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An Update on Immune System Activation in the Pathogenesis of Hypertension

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Hypertension remains an enormous health and economic burden in the United States despite the large number of antihypertensive treatments that are available[1]. In addition, the prevalence of uncontrolled hypertension continues to rise globally[2] suggesting that that there is an important need to better understand the underlying causes of this disease. An association between hypertension and immune system activation has long been recognized, but perhaps not fully appreciated until now, and represents a potentially important mechanism in the pathogenesis of hypertension. Studies of human hypertension support this association and implicate a mechanistic role for immune activation and inflammation in the development of hypertension[3–8]. Experimental animal models have proven especially useful for determining the impact of specific immune cells (innate and adaptive immunity) and cytokines, with a heavy emphasis on angiotensin II (AngII) dependent hypertension in rodent models[9–17]. *Hypertension* has been, and continues to be, one of the leading journals for studies that have accelerated our understanding of immune regulation of blood pressure having already provided excellent overviews of basic immune responses and their interaction with the cardiovascular system[18–20]. The objective of this brief review is to discuss the most recent advances published in *Hypertension* that relate to immune system activation and the pathogenesis of hypertension. Because blood pressure is regulated by the integrated function of the kidneys, central nervous system and vasculature, the review will focus on the potential for inflammatory mediators to impact each of these organ systems.

Renal Mechanisms

The central role of the kidneys in long term blood pressure control through the regulation of body fluid and salt homeostasis is widely recognized. This is supported by work showing that the ability of the kidneys to excrete a sodium load is impaired regardless of whether the origins of hypertension are vascular, renal or sympathetically driven. The association between innate or adaptive immune system activation leading to renal inflammation and hypertension is observed across a number of experimental models including AngII[21–24], aldosterone[25], salt-sensitive[26,27], autoimmune-associated[28,29], cold induced[30], and spontaneously hypertensive[31] rodent models. One characteristic commonly observed in

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DISCLOSURES
None

these models is the increased number of infiltrating immune cells, including macrophage and T lymphocytes, in the kidneys.

The participatory role for renal T cells in the pathogenesis of hypertension continues to be supported by studies using experimental animal models of hypertension. For example, Mattson's group reported that a high protein diet exacerbates hypertension in Dahl salt-sensitive rats, and that treatment with mycophenolate mofetil (MMF) attenuates the hypertension in association with reduced renal cortical T cell infiltration[27]. The important contribution of T cells to AngII dependent hypertension in mice has been well documented in seminal studies like those from Harrison's group showing that RAG1−/− mice have a blunted pressor response to AngII which is only fully restored with adoptive transfer of T cells[15]. However, the mechanisms by which AngII directly regulate immune system function, and how chronic immune system activation alters renal hemodynamic and tubular function to promote hypertension continue to be elucidated. The work of Crowley et al[24] tested whether activation of angiotensin type 1 receptors (AT1R) specifically on hematopoietic cells were responsible for driving AngII dependent hypertension in mice. Using an elegant experimental design, they generated bone marrow chimeras deficient only in hematopoietic AT1R. Surprisingly, AngII hypertension was exaggerated in these bone marrow specific AT1R knockout mice in association with increased renal macrophage and CD3+ T cells, the latter of which were mostly confined to the renal vasculature. In addition, their data showed that renal IL-1β was increased leading the authors to speculate on the potential impact of this cytokine on renal vascular reactivity. Taken together, these data uncovered an unexpected potential protective role for AngII stimulated hematopoietic cells, and revealed the complex interplay between AT1 receptor activation on immune cells and non-hematopoietic cells to promote the pathogenesis of hypertension.

Adding a layer of complexity to understanding the impact of an integrated immune response on blood pressure control is a subset of T cells (T regulatory) with the potential to prevent or delay the progression of hypertension. T regulatory cells are CD4+CD25+Foxp3+ cells that have an important role to suppress auto-reactive T cells and promote immune tolerance[32,33]. T regulatory cell function is impaired in human autoimmune disorders like systemic lupus erythematosus (SLE) that are associated with prevalent hypertension and their role in experimental models of hypertension has recently been investigated. Schiffrin's group demonstrated that T regulatory cells are reduced in the renal cortex during AngII mediated hypertension and that adoptive transfer to increase T regulatory cells reduces blood pressure in association with reduced renal inflammatory cytokines[22]. However, Muller's laboratory reported that adoptive transfer of T regulatory cells into a mouse model of AngII dependent hypertension did not alter blood pressure but reduced cardiac injury[34] suggesting the need for further investigation into the impact of T regulatory cells (and other T cell subsets) in different experimental models of hypertension.

Immune cells are attracted to the site of injury by a variety of different chemokines including MCP-1 (CCL2) which is increased in the kidneys from experimental models of hypertension. Once localized in the kidneys, immune cells release inflammatory cytokines like TNF-α, IL-6, IL-1β, IL-17 and IFN-γ, all of which are elevated in the kidneys from hypertensive models and contribute to local tissue injury. A causal role for renal inflammatory cytokines in the pathogenesis of hypertension is supported by studies designed to test the impact of cytokine inhibition on blood pressure. For example, administration of etanercept to reduce TNF-α biological activity in a mouse model of SLE attenuates the development of hypertension in association with a reduction in renal cortical MCP-1 expression[29]. Similarly, inhibition of IL-6 using adenoviral delivery of a small hairpin RNA prevented cold induced hypertension in association with reduced renal IL-6 expression, macrophage and T cell infiltration[30]. Among the potential mechanisms by which cytokines like TNF-α and IL-6 can promote impaired renal function are the activation of downstream mediators like NFκB and the generation of reactive oxygen species.

The contribution of oxidative stress to impaired renal hemodynamic and tubular function has been reviewed[35,36]. Renal oxidative stress is common in experimental models of hypertension, and studies continue to point to reactive oxygen species as an important mediator of AngII hypertension. For example, attenuation of AngII hypertension through the administration of recombinant ACE2 (responsible for converting AngII to Ang1-7) reduces renal markers of oxidative stress in association with a reduction in the expression of inflammatory cytokines and T cell infiltration[23]. The role of cytokines to promote renal oxidative stress is also supported by data showing that TNF-α blockade in a hypertensive mouse model of SLE is associated with a reduction in phosphorylated NFκB and NADPH generated superoxide in the renal cortex[29]. A subsequent study in this model demonstrated that antioxidants prevented the development of hypertension, thus strengthening the link between renal inflammatory cytokines, NFκB signaling and reactive oxygen species in the development of hypertension[28]. Pharmacological blockade of NFκB in spontaneously hypertensive rats (SHR) reduces blood pressure in association with lower NFκB activation in the kidneys and in the hypothalamus, but not the peripheral vasculature or brain cortex[31]. These data not only demonstrate a direct role for NFκB activation in the pathogenesis of hypertension, but also signals the importance of recognizing blood pressure control as an integrated response of multiple organ systems. Overall, renal immune cell infiltration and the subsequent cytokine release promote pro-inflammatory pathways resulting in oxidative stress and impaired renal function. In this way, immune system activation in the kidneys can have a prominent role in the pathogenesis of hypertension; however, important remaining work will be required fully understand the impact of different immune cell subsets and cytokines on chronic renal hemodynamic and tubular function.

Central Mechanisms

The central control of blood pressure is achieved through a balance of sympathetic and parasympathetic innervation of vasculature and kidneys, in addition to hypothalamic hormones that regulate thirst, renal sodium handling, and/or peripheral and renal vascular function. Central nervous system control of blood pressure is particularly relevant given the promise, and controversy, surrounding renal nerve ablation for the treatment of hypertension in humans[37–41]. Importantly, cardiovascular control centers in the brain may be influenced by, or influence, immune system function. The subfornical organ (SFO) of the hypothalamus is highly vascularized and is without an intact blood brain barrier, making it an ideal interface between the central nervous system and peripheral circulation. The concept of a role for the SFO in AngII dependent hypertension is not new, and a recent report shows that knocking down SFO AT1R in DOCA salt hypertensive mice reduces blood pressure in association with lower urinary excretion of copeptin (marker of vasopressin)[42]. A link between the SFO, immune system activation and hypertension is supported by data showing that knock down of the extracellular superoxide dismutase (SOD3) in the circumventricular organs (specifically the SFO) exaggerates AngII dependent hypertension while increasing peripheral vascular infiltration of activated T cells[43]. When the p22 subunit of the NADPH oxidase is specifically knocked down in the SFO to inhibit superoxide generation, AngII hypertension in mice is attenuated[44]. Therefore, much as the generation of reactive oxygen species can regulate renal function, these studies highlight the importance of central oxidative stress in AngII hypertension. The connection between inflammation and other known cardiovascular control centers like the paraventricular nucleus (PVN) has also been recently reported with data showing that intracerebroventricular (ICV) administration of minocycline (anti-inflammatory antibiotic) reduces AngII dependent hypertension in association with reduced PVN IL-1β, IL-6 and TNF-α[45]. The effect of minocycline was mimicked by ICV administration of an adenovirus containing IL-10, considered by many to be an “anti-inflammatory” cytokine. The subject of hypertension and the role of inflammation in specific brain nuclei has recently been reviewed in more depth[19]. These studies suggest an important interaction between known cardiovascular control centers of the brain and the immune system.

An important and emerging area of central nervous system control of blood pressure is related to the fact that peripheral lymphoid organs like the spleen are highly innervated. A recent review highlights the importance of the cholinergic inflammatory reflex, activated by α-7 nicotinic acetylcholine receptors, to cardiovascular regulation[20]. Increased sympathetic activity to the spleen impairs this pathway leading to enhanced inflammatory cytokine production, suggesting this as a novel pathway by which central nervous system activity can promote the pathogenesis of hypertension, even if direct increases in renal or vascular sympathetic nerve activity are not evident. Consistent with a potential role for this pathway, expression of the α-7 nicotinic receptor in the spleen is reduced in two different models of hypertension (SHR and 2 kidney 1 clip hypertension in mice), and is associated with increased inflammatory cytokines in the kidney, aorta and spleen[46]. However, while pharmacological activation of the α-7 nicotinic receptor (abrogating renal and vascular injury), or conducting studies with α-7 receptor knockout mice (exacerbating the injury), suggest that this is an important pathway for hypertensive end-organ damage, its role in the pathogenesis of hypertension remains to be determined. Taken together, these studies continue to provide supportive data that specific regions within the brain are important mediators of hypertension, and suggest that the sympathetic regulation of, and by, peripheral immune organs may be a critical factor in forming an integrative whole body understanding of the pathogenesis of hypertension. Going forward, it will be important to carefully investigate how these centrally mediated pathways that regulate immune system function ultimately impact renal vascular or tubular function to promote long term changes in blood pressure.

Vascular Mechanisms

Impaired vascular function is common in human and experimental hypertension. Therefore, vascular inflammation can be an important mechanism to promote the pathogenesis of hypertension, particularly if that impaired function restricts flow to the kidney and impairs the normal natriuretic response to changes in blood pressure. Growing evidence continues to support the association of experimental hypertension with inflammatory cytokines and/or immune cells in the vascular wall[30,47–50]. Cells of the innate immune system, including macrophages and neutrophils, have been implicated in vascular inflammation that accompanies experimental hypertension[51,52]. This concept is further supported by evidence showing that blocking the chemokine CCR2 in mineralocorticoid induced hypertension reduced aortic infiltration of macrophage, even when the treatment began after the hypertension was established[53]. Although aldosterone is often considered as a pro-inflammatory hormone, it appears as though aldosterone can directly bind to mineralocorticoid receptors in human neutrophils and suppress inflammatory signaling pathways like NFκB activation[54]. This suggests that additional work is required to better understand the impact of hormones important for blood pressure control on cells of the innate immune system, and how they impact vascular inflammation.

Several recent studies suggest a vascular protective effect of T regulatory cells, much in the same way that these cells may provide renal protection. An association between vascular inflammation and T regulatory cells was initially described in salt-sensitive hypertension by comparing vascular inflammatory markers and T cells in Dahl rats and consomic Dahl rats with chromosome 2 from the Brown Norway rat. The consomic rats exhibited reduced vascular inflammation and increased vascular expression of Foxp3, a transcription factor specific to T regulatory cells[55]. In both mineralocorticoid and AngII dependent hypertension, adoptive transfer of T regulatory cells blunts the hypertension and prevents the development of impaired mesenteric artery dysfunction and remodeling[22] and reduces immune cell infiltration (macrophage and CD3+ T cells) in the aorta[56]. The potential role for vascular T cells in regulating blood pressure is further supported in a study designed to determine the mechanisms by which tacrolimus, used to prevent transplant rejection, promotes hypertension[48]. Treatment with tacrolimus in mice resulted in hypertension with endothelial dysfunction in association with reduced vascular wall T regulatory cells and increased pro-inflammatory T helper 17 cells, thus implicating a shift in vascular immune cell subsets as a mechanism for the dysfunction.

Chemokines are important mediators of vascular immune cell infiltration and there is good evidence for their involvement in the development of hypertension. DOCA salt induced hypertension is associated with the expression of several chemokines in the aorta (i.e. CCR2, CCL7, CCL8 and CCL12) and with increased macrophage numbers[53]. Pharmacological blockade of CCR2 blunts the hypertension and reduces aortic macrophage numbers supporting the concept that chemokines mechanistically contributes to the pathogenesis of hypertension[53]. AngII dependent hypertension is also associated with increased vascular wall expression of chemokines including VCAM-1, ICAM-1 and MCP-1, all of which are attenuated when the AngII infusion is performed in map kinase 2 deficient mice (MK2)[49].

Consistent with the impact of immune system activation in the kidney and brain, there is considerable evidence tying vascular NFκB activation and oxidative stress to the development of hypertension. An in vitro study recently described a potential pathway by which inflammatory cytokines (TNF-α, IL-1β) can promote NFκB activation in the vascular endothelium through a mechanism that involves opening of an outwardly rectifying chloride channel[57]. In addition, it has been proposed that NFκB can directly impair the vasodilatory actions of β2 alpha adrenergic receptor through a mechanism that involves matrix metalloproteinase (MMP) mediated receptor cleavage[31]. Just as NFκB activation and oxidative stress are common in the brain and kidney, the impact of the vascular production of reactive oxygen species on vascular function has been widely reported, and a number of studies continue to affirm that relationship[30,49,56,58]. That oxidative stress is well known to impact vascular function under conditions of immune system activation and inflammation is not intended to suggest that the role of vascular reactive oxygen species in blood pressure control is a simple one. For example, whereas SOD3 deletion in the SFO of the brain accelerates AngII hypertension, genetic deletion of SOD3 specifically in the vascular smooth muscle appears not to regulate blood pressure[47]. Whether the association between vascular inflammation and hypertension in the conduit vessels reflects what is occurring in resistance vessels, especially the renal microvasculature, as a mechanism to promote the development of hypertension is an important remaining question. Moreover, whether vascular inflammation has causal role in the development of hypertension, or results from the hypertension, should remain an important consideration.

Perspectives

The large, and growing, number of studies related to inflammation, (innate and adaptive) immune system activation and hypertension support this is an important area of investigation to better understand the pathogenesis of hypertension. The impact of immune system on renal, central nervous system, and vascular function is strongly associated with an imbalance between pro- and anti-inflammatory pathways that lead to the accumulation of immune cells (i.e. T cells, macrophage) in each tissue. The presence of these cells can increase local production of inflammatory cytokines and activate signaling pathways like NFκB leading to oxidative stress that further perpetuates declining organ function. While a great deal has been learned from the most commonly used experimental models of hypertension, it will be important to continue asking whether these activated immune pathways function in the same way across different models, organ systems, and in human hypertension. Moreover, determining how immune mediated alterations of central nervous system and peripheral vascular function ultimately promote the changes in body fluid homeostasis required for chronic increases in blood pressure will make it possible to build a more complete and integrative view of the mechanisms underlying the development of hypertension.

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