INTERACTIONS BETWEEN THE IMMUNE AND RENIN ANGIOTENSIN SYSTEMS IN HYPERTENSION

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INTRODUCTION

The renin-angiotensin system (RAS) is an essential regulator of blood pressure homeostasis. The primary effector molecule of the RAS is angiotensin (Ang) II, an eight-amino acid peptide that initiates tissue-specific processes via binding to the type 1 or 2 angiotensin II receptors (AT_1 or AT_2). The AT_1 receptor is a G-protein coupled receptor expressed in most tissues throughout the body. While the rodent expresses 2 AT_1 receptor isoforms, AT_{1A} and AT_{1B}, the closest functional homolog to the human AT_1 receptor in most rodent tissues is AT_{1A}. The most widely appreciated functions of Ang II signaling via the AT_1 receptor are to augment global vascular tone and promote sodium retention in the kidney, thus playing a crucial role in acute and long-term maintenance of blood pressure.[1, 2] Ang II elicits these effects by increasing the contractility of vascular smooth muscle, promoting the release of aldosterone from the adrenal cortex, and directly increasing the expression and/or activity of solute transporters in the renal tubules that promote sodium reabsorption. As such, blockade of the renin-angiotensin system (RAS) has been a mainstay in the treatment for hypertension and its complications, including cardiovascular and kidney disease.[2, 3] Although the etiology of essential hypertension is unclear, inhibition of the RAS is effective in reducing blood pressure in a wide variety of patients, which suggests that inappropriate RAS activation is common in the pathogenesis of this idiopathic condition. Global RAS inhibitors ameliorate hypertension by blocking the production of Ang II or by preventing activation of the AT_1 receptor. These medications are "global" inhibitors in the sense that they disrupt AT_1 receptor signaling concomitantly in all tissues.

The ongoing effort to uncover novel pathogenic mechanisms of hypertension has revealed a significant role for the immune system.[4] Although augmentation of hypertension and associated organ damage by the immune system has been appreciated for over 5 decades, intense experimental investigation of this phenomenon commenced roughly 15 years ago. Over this period, leukocytes have been shown to modulate the hypertensive response in a plethora of experimental models.[5] Immune cells infiltrate cardiovascular control centers that regulate blood pressure, such as the kidney, blood vessels, and brain. There they produce

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DISCLOSURES
None.

factors that promote local inflammation and sodium retention and mediate tissue injury, ultimately leading to elevated blood pressure. Human data regarding this phenomenon are currently sparse, yet indicative of an immune-related component to hypertension.[6, 7]

The dominant angiotensin receptor expressed on immune cells is the AT_1 receptor, and their inflammatory functions are altered by its activation.[8–10] Furthermore activation of the AT_1 receptor on distinct cell populations within the immune compartment has effects on blood pressure and/or renal damage that contrast starkly with AT_1 receptor actions in the kidney and vasculature.[11] These emerging data suggest that global inhibition of the RAS may not be optimal in the treatment of hypertension, and that understanding cell-specific actions of the AT_1 receptor in the setting of hypertension may guide novel therapeutics that manipulate the RAS via tissue-specific strategies. The aim of this review is to describe the interplay between the renin-angiotensin and immune systems in hypertension.

THE IMMUNE SYSTEM, THE AT_1 RECEPTOR, AND HYPERTENSION

The immune system is composed of two arms: the innate immune system, which mounts a rapid, non-specific response to a wide array of pathogens, and the adaptive immune system, which executes an antigen-specific response subsequent to the innate response. Myeloid cells largely comprise the innate arm and trigger engagement of the adaptive immune response. By contrast, lymphoid cells contribute primarily to adaptive immunity. The myeloid compartment contains a vast collection of immune cells, including monocytes, macrophages, and dendritic cells, with varying capacities to fight invading pathogens, while the lymphoid compartment is largely comprised of two cell types, T and B lymphocytes.

A link between the immune system and hypertension has long been recognized, as inflammatory cells were shown to traffick to organs that regulate blood pressure decades ago. For example, Sommers *et al.* recognized a positive correlation between lymphocyte aggregation and the degree of arteriolar nephrosclerosis in kidney biopsies from hypertensive patients.[12] Experimentally in 1967, monocytes were shown to accumulate in the aortic intima as early as 4 hours after hypertension was induced in rats by aortic constriction.[13] Moreover in 1969, studies of kidney glomeruli in the hypertensive rat revealed a marked accrual of monocytes compared to normotensive controls.[14] Olsen then showed that transfer of splenocytes from a hypertensive rat could recapitulate hypertension in a normotensive rat.[15] Inversely, Svendsen reported that athymic mice were protected from DOCA hypertension.[16] Since these initial observations and in several hypertensive models, immune cells have been implicated in vascular injury, kidney damage, and inappropriate sodium retention – all pathological amplifiers of blood pressure elevation. Moreover, hypertension emerges in autoimmune disorders such as systemic lupus erythematosus (SLE), and blocking inflammatory responses in SLE can dramatically reduce blood pressure.[17, 18]

As RAS stimulation and immune system activation both contribute to the pathogenesis of hypertension, several investigators have explored whether ligation of AT_1 receptors on immune cells can modulate blood pressure and/or target organ damage in hypertension. Bone marrow transplant (BMT) experiments, utilizing donor mice that are genetically

deficient of the dominant rodent AT_1 receptor isoform, AT_{1A} ($Agtr1a^{-/-}$), have demonstrated context-specific effects of the immune AT_1 receptor in hypertension and cardiovascular disease. One such study employed the Tsukuba mouse, which carries the human renin and angiotensinogen transgenes. This mouse is a model of RAS-mediated, persistent hypertension and atherosclerosis precipitated by an atherogenic diet.[19] Tsukuba mice underwent BMT using $Agtr1a^{-/-}$ or $Agtr1a^{+/+}$ donors and were placed on the atherogenic diet 6 weeks later. The level of hypertension was similar between Tsukuba mice receiving $Agtr1a^{-/-}$ or $Agtr1a^{+/+}$ BMCs, but the absence of the AT_{1A} receptor on BM cells increased the severity of atherosclerotic lesions in the aorta.[20] Our lab utilized BMT to explore the actions of AT_{1A} receptors on immune cells in Ang II-induced hypertension.[21] Although the absence of AT_{1A} on bone marrow cells did not affect baseline blood pressure, the mice that received $Atgr1a^{-/-}$ BM cells had an augmented hypertensive response to chronic Ang II infusion compared to mice receiving $Atgr1a^{+/+}$ BM cells, along with exaggerated accumulation of macrophages and T cells in the hypertensive kidney. Together, these studies pointed to a protective effect of the immune cell AT_1 receptor in hypertension and associated complications.

AT_{1A} receptors on bone marrow-derived cells can similarly ameliorate kidney damage even in the absence of hypertension. For example, in a RAS-dependent model of kidney fibrosis induced by unilateral ureteral obstruction (UUO), transplantation of $Agtr1a^{-/-}$ bone marrow into WT mice induced greater renal expression of pro-fibrotic genes and more severe interstitial fibrosis compared to WT transplant controls.[22] Ma and Fogo similarly found that AT_{1A} receptor-deficient mice had exaggerated obesity-dependent kidney damage, attributed to enhanced pro-inflammatory macrophage responses.[23] By contrast, in the apolipoprotein E deficient mouse model of atherosclerosis, reconstitution with $Agtr1a^{-/-}$ BM cells significantly blunted the formation of atherosclerotic lesions in the aorta and kidney,[24, 25] consistent with pathogenic actions of AT_1 receptors on bone marrow-derived cells.

We speculate that these conflicting actions of the immune cell AT_1 receptor in hypertension and cardiovascular disease may relate to the specific subsets of immune cells involved in mediating tissue pathology in the respective models. To this point, a variety of immune cells have been implicated in regulating blood pressure and the extent of tissue injury in hypertension. These include both pro- and anti-inflammatory subsets that are proposed to have deleterious and salutary functions, respectively, in target organ pathology.[26] Because the bone marrow transplant studies mentioned above abrogated AT_{1A} receptor signaling on all immune cell populations, more precise approaches are required to determine *in vivo* how AT_1 receptor signaling influences the function of particular immune cell subsets in the setting of hypertension. We have pursued cell-specific, conditional deletion strategies to confront this problem, and others have utilized adoptive transfer approaches. Below we will review the current understanding of how particular myeloid and lymphoid subsets participate in the pathogenesis of hypertension and discuss recent findings regarding the effects of AT_{1A} receptor activation on immune cell function in this setting. We will focus predominantly on monocytes, macrophages, and T cells, as the majority of studies in the field of hypertension to date have generated data regarding these immune cell subsets.

MONOCYTES/MACROPHAGES, THE AT$_1$ RECEPTOR, AND HYPERTENSION

Monocytes are a subset of circulating myeloid cells that originate in the bone marrow and play a pivotal role in immunity during homeostasis and disease.[27] The stratification of murine monocytes into functionally distinct populations is continually revised, but one schema parses monocytes based on their expression of the surface marker Ly6C.[28] Robust expression of Ly6C (Ly6C^{hi}) designates a pro-inflammatory subset of monocytes that are heavily recruited to sites of inflammation and produce reactive oxygen species (ROS), interleukin 1β (IL-1β), and tumor necrosis factor-α (TNF). The human counterpart is the pro-inflammatory CD14^{hi}CD16$^-$ monocyte population. Minimal or no expression of Ly6C (Ly6C^{lo}) identifies an anti-inflammatory subset of murine monocytes said to "patrol" the luminal endothelium under homeostatic conditions in order to rapidly detect vascular insult.[29] In humans, these patrolling monocytes are identified by CD14^{lo}CD16^{hi} double positivity. Besides their direct inflammatory capacity, monocytes have long been thought to maintain appropriate levels of resident tissue macrophages via differentiation, although recent evidence suggests a more complex relationship between circulating and resident tissue myeloid cell pools.[30, 31]

Macrophages are resident tissue phagocytes that play a critical role in innate immunity. Apart from their phagocytic capacity, macrophages release inflammatory mediators and recruit and program other immune cells. In one paradigm, macrophages are divided into two subsets, M1 and M2.[31] M1, or classically activated, macrophages are pro-inflammatory and, like their Ly6C^{hi} monocyte precursors, release the cytokines IL-1β and TNF and produce ROS. M2, or alternatively activated, macrophages display an ant-inflammatory phenotype, are involved in tissue repair, and elaborate regulatory cytokines such as interleukin-10 (IL-10) and transforming growth factor β (TGFβ).[32] Although monocytes and macrophages are essential for proper immune homeostasis, their dysregulation contributes to diverse pathologies ranging from classic autoimmune diseases to hypertension.[4, 33]

Both experimental and clinical data point to a key role for monocytes and macrophages in hypertension. The monocyte chemokine CCL2 (MCP-1) is highly expressed in the kidney and vasculature during hypertension,[34, 35] leading to the infiltration of monocytes expressing CCR2, the receptor for MCP-1, into these tissues.[36, 37] Accordingly, depletion of LysM-expressing monocytes blunts the chronic hypertensive response to Ang II,[38] whereas inhibition of MCP-1 or CCR2 blunts renal and aortic myeloid cell invasion and attenuates both hypertension and consequent tissue injury.[37, 39] Within the target organ, monocytes and macrophages instigate and sustain inflammation that causes tissue damage and augments blood pressure elevation. In the Ang II hypertension model, pro-inflammatory monocytes and macrophages expressing M1 markers infiltrate the aorta by day 7,[40] whereas later, at day 14, these aortic macrophages favor an M2 phenotype featuring CD206 expression.[34] Whether this phenotypic shift reflects temporal plasticity of the initial M1 macrophage infiltrate or its replacement by M2 macrophages is unclear, but there is precedent for plasticity of macrophages in tissue injury and repair.[32, 41] In clinical hypertension, histological analysis of post-mortem kidneys show a significant increase in cortical density

of CD68^{+} monocytes/macrophages compared to normotensive controls.[42] Moreover, circulating monocytes from hypertensive patients have an enhanced pro-inflammatory phenotype when stimulated ex-vivo,[43] and circulating levels of inflammatory chemokines are elevated in hypertensive patients.[44–46]

Pro-inflammatory monocytes/macrophages have the capacity to potentiate hypertension through multiple mechanisms. As part of the innate immune response, myeloid cells can promote remodeling in the vasculature and epithelial cell injury in the kidney, prompting endothelial dysfunction and impairing appropriate excretion of sodium in the setting of hypertension. However, even in the absence of renal injury, M1 macrophages can promote sodium retention in the kidney through the elaboration of ROS and/or inflammatory cytokines including TNF or IL-1β. Regarding the role of ROS, ablation of monocytes/ macrophages significantly reduces aortic superoxide production, vascular dysfunction, and blood pressure during Ang II-induced hypertension.[38] Inversely, adoptive transfer of WT, but not NADPH oxidase-null monocytes, can restore vascular oxidative stress and hypertension.[47] Complementing their intrinsic production of ROS, infiltrating monocytes in the aorta can uncouple NOS3, thus amplifying vascular oxidative stress in hypertension.[40]

Regarding the role of macrophage cytokines, TNF augments salt appetite and promotes sodium reabsorption in the thick ascending limb of the nephron by suppressing NOS3 expression.[48–50] TNF deficiency therefore ameliorates hypertension during RAS activation.[47, 48] Our recent studies suggest that macrophages may similarly potentiate hypertension through their secretion of IL-1.[51] Accordingly, mice lacking the receptor for IL-1α and β have enhanced accumulation of nitric oxide (NO)-expressing macrophages in the kidney early in the course of hypertension and are partially protected from Ang II-induced blood pressure elevation. In our model, IL-1 receptor stimulation releases the NKCC2 sodium co-transporter from tonic inhibition by nitric oxide (NO) leading to enhanced salt retention during RAS activation. IL-1 receptor activation appears to attenuate NO secretion from intra-renal macrophages by curtailing NOS2 expression. Thus, monocytes/macrophages can promote hypertension via the interlocking actions of ROS and M1 cytokines. Nevertheless, the effects of these M1 cytokines on blood pressure may depend on their absolute levels and localization as pharmacologic infusions of TNF or IL-1 can promote natriuresis.[49, 52, 53]

Two important recent findings further confound the simplistic notion that myeloid cells uniformly promote blood pressure elevation. First, mononuclear phagocytes in the dermis exert anti-hypertensive actions by allowing the mobilization and removal of non-osmotically stored sodium and by driving vasodilatory prostanoid production.[54, 55] Second, a unique population of Gr-1-expressing myeloid derived-suppressor cells can attenuate chronic elevations in blood pressure, at least in part by curtailing the pro-hypertensive effects of activated T lymphocytes in the vasculature.[56] Accordingly, the actions of myeloid cell populations in hypertension depend on the inflammatory mediators they elaborate and their effects on oxidant stress in cardiovascular control centers, analogous to the actions of T lymphocyte subsets discussed below.

As monocytes and macrophages express AT_1 receptors, the hypothesis that Ang II promotes hypertension in part by stimulating the macrophage AT_1 receptor would be consistent with the pathogenic actions of AT_1 receptors in the target organ. Indeed, several in vitro experiments support this possibility. For example, incubation of a human monocyte cell line with Ang II elicits activation of NF-κB signaling and promotes the release of TNF via an AT_1 receptor-dependent pathway.[57–59] Moreover, phagocytic capacity is reduced in rodent macrophages lacking the AT_{1A} receptor.[22] The reported effects of AT_1 receptor activation of macrophage migration have been inconsistent. Whereas AT_1 receptor inhibition attenuated CCR2-dependent migration of monocytes isolated from hypertensive rats,[60] we were not able to appreciate alterations in CCL2-induced migration of macrophages from AT_{1A} receptor-deficient mice. Collectively the *in vitro* studies above would suggest that disrupting AT_{1A} receptor signals may interfere with several important monocyte/macrophage functions. Nevertheless, approaches using pharmacologic antagonists may be confounded by off-target effects, and the development or phenotype of a macrophage from a mouse that is globally deficient of the AT_{1A} receptor may be altered by the absence of AT_{1A} receptor signaling in other immune and even non-immune cell lineages.

To circumvent these potential confounders, we used a conditional gene targeting strategy to selectively delete the coding exon from the *Agtr1a* gene in LysM-expressing myeloid cells of mice (*LysM Cre$^+$ Agtr1a$^{flox/flox}$* = "Macro KO"). We then compared renal injury and blood pressure elevation in these animals and wild-type controls (*LysM Cre$^-$ Agtr1a$^{flox/flox}$* = "WT") during RAS activation.[10] We found that the Macro KO animals had a chronic hypertensive response to Ang II similar to that of the WTs but had exaggerated levels of tubular and interstitial injury in the kidney. These findings were consistent with the protective actions of AT_{1A} receptors on immune cells detected in our earlier BMT study[21] but could not explain the exaggerated levels of hypertension seen in our AT_{1A} receptor-deficient bone marrow chimeras. In particular, our conditional gene targeting approach revealed a capacity for the macrophage AT_{1A} receptor to mitigate fibrosis in the kidney,[10] confirming earlier studies from the Ichikawa group using bone marrow chimeras.[22] In our hands, activating the AT_{1A} receptor on macrophages *in vitro* suppressed the emergence of the pro-inflammatory M1 phenotype, which was reflected *in vivo* by attenuated expression of M1 cytokines including TNF and IL-1β in the Macro KO kidney during RAS activation,[10] consistent with the findings of Ma and Fogo in their model of obesity related glomerulopathy.[23] One caveat with our *LysM Cre* deletion strategy is that this approach may have also deleted AT_{1A} receptors from neutrophils, and neutrophils are now receiving attention for their potential role in blood pressure regulation.[61] Notwithstanding this limitation, our studies would indicate that activating the AT_1 receptor directly on macrophages actually suppresses target organ damage in hypertension, particularly within the kidney, raising the possibility that the effects of global RAS activation to promote inflammation accrue from the activation of AT_1 receptors in the target organ or, at least, in non-myeloid hematopoietic cells (Figure 1).

T LYMPHOCYTES, THE AT_1 RECEPTOR, AND HYPERTENSION

T lymphocytes are key constituents of the adaptive immune system. As such, they are recruited by innate immune cells to aide in the specific response against pathogens. Innate

immune cells present pathogen-derived antigens to T cells in peripheral lymphoid tissue. T cells express specific antigen receptors and respond to a cognate antigen by clonal expansion. Following expansion, T cells travel to the site of inflammation and perform their effector functions, which vary depending on their sub-classification. CD4^{+} T cells can release a wide range of cytokines and are often referred to as T helper (Th) cells. CD8^{+} T cells, on the other hand, directly kill cells by the release of cytotoxic factors. CD4^{+} T cells are generally divided into four subtypes depending on their cytokine profile: Th1, Th2, Th17, and Treg. Although additional T helper subsets have recently been defined, such as Th9 and Th22, our understanding of their role in cardiovascular physiology is limited.[62–64] Pro-inflammatory Th1 cells release cytokines such as interferon-γ (IFN), TNF, and IL-12, and stimulate macrophages and CD8^{+} T cells.[65] Th2 cells stimulate B cell antibody production by secreting the cytokines IL-4, IL-9, and IL-13. Th17 cells are pro-inflammatory and have been implicated in the pathogenesis of several autoimmune diseases.[66] Th17 cells produce IL-17, a potent pro-inflammatory cytokine. Finally T regulatory cells, or Tregs, are anti-inflammatory and release cytokines that inhibit other immune cell types, including IL-10 and TGFβ.[67] As with myeloid cells, the distinction among different T cell subsets in vivo is imprecise, since they share many of the same surface receptors. However, each subset is driven by unique transcription factors and produce distinct cytokines that can, with some difficulty, be measured *ex vivo*.[66, 68–70]

T lymphocytes were experimentally linked to hypertension many years ago. However, a landmark study by Guzik et al. in 2007 sparked a recent upsurge of studies examining the actions of T cells in hypertension.[47] In the Guzik studies, lymphocyte-deficient ($Rag1^{-/-}$) mice had attenuated Ang II-induced hypertension, and adoptive transfer of WT T cells, but not B cells, restored the hypertensive response. Since then, T cells have been implicated in experimental models of preeclampsia,[71] pulmonary hypertension,[72] salt-sensitive hypertension,[73] DOCA-salt hypertension[47], and others. The mechanisms by which T cells intensify tissue injury and elevate blood pressure during hypertension are areas of intense investigation but include contributions to endothelial dysfunction in the vasculature[47] and inappropriate sodium retention in the kidney,[74] both of which accrue at least in part from local generation of reactive oxygen species (ROS).[75]

Canonical T cell activation occurs in peripheral lymphoid tissue and requires recognition of peptide antigens on the surface of antigen presenting cells (APCs) via the T cell receptor (TCR). Also required for T cell activation are APC co-stimulatory signals via receptors proximal to the TCR.[76] Whereas the proportion of activated circulating CD4^{+} T cells increases during Ang II-induced or DOCA-salt hypertension, genetic or pharmacological inhibition of T cell co-stimulation blocks T cell activation and attenuates blood pressure elevation in these models.[77] With regard to the antigen(s) responsible for eliciting T cell activation in hypertension, little is known. A novel hypothesis from Harrison and colleagues suggests that intrinsic proteins within APCs are structurally modified via byproducts of NADPH oxidase activity during hypertension, and thus are presented as antigens to T cells.[78] Pharmacological prevention of this protein modification in vivo attenuated hypertension. In separate studies, Dr. Rodriguez-Iturbe's group implicated heat shock proteins, particularly HSP70, as a renal autoantigen in salt-sensitive hypertension.[79] These studies would suggest that T cell immunity in hypertension is driven by antigen presentation.

Both CD4$^+$ and CD8$^+$ T cells infiltrate the kidney and vasculature during hypertension and contribute to tissue injury and dysfunction by a variety of putative mechanisms, including the production of ROS and the release of pro-inflammatory cytokines. CD8$^+$ T cells are capable of elaborating ROS and appear to play a more critical role than CD4$^+$ T cells in potentiating blood pressure elevation.[80] ROS drive endothelial dysfunction, sodium retention, and tissue injury. The amount of ROS in T cells increases upon activation[81] and adoptive transfer of NADPH oxidase-null T cells into *Rag1$^{-/-}$* mice failed to fully restore the Ang II-induced hypertension and vascular dysfunction seen in *Rag1$^{-/-}$* mice repopulated with WT T cells.[47] Moreover, CD4$^+$ Th1 cells elaborate TNF, a potent pro-inflammatory cytokine that induces ROS production, activates other immune cells,[82] and potentiates sodium retention, as mentioned above. Inhibition of TNF signaling attenuates hypertension and reduces end organ damage.[47, 83] Nevertheless, genetic deletion of pro-inflammatory Th1 cells ameliorates glomerular damage without impacting blood pressure[11], suggesting that the actions of TNF produced by non-lymphoid cells in the CNS and the kidney to promote salt appetite and reabsorption, respectively,[48–50] may figure more prominently in the pathogenesis of hypertension than T cell TNF. The release of IL-17 by tissue-infiltrating Th17 cells exacerbates hypertension during RAS activation.[84] By contrast, repeated adoptive transfer of T regulatory cells diminishes vascular injury and Ang II-induced blood pressure elevation.[85] Thus, T cell subsets can have drastically varying effects on the hypertensive response depending on their capacities to generate ROS and/or their effects on the cytokine milieu in the kidney and vasculature.

As with other immune cells, expression of the AT$_1$ receptor on T cells guides their differentiation and function with surprising consequences in the setting of hypertension. In our hands, a conditional gene targeting strategy revealed protective actions of the T cell AT$_{1A}$ receptor in hypertension similar to our findings with the macrophage AT$_{1A}$ receptor.[10, 11] Specifically, deleting the AT$_{1A}$ receptor from T cells in mice yielded exaggerated perivascular T cell infiltration in the kidney and augmented albuminuria, recapitulating our earlier findings with the AT$_{1A}$ receptor-deficient bone marrow chimeras.[21] Consistent with these findings, the T cell AT$_{1A}$ receptor limited damage to the kidney glomerulus and renal expression of the injury marker *Ngal* (*Lcn2*) during RAS-mediated hypertension. However, in contrast to the macrophage AT$_{1A}$ receptor, the actions of the T cell AT$_{1A}$ receptor did not influence the extent of tubular injury or interstitial fibrosis in our model. Congruent with the capacity of AT$_{1A}$ receptor activation on T cells to limit glomerular injury in hypertension, CD4$^+$ T cells isolated from the kidney and spleen of the animals lacking the T cell AT$_{1A}$ receptor had enhanced expression of the Th1 cytokines IFN and TNF. Further studies revealed that activating the T cell AT$_{1A}$ receptor limits Th1 differentiation of the T cell and thereby attenuates hypertensive kidney damage by suppressing the Th1 transcription factor T-bet (Figure 1).[11, 50, 68]

Studies using T lymphocytes isolated from mice that are globally deficient of the AT$_{1A}$ receptor are more consistent with the view that the T cell AT$_{1A}$ receptor promotes rather than suppresses inflammation. For example, splenic lymphocytes from *Atgr1a$^{-/-}$* animals showed blunted proliferative responses following allogeneic stimulation.[8] In vitro, these *Agtr1a$^{-/-}$* T cells had impaired cytokine generation,[9] and adoptive transfer of these cells into *Rag1$^{-/-}$* mice only partly restored the hypertension and vascular dysfunction observed

following adoptive transfer of wild-type T cells.[47] One interpretation to reconcile the discrepant findings with the global versus conditional *Agtr1a* mutants is that activation of the AT_{1A} receptors on non-immune cell lineages indirectly influences AT_{1A} receptor functions in immune cells. The protective effect of the immune cell AT_{1A} receptor in our bone marrow chimera studies would not conflict with this interpretation as bone marrow cells from the globally $Agtr1a^{-/-}$ donors in those studies were permitted to differentiate and repopulate a niche in an environment of non-immune cells with a full complement of AT_{1A} receptors. Another intriguing hypothesis is that AT_{1A} receptor activation on immune cells suppresses hypertensive kidney damage in our conditional mutant and bone marrow chimera studies by triggering apoptosis in leukocytes due to sustained overactivation.[86] In this scenario, the direct effects of AT_1 receptors on the differentiation of immune cells become less physiologically relevant in vivo.

CONCLUSIONS AND FUTURE DIRECTIONS

Innate and adaptive immune cells can potentiate hypertension and end organ damage by mediating chronic inflammation in cardiovascular control centers including the vasculature and the kidney. After infiltrating these tissues, mononuclear cells release ROS and inflammatory cytokines that regulate tissue injury and alter the release of vasoactive mediators, leading to endothelial dysfunction and/or sodium retention. Ongoing studies continue to parse actions of myeloid and T lymphocyte subpopulations in hypertension, and recent data indicate that distinct pro-inflammatory subsets within these broad populations, for example effector memory T cells,[87, 88] play important roles in blood pressure elevation and consequent target organ damage. By contrast, unique anti-inflammatory immune cell populations, including myeloid-derived suppressor cells and Tregs, can attenuate hypertension.[56, 85] Further investigation into these pro-and anti-inflammatory subsets should identify novel therapeutic targets for preventing the catastrophic complications of hypertension including cardiovascular and end stage kidney disease. Further exploration of the proximal determinants leading to T cell activation in hypertension, particularly if it accrues from antigen presentation and clonal T cell expansion will allow us to more precisely confront essential hypertension as an autoimmune disease. Another important emerging area of research in hypertension will be to elucidate the role of B lymphocytes in hypertension. Although adoptive transfer of B cells into an empty lymphocyte niche could not recapitulate the hypertensive response,[47] B cell deficiency (BAFF-R$^{-/-}$) in an otherwise intact immune system ameliorates hypertension,[89] which suggests that B cells can promote blood pressure elevation through interactions with other immune cell populations. Thus, studies to date implicate several major myeloid and lymphoid populations in promoting hypertension. Despite important actions of some small mononuclear cell subsets to limit the hypertensive response, one might speculate that the broad thrust of pro-inflammatory innate and adaptive immune responses to elevate blood pressure have evolved to prevent circulatory collapse in the wake of overwhelming sepsis. The predilection for oxidant and even environmental stress to enhance susceptibility to hypertension through immune-mediated mechanisms is consistent with this hypothesis.[90]

The interactions between the immune system and the RAS add yet another layer of complexity to re-interpreting essential hypertension as an autoimmune disease. We

acknowledge that our studies highlighting a protective effect of AT_1 receptors on macrophages and T cells in hypertension are controversial and await corroboration. Nevertheless, our results with bone marrow chimera studies and conditional mutant approaches are directionally consistent, and the notion that nature may have evolved a protective function for immune cell AT_1 receptors to temper the pathogenic actions of AT_1 receptors in the vasculature and kidney during hypertension offers an attractive "feedback" paradigm. Moreover, we find evidence that activating AT_1 receptors on immune cells also attenuates normotensive kidney fibrosis[10] and acute kidney injury.[91] Given the well-documented detrimental actions of renal and vascular AT_1 receptors in hypertension, confirmation that AT_1 receptors on immune cells are protective would not diminish the utility of ARBs for the treatment of hypertension, but, rather, would suggest that adjunct immunomodulatory therapy may be warranted to mitigate the off-target, pro-inflammatory effects of blocking the AT_1 receptors in myeloid cells and lymphocytes.

Acknowledgments

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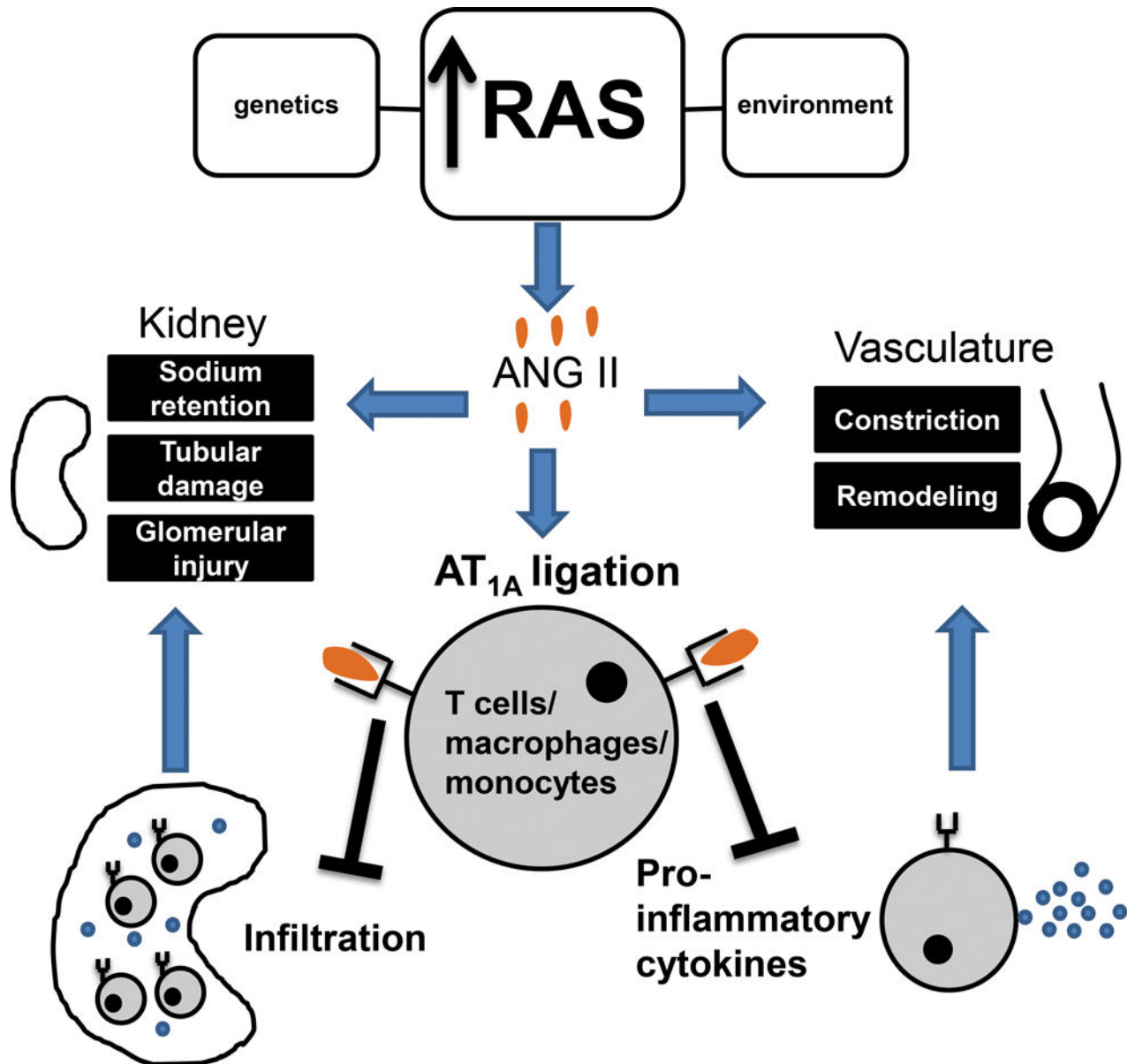
Figure 1.
Interactions between the renin angiotensin system (RAS) and immune system during the pathogenesis of hypertension. Inappropriate RAS activation increases circulating Ang II. Elevated Ang II directly promotes sodium retention in the kidney and systemic vascular constriction. During hypertension, T cells and monocytes/macrophages accumulate in the kidney and vasculature where they mediate tissue injury and deleterious remodeling. Immune cells harbor the type 1 Ang II receptor, AT_{1A}. In an apparent feedback mechanism, ligation of the AT_{1A} receptor constrains T cell accumulation around the renal blood vessels, and activation of the AT_{1A} receptor on T cells and macrophages limits their differentiation toward the pro-inflammatory Th1 and M1 subsets, respectively. This inhibition of Th1 and

M1 polarization attenuates damage to the kidney during hypertension and mitigates the emergence of renal fibrosis that culminates in organ failure.