguez-Iturbe B, Pons H, Quiroz Y, Johnson RJ: The immunological basis of hypertension. *Am J Hypertens* 27: 1327–1337, 2014 https://doi.org/10.1093/ajh/hpu142
61. Jameson SC: Maintaining the norm: T-cell homeostasis. *Nat Rev Immunol* 2: 547–556, 2002 https://doi.org/10.1038/nri853
62. Gagnon J, Ramanathan S, Leblanc C, Cloutier A, McDonald PP, Ilangumaran S: IL-6, in synergy with IL-7 or IL-15, stimulates TCR-independent proliferation and functional differentiation of CD8+ T lymphocytes. *J Immunol* 180: 7958–7968, 2008 https://doi.org/10.4049/jimmunol.180.12.7958
63. Zeng R, Spolski R, Finkelstein SE, Oh S, Kovanen PE, Hinrichs CS, Pise-Masison CA, Radonovich MF, Brady JN, Restifo NP, Berzofsky JA, Leonard WJ: Synergy of IL-21 and IL-15 in regulating CD8+ T cell expansion and function. *J Exp Med* 201: 139–148, 2005 https://doi.org/10.1084/jem.20041057
64. Kishida T, Asada H, Itokawa Y, Cui FD, Shin-Ya M, Gojo S, Yasutomi K, Ueda Y, Yamagishi H, Imanishi J, Mazda O: Interleukin (IL)-21 and IL-15 genetic transfer synergistically augments therapeutic antitumor immunity and promotes regression of metastatic lymphoma. *Mol Ther* 8: 552–558, 2003 https://doi.org/10.1016/S1525-0016(03)00222-3
65. Davey GM, Starr R, Cornish AL, Burghardt JT, Alexander WS, Carbone FR, Surh CD, Heath WR: SOCS-1 regulates IL-15-driven homeostatic proliferation of antigen-naive CD8 T cells, limiting their autoimmune potential. *J Exp Med* 202: 1099–1108, 2005 https://doi.org/10.1084/jem.20050003
66. Ramanathan S, Gagnon J, Ilangumaran S: Antigen-nonspecific activation of CD8+ T lymphocytes by cytokines: Relevance to immunity, autoimmunity, and cancer. *Arch Immunol Ther Exp (Warsz)* 56: 311–323, 2008 https://doi.org/10.1007/s00005-008-0033-2
67. Hou H, Zhou Y, Yu J, Mao L, Bosco MJ, Wang J, Lu Y, Mao L, Wu X, Wang F, Sun Z: Establishment of the reference intervals of lymphocyte function in healthy adults based on IFN-γ secretion assay upon phorbol-12-myristate-13-acetate/ionomycin stimulation. *Front Immunol* 9: 172, 2018 https://doi.org/10.3389/fimmu.2018.00172
68. Crawford TQ, Jalbert E, Ndhlovu LC, Barbour JD: Concomitant evaluation of PMA+ionomycin-induced kinase phosphorylation and cytokine production in T cell subsets by flow cytometry. *Cytometry A* 85: 268–276, 2014 https://doi.org/10.1002/cyto.a.22444
69. Eissmann P: Natural Killer Cells. Available at: https://www.immunology.org/public-information/bitesized-immunology/cells/natural-killer-cells. Accessed January 17, 2022
70. Kossmann S, Schwenk M, Hausding M, Karbach SH, Schmidgen MI, Brandt M, Knorr M, Hu H, Kröller-Schön S, Schönfelder T, Grabbe S, Oelze M, Daiber A, Münzel T, Becker C, Wenzel P: Angiotensin II-induced vascular dysfunction depends on interferon-γ-driven immune cell recruitment and mutual activation of monocytes and NK-cells. *Arterioscler Thromb Vasc Biol* 33: 1313–1319, 2013 https://doi.org/10.1161/ATVBAHA.113.301437
71. Soderquest K, Powell N, Luci C, van Rooijen N, Hidalgo A, Geissmann F, Walzer T, Lord GM, Martín-Fontecha A: Monocytes control natural killer cell differentiation to effector phenotypes. *Blood* 117: 4511–4518, 2011 https://doi.org/10.1182/blood-2010-10-312264
72. D'Andrea A, Rengaraju M, Valiante NM, Chehimi J, Kubin M, Aste M, Chan SH, Kobayashi M, Young D, Nickbarg E, Chizzonite R, Wolf SF, Trinchieri G: Production of natural killer

cell stimulatory factor (interleukin 12) by peripheral blood mononuclear cells. *J Exp Med* 176: 1387–1398, 1992 https://doi.org/10.1084/jem.176.5.1387
73. Mickael C, Lee MH, Gu S, Graham BB: Comparing pulmonary hypertension severity between rat strains suggests right ventricle NK cells are protective. *Cardiovasc Res* 115: 699–700, 2019 https://doi.org/10.1093/cvr/cvy299
74. Justin Rucker A, Crowley SD: The role of macrophages in hypertension and its complications. *Pflugers Arch* 469: 419–430, 2017 https://doi.org/10.1007/s00424-017-1950-x
75. Ozawa Y, Kobori H, Suzaki Y, Navar LG: Sustained renal interstitial macrophage infiltration following chronic angiotensin II infusions. *Am J Physiol Renal Physiol* 292: F330–339, 2007 https://doi.org/10.1152/ajprenal.00059.2006
76. Wenzel P, Knorr M, Kossmann S, Stratmann J, Hausding M, Schuhmacher S, Karbach SH, Schwenk M, Yogev N, Schulz E, Oelze M, Grabbe S, Jonuleit H, Becker C, Daiber A, Waisman A, Münzel T: Lysozyme M-positive monocytes mediate angiotensin II-induced arterial hypertension and vascular dysfunction. *Circulation* 124: 1370–1381, 2011 https://doi.org/10.1161/CIRCULATIONAHA.111.034470
77. Shah KH, Shi P, Giani JF, Janjulia T, Bernstein EA, Li Y, Zhao T, Harrison DG, Bernstein KE, Shen XZ: Myeloid suppressor cells accumulate and regulate blood pressure in hypertension. *Circ Res* 117: 858–869, 2015 https://doi.org/10.1161/CIRCRESAHA.115.306539
78. Ko EA, Amiri F, Pandey NR, Javeshghani D, Leibovitz E, Touyz RM, Schiffrin EL: Resistance artery remodeling in deoxycorticosterone acetate-salt hypertension is dependent on vascular inflammation: Evidence from m-CSF-deficient mice. *Am J Physiol Heart Circ Physiol* 292: H1789–H1795, 2007 https://doi.org/10.1152/ajpheart.01118.2006
79. Rodríguez-Iturbe B, Vaziri ND, Herrera-Acosta J, Johnson RJ: Oxidative stress, renal infiltration of immune cells, and salt-sensitive hypertension: All for one and one for all. *Am J Physiol Renal Physiol* 286: F606–F616, 2004 https://doi.org/10.1152/ajprenal.00269.2003
80. Bravo J, Quiroz Y, Pons H, Parra G, Herrera-Acosta J, Johnson RJ, Rodríguez-Iturbe B: Vimentin and heat shock protein expression are induced in the kidney by angiotensin and by nitric oxide inhibition. *Kidney Int Suppl* 64: S46–S51, 2003 https://doi.org/10.1046/j.1523-1755.64.s86.9.x
81. Quiroz Y, Bravo J, Herrera-Acosta J, Johnson RJ, Rodríguez-Iturbe B: Apoptosis and NFkappaB activation are simultaneously induced in renal tubulointerstitium in experimental hypertension. *Kidney Int Suppl* 64: S27–S32, 2003 https://doi.org/10.1046/j.1523-1755.64.s86.6.x
82. Xue J, Schmidt SV, Sander J, Draffehn A, Krebs W, Quester I, De Nardo D, Gohel TD, Emde M, Schmidleithner L, Ganesan H, Nino-Castro A, Mallmann MR, Labzin L, Theis H, Kraut M, Beyer M, Latz E, Freeman TC, Ulas T, Schultze JL: Transcriptome-based network analysis reveals a spectrum model of human macrophage activation. *Immunity* 40: 274–288, 2014 https://doi.org/10.1016/j.immuni.2014.01.006
83. Zhang WC, Zheng XJ, Du LJ, Sun JY, Shen ZX, Shi C, Sun S, Zhang Z, Chen XQ, Qin M, Liu X, Tao J, Jia L, Fan HY, Zhou B, Yu Y, Ying H, Hui L, Liu X, Yi X, Liu X, Zhang L, Duan SZ: High salt primes a specific activation state of macrophages, M(Na). *Cell Res* 25: 893–910, 2015 https://doi.org/10.1038/cr.2015.87
84. Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, Locati M: The chemokine system in diverse forms of macrophage activation and polarization. *Trends Immunol* 25: 677–686, 2004 https://doi.org/10.1016/j.it.2004.09.015
85. Gessani S, Belardelli F: IFN-γ expression in macrophages and its possible biological significance. *Cytokine Growth Factor Rev* 9: 117–123, 1998 https://doi.org/10.1016/S1359-6101(98)00007-0
86. Mirhafez SR, Mohebati M, Feiz Disfani M, Saberi Karimian M, Ebrahimi M, Avan A, Eslami S, Pasdar A, Rooki H, Esmaeili H, Ferns GA, Ghayour-Mobarhan M: An imbalance in serum concentrations of inflammatory and anti-inflammatory cytokines in hypertension. *J Am Soc Hypertens* 8: 614–623, 2014 https://doi.org/10.1016/j.jash.2014.05.007
87. Parissis JT, Korovesis S, Giazitzoglou E, Kalivas P, Katritsis D: Plasma profiles of peripheral monocyte-related inflammatory markers in patients with arterial hypertension. Correlations with plasma endothelin-1. *Int J Cardiol* 83: 13–21, 2002 https://doi.org/10.1016/S0167-5273(02)00021-9
88. Huang L, Wang A, Hao Y, Li W, Liu C, Yang Z, Zheng F, Zhou MS: Macrophage depletion lowered blood pressure and attenuated hypertensive renal injury and fibrosis. *Front Physiol* 9: 473, 2018 https://doi.org/10.3389/fphys.2018.00473
89. Moore JP, Vinh A, Tuck KL, Sakkal S, Krishnan SM, Chan CT, Lieu M, Samuel CS, Diep H, Kemp-Harper BK, Tare M, Ricardo SD, Guzik TJ, Sobey CG, Drummond GR: M2 macrophage accumulation in the aortic wall during angiotensin II infusion in mice is associated with fibrosis, elastin loss, and elevated blood pressure. *Am J Physiol Heart Circ Physiol* 309: H906–H917, 2015 https://doi.org/10.1152/ajpheart.00821.2014
90. Rosales C: Neutrophil: A cell with many roles in inflammation or several cell types? *Front Physiol* 9: 113, 2018 https://doi.org/10.3389/fphys.2018.00113
91. Netea MG, Fantuzzi G, Kullberg BJ, Stuyt RJL, Pulido EJ, McIntyre Jr RC, Joosten LAB, Van der Meer JWM, Dinarello CA: Neutralization of IL-18 reduces neutrophil tissue accumulation and protects mice against lethal *Escherichia coli* and *Salmonella typhimurium* endotoxemia. *J Immunol* 164: 2644–2649, 2000 https://doi.org/10.4049/jimmunol.164.5.2644
92. Kak G, Raza M, Tiwari BK: Interferon-gamma (IFN-γ): Exploring its implications in infectious diseases. *Biomol Concepts* 9: 64–79, 2018 https://doi.org/10.1515/bmc-2018-0007
93. Morton J, Coles B, Wright K, Gallimore A, Morrow JD, Terry ES, Anning PB, Morgan BP, Dioszeghy V, Kühn H, Chaitidis P, Hobbs AJ, Jones SA, O'Donnell VB: Circulating neutrophils maintain physiological blood pressure by suppressing bacteria and IFNgamma-dependent iNOS expression in the vasculature of healthy mice. *Blood* 111: 5187–5194, 2008 https://doi.org/10.1182/blood-2007-10-117283
94. Aydin M, Yuksel M, Yildiz A, Polat N, Bilik MZ, Akil MA, Acet H, Demir M, Inci U, Toprak N: Association between the neutrophil to lymphocyte ratio and prehypertension. *Bratisl Lek Listy* 116: 475–479, 2015 https://doi.org/10.4149/BLL_2015_090
95. Tatsukawa Y, Hsu WL, Yamada M, Cologne JB, Suzuki G, Yamamoto H, Yamane K, Akahoshi M, Fujiwara S, Kohno N: White blood cell count, especially neutrophil count, as a predictor of hypertension in a Japanese population. *Hypertens Res* 31: 1391–1397, 2008 https://doi.org/10.1291/hypres.31.1391
96. Liu X, Zhang Q, Wu H, Du H, Liu L, Shi H, Wang C, Xia Y, Guo X, Li C, Bao X, Su Q, Sun S, Wang X, Zhou M, Jia Q, Zhao H, Song K, Niu K: Blood neutrophil to lymphocyte ratio as a predictor of hypertension. *Am J Hypertens* 28: 1339–1346, 2015 https://doi.org/10.1093/ajh/hpv034
97. Araos P, Figueroa S, Amador CA: The role of neutrophils in hypertension. *Int J Mol Sci* 21: 8536, 2020 https://doi.org/10.3390/ijms21228536
98. Veglia F, Sanseviero E, Gabrilovich DI: Myeloid-derived suppressor cells in the era of increasing myeloid cell diversity. *Nat Rev Immunol* 21: 485–498, 2021 https://doi.org/10.1038/s41577-020-00490-y
99. Peranzoni E, Zilio S, Marigo I, Dolcetti L, Zanovello P, Mandruzzato S, Bronte V: Myeloid-derived suppressor cell heterogeneity and subset definition. *Curr Opin Immunol* 22: 238–244, 2010 https://doi.org/10.1016/j.coi.2010.01.021
100. Gallina G, Dolcetti L, Serafini P, De Santo C, Marigo I, Colombo MP, Basso G, Brombacher F, Borrello I, Zanovello P, Bicciato S, Bronte V: Tumors induce a subset of inflammatory monocytes with immunosuppressive activity on CD8+ T cells. *J Clin Invest* 116: 2777–2790, 2006 https://doi.org/10.1172/JCI28828
101. Kondělková K, Vokurková D, Krejsek J, Borská L, Fiala Z, Ctirad A: Regulatory T cells (TREG) and their roles in immune system with respect to immunopathological disorders. *Acta Medica (Hradec Kralove)* 53: 73–77, 2010 https://doi.org/10.14712/18059694.2016.63

102. Kirabo A, Fontana V, de Faria APC, Loperena R, Galindo CL, Wu J, Bikineyeva AT, Dikalov S, Xiao L, Chen W, Saleh MA, Trott DW, Itani HA, Vinh A, Amarnath V, Amarnath K, Guzik TJ, Bernstein KE, Shen XZ, Shyr Y, Chen SC, Mernaugh RL, Laffer CL, Elijovich F, Davies SS, Moreno H, Madhur MS, Roberts 2nd J, Harrison DG: DC isoketal-modified proteins activate T cells and promote hypertension. *J Clin Invest* 124: 4642–4656, 2014 https://doi.org/10.1172/JCI74084
103. Barbaro NR, Foss JD, Kryshtal DO, Tsyba N, Kumaresan S, Xiao L, Mernaugh RL, Itani HA, Loperena R, Chen W, Dikalov S, Titze JM, Knollmann BC, Harrison DG, Kirabo A: Dendritic cell amiloride-sensitive channels mediate sodium-induced inflammation and hypertension. *Cell Rep* 21: 1009–1020, 2017 https://doi.org/10.1016/j.celrep.2017.10.002
104. Lu X, Rudemiller NP, Privratsky JR, Ren J, Wen Y, Griffiths R, Crowley SD: Classical dendritic cells mediate hypertension by promoting renal oxidative stress and fluid retention. *Hypertension* 75: 131–138, 2020 https://doi.org/10.1161/HYPERTENSIONAHA.119.13667
105. Van Beusecum JP, Barbaro NR, McDowell Z, Aden LA, Xiao L, Pandey AK, Itani HA, Himmel LE, Harrison DG, Kirabo A: High salt activates CD11c + antigen-presenting cells *via* SGK (serum glucocorticoid kinase) 1 to promote renal inflammation and salt-sensitive hypertension. *Hypertension* 74: 555–563, 2019 https://doi.org/10.1161/HYPERTENSIONAHA.119.12761
106. Lu X, Zhang J, Wen Y, Ren J, Griffiths R, Rudemiller NP, Ide S, Souma T, Crowley SD: Type 1 angiotensin receptors on CD11c-expressing cells protect against hypertension by regulating dendritic cell-mediated T cell activation. *Hypertension* 79: 1227–1236, 2022 https://doi.org/10.1161/HYPERTENSIONAHA.121.18734
107. Han Y-L, Li Y-L, Jia L-X, Cheng J-Z, Qi Y-F, Zhang H-J, Du J: Reciprocal interaction between macrophages and T cells stimulates IFN-γ and MCP-1 production in Ang II-induced cardiac inflammation and fibrosis. *PLoS One* 7: e35506, 2012 https://doi.org/10.1371/journal.pone.0035506
108. Markó L, Kvakan H, Park JK, Qadri F, Spallek B, Binger KJ, Bowman EP, Kleinewietfeld M, Fokuhl V, Dechend R, Müller DN: Interferon-γ signaling inhibition ameliorates angiotensin II-induced cardiac damage. *Hypertension* 60: 1430–1436, 2012 https://doi.org/10.1161/HYPERTENSIONAHA.112.199265
109. Garcia AG, Wilson RM, Heo J, Murthy NR, Baid S, Ouchi N, Sam F: Interferon-γ ablation exacerbates myocardial hypertrophy in diastolic heart failure. *Am J Physiol Heart Circ Physiol* 303: H587–H596, 2012 https://doi.org/10.1152/ajpheart.00298.2012
110. Kimura A, Ishida Y, Furuta M, Nosaka M, Kuninaka Y, Taruya A, Mukaida N, Kondo T: Protective roles of interferon-γ in cardiac hypertrophy induced by sustained pressure overload. *J Am Heart Assoc* 7: e008145, 2018 https://doi.org/10.1161/JAHA.117.008145
111. Ivanov II, Atarashi K, Manel N, Brodie EL, Shima T, Karaoz U, Wei D, Goldfarb KC, Santee CA, Lynch SV, Tanoue T, Imaoka A, Itoh K, Takeda K, Umesaki Y, Honda K, Littman DR: Induction of intestinal Th17 cells by segmented filamentous bacteria. *Cell* 139: 485–498, 2009 https://doi.org/10.1016/j.cell.2009.09.033
112. Rosshart SP, Herz J, Vassallo BG, Hunter A, Wall MK, Badger JH, McCulloch JA, Anastasakis DG, Sarshad AA, Leonardi I, Collins N, Blatter JA, Han SJ, Tamoutounour S, Potapova S, Foster St Claire MB, Yuan W, Sen SK, Dreier MS, Hild B, Hafner M, Wang D, Iliev ID, Belkaid Y, Trinchieri G, Rehermann B: Laboratory mice born to wild mice have natural microbiota and model human immune responses. *Science* 365: eaaw4361, 2019 https://doi.org/10.1126/science.aaw4361
113. Jama HA, Kaye DM, Marques FZ: The gut microbiota and blood pressure in experimental models. *Curr Opin Nephrol Hypertens* 28: 97–104, 2019 https://doi.org/10.1097/MNH.0000000000000476
114. de la Visitación N, Robles-Vera I, Toral M, Gómez-Guzmán M, Sánchez M, Moleón J, González-Correa C, Martín-Morales N, O'Valle F, Jiménez R, Romero M, Duarte J: Gut microbiota contributes to the development of hypertension in a genetic mouse model of systemic lupus erythematosus. *Br J Pharmacol* 178: 3708–3729, 2021 https://doi.org/10.1111/bph.15512
115. Li J, Zhao F, Wang Y, Chen J, Tao J, Tian G, Wu S, Liu W, Cui Q, Geng B, Zhang W, Weldon R, Auguste K, Yang L, Liu X, Chen L, Yang X, Zhu B, Cai J: Gut microbiota dysbiosis contributes to the development of hypertension. *Microbiome* 5: 14, 2017 https://doi.org/10.1186/s40168-016-0222-x
116. Avery EG, Bartolomaeus H, Maifeld A, Marko L, Wiig H, Wilck N, Rosshart SP, Forslund SK, Müller DN: The gut microbiome in hypertension: Recent advances and future perspectives. *Circ Res* 128: 934–950, 2021 https://doi.org/10.1161/CIRCRESAHA.121.318065
117. Divac N, Naumović R, Stojanović R, Prostran M: The role of immunosuppressive medications in the pathogenesis of hypertension and efficacy and safety of antihypertensive agents in kidney transplant recipients. *Curr Med Chem* 23: 1941–1952, 2016 https://doi.org/10.2174/0929867323666151221150052
118. Morales JM: Influence of the new immunosuppressive combinations on arterial hypertension after renal transplantation. *Kidney Int Suppl* 62: S81–S87, 2002 https://doi.org/10.1046/j.1523-1755.62.s82.16.x
119. Ferro CJ, Edwards NC, Hutchison C, Cockwell P, Steeds RP, Savage CO, Townend JN, Harper L: Does immunosuppressant medication lower blood pressure and arterial stiffness in patients with chronic kidney disease? An observational study. *Hypertens Res* 34: 113–119, 2010 https://doi.org/10.1038/hr.2010.193
120. Chen J, Bundy JD, Hamm LL, Hsu CY, Lash J, Miller ER, Thomas G, Cohen DL, Weir MR, Raj DS, Chen HY, Xie D, Rao P, Wright JT, Rahman M, He J. Inflammation and apparent treatment-resistant hypertension in patients with chronic kidney disease. *Hypertension* 73: 785–793, 2019 https://doi.org/10.1161/HYPERTENSIONAHA.118.12358
121. Bomfim GF, Cau SBA, Bruno AS, Fedoce AG, Carneiro FS: Hypertension: A new treatment for an old disease? Targeting the immune system. *Br J Pharmacol* 176: 2028–2048, 2019 https://doi.org/10.1111/bph.14436

Received: May 26, 2022 **Accepted:** October 19, 2022