Guyton suggested over 40 years ago that the kidney, by regulating volume homeostasis and sodium reabsorption, is critically involved in maintaining normal blood pressure through the pressure natriuresis response and that alterations in these processes lead to hypertension. The importance of the kidney in the pathophysiology of hypertension is also evidenced by kidney transplantation studies in rodents, where grafting of kidneys from normotensive rats normalized blood pressure in bilaterally nephrectomized hypertensive rats, and vice versa. These data suggest that the blood pressure trait follows the kidney phenotype and may relate to the nephron number, where fewer nephrons are associated with impaired pressure natriuresis and predisposition to hypertension. To further support a role for the kidney in hypertension are human genetic studies, which demonstrated that the majority of inherited monogenetic forms of hypertension affect the distal nephron and volume and sodium homeostasis. Moreover, increased renal sympathetic nerve activity causes an increase in blood pressure, whereas renal sympathectomy lowers blood pressure in experimental models of hypertension and in human hypertensive patients, indicating the importance of the sympathetic nervous system in renal function in hypertension.

The functional significance of the renal sympathetic nerves in the kidney became more apparent when it was shown anatomically that nerve fibers are in direct contact with tubular segments and that they directly influence renal tubular function through norepinephrine-containing renal sympathetic nerve terminals. Activation of the renal sympathetic system increases norepinephrine release with increased sodium and water reabsorption by renal tubular epithelial cells, smooth muscle contraction, and renin release from granular cells of the juxtaglomerular apparatus, processes that contribute to blood pressure elevation. In addition, growing evidence indicates that activation of renal sympathetic nerves promotes renal inflammation through adaptive and innate immune mechanisms. In hypertension, T cells and macrophages accumulate in the kidney and have been implicated in renal pathology. The relationship between the sympathetic nervous system and inflammation is not new. Already in 1903, it was demonstrated that staphylococcal-induced inflammation in the rabbit ear was ameliorated by sympathectomy. However, it is only more recently that mechanisms whereby the sympathetic nervous system influences immune cell function and tissue damage have been uncovered. This involves direct effects on antigen-presenting immune cells or indirect effects via regulation of blood or lymphatic flow, regulation of distribution and production of lymphocytes, or modulation of proinflammatory peptide release. Inflammatory cell recruitment and redistribution are also regulated by the sympathetic nervous system.

Neuroimmune regulation is not organ-specific but seems to be particularly important in kidney inflammation during the development of hypertension, as highlighted in the current issue. Xiao et al demonstrate that chemically induced renal denervation not only attenuates development of hypertension but also ameliorates renal inflammation and fibrosis, decreases oxidative stress, and improves renal function. Although others have also shown renoprotective and blood pressure–lowering effects of renal denervation, what is novel about the present study is that putative molecular and cellular mechanisms underlying these complex processes have now been unraveled. Using a multidisciplinary approach, Xiao et al identified renal dendritic cells as major players in response to renal sympathetic activation. Dendritic cells, commonly found as precursor populations from myeloid and lymphoid lineages in bone marrow and blood and as mature immune cells or indirect effects via regulation of blood or lymphatic flow, regulation of distribution and production of lymphocytes, or modulation of proinflammatory peptide release. Inflammatory cell recruitment and redistribution are also regulated by the sympathetic nervous system. Dendritic cells, the most potent antigen-presenting cells, and because they communicate through direct cell–cell interaction with other immune cells and through the production of inflammatory signals, they drive immune-based kidney inflammation and renal pathology.

Although it is clear that T cells are key players in renal inflammation in hypertension, the intermediary factors stimulating these cells by dendritic cells remain elusive. However, Xiao et al now provide good evidence that immunogenic γ-ketoaldehydes (isoketals) protein adducts in dendritic cells are the missing link because these molecules act as neoantigens, which stimulate T cells and initiation of the inflammatory response. These phenomena, together with enhanced expression of costimulatory molecules and increased production of
proinflammatory cytokines interleukin (IL)-1α, IL-1β, IL-2, and IL-6, are key modulators of renal injury in hypertension. The IL-1 family members are themselves potent regulators of dendritic cell maturation, which may suggest a novel system whereby inflammatory cytokines promote dendritic cell maturation and activation, which in turn stimulate T cells and further production of proinflammatory cytokines. This feedforward system could act as an amplifier in the renal inflammatory response in hypertension, which may be important in progressive renal pathology and target organ damage. To unambiguously demonstrate the critical role of these processes, the article under discussion showed adoptive transfer of splenic dendritic cells from angiotensin II (Ang II)–treated mice, primed T-cell activation, and hypertension in recipient mice, with renal denervation preventing these effects of hypertension on dendritic cells. Together these data advance the field on neuroimmunology by defining a mechanistic interaction between the sympathetic nervous system and renal inflammation in Ang II–induced hypertension.

Fundamental to the link between isoketals and the immune system is oxidative stress because increased O$_2^*$ and H$_2$O$_2$ facilitate isoketal-induced oxidative modification of proteins, which in turn act as putative neoantigens in the T cell–based response in hypertension-associated renal inflammation. Isoketals may also play a role in inflammation through endoplasmic reticulum stress, disrupted mitochondrial respiration, and impaired cellular calcium homeostasis. Whether this system is specific for kidney inflammation or whether it is a systemic effect in conditions of high oxidative stress, such as hypertension, awaits further clarification.

Neuroimmune regulation of dendritic cells has been demonstrated in many organs, including the gastrointestinal system, skin, and liver, and now in the hypertensive kidney. Resident or infiltrating dendritic cells and macrophages are major cell types involved in the initiation and propagation of renal injury and are important players in subsequent tissue repair and regeneration. In the kidney, this phenomenon is not specific for hypertension and has been shown to be important in chronic kidney disease, diabetic nephropathy, and glomerulonephritis. In fact, regulation of dendritic cells by the renal sympathetic nervous system has been previously shown in glomerulonephritis. Veelken et al demonstrated that tyrosine hydroxylase–positive sympathetic efferent nerve fibers and calcitonin gene–related peptide–positive primary afferent nerve fibers are in close proximity to dendritic cells and macrophages. Renal denervation in experimental glomerulonephritis ameliorated renal inflammation and as such this approach has been suggested as a novel strategy in the management of renal disease.

Mechanisms whereby renal sympathetic nerves regulate dendritic cells involve release of sympathetic neurotransmitters and close interaction between nerve terminals and cells. Anatomically, afferent and efferent nerve fibers are in close proximity to dendritic cells, ensuring efficient neuroimmune crosstalk. Major sympathetic neurotransmitters include norepinephrine, ATP, neuropeptide Y, and nitric oxide. Although all these neurotransmitters directly influence immune cells, the best characterized is norepinephrine. This seems to hold true in Ang II–induced hypertension, where it was shown that dendritic cells express adrenergic receptors and that β2 receptor expression is increased. The exact signaling in dendritic cells to promote isoketal generation remains unclear but redox-sensitive processes seem to be important.

Xiao et al provide new insights into mechanisms of renal inflammation by showing important networking between the sympathetic nervous system and the immune system in the kidney in hypertension. However, these findings need to be interpreted within the context of the experimental conditions. Some caveats warrant further consideration:

First, the paradigm was examined in a model of Ang II–induced hypertension and as such there is no evidence that similar processes of renal inflammation may occur in other forms of hypertension or kidney injury. This is especially important because the phenomena described may actually be independent of hypertension, as previously shown and suggested in the study under discussion, and accordingly may truly reflect a process that is Ang II–specific. If this is indeed the case, the relevance in human hypertension remains unclear.

Second, studies were performed in male mice. It is now evident that there are sex differences in the ability of the adaptive immune system to facilitate Ang II–induced hypertension. Males have greater increases in proinflammatory T cells, whereas females have greater increases in anti-inflammatory T-regulatory cells. Accordingly, whether the adrenergic–dendritic cell–isoketal axis described is also active in females remains unclear.

Third, although there is extensive experimental evidence linking hyperactivation of the immune system and renal inflammation to the development of hypertension, there is still a paucity of information showing such a relationship in human hypertension. In fact, immunosuppression with drugs, such as calcineurin inhibitors, actually promotes development of hypertension, and patients with immunodeficiency, such as HIV, may actually become hypertensive, independently of retroviral drugs. Accordingly, before the elegant paradigm described by Xiao et al is extrapolated to clinical hypertension, more definitive information about the neuroimmune status, blood pressure regulation, and kidney function in humans is warranted. It may be especially useful to know whether patients with hyperactivation of the sympathetic nervous system or those with pheochromocytoma have activation of the immune system with associated renal inflammation and dysfunction. This may be relevant, because pheochromocytomas have been shown to express and produce proinflammatory interleukins.

Finally, if indeed the sympathetic nervous system is driving the renal immune response, it may be possible that every stress-induced fight or flight response leads to a renal inflammatory response. It will be important to know what factors modulate dendritic cell activation in response to adrenergic activation and what tips the system where immune-regulated inflammation switches from a repair and regenerative process to an irreversible pathological process.

Despite its limitations, the study of Xiao et al is important because it advances the field of neuroimmunology and inflammation by identifying an important mechanism in the kidney.
in hypertension whereby the sympathetic nervous system regulates the immune system through dendritic cell activation and production of neoantigens, namely isoketal-modified proteins. Discovering isoketals as the missing link between antigen-presenting dendritic cells and T cells provides exciting opportunities for novel therapeutic targets in kidney inflammation and injury. Moreover, results from the study by Xiao et al11 provide some new insights into putative mechanisms whereby renal denervation in hypertensive patients may have added renoprotective effects by reducing immune-regulated renal inflammation.6 Future studies will define the clinical relevance of the neuroinflammatory axis in kidney health and disease.

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Disclosures

None.

References


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