Hypertension: An Autoimmune Disease?

By Steven Crowley

Although cardiologists and nephrologists have debated for years about the relative contributions of the vasculature and the kidney to the pathogenesis of hypertension, new data have emerged that may recast essential hypertension as an autoimmune disease. These studies do not discount the importance of vascular tone and regulation of intravascular volume in the determination of blood pressure. Rather, these novel experiments illustrate that immune cells and inflammatory mediators can influence blood pressure precisely by impacting vascular function and renal sodium handling. Moreover, these recent findings have stimulated renewed interest in earlier, pioneering studies that first hinted at a role for immunity in hypertension.

Long before the era of transgenic models, researches first drew a link between lymphocyte functions and blood pressure elevation. For example, adoptive transfer of lymph node cells from a rat made hypertensive by renal infarction recapitulated the hypertensive response in the recipient. Conversely, mice lacking a thymus, the organ in which T lymphocytes mature through selective processes, were protected from blood pressure elevation in a model of spontaneous hypertension, and thymectomy in genetically hypertensive rats reduced blood pressure. Later, during the study of atherosclerosis, the walls of resistance vessels undergoing remodeling in the setting of hypertension were noted to contain inflammatory cell clusters. Furthermore, in several animal models of hypertension, broad pharmacologic blockade of inflammatory cell clusters, with or without treatment of the underlying disease, has been associated with attenuation of target organ damage. These findings do not discount the importance of vascular tone and renal sodium handling, but they do suggest that immune cells and inflammatory mediators can influence blood pressure precisely by impacting vascular function and renal sodium handling. Moreover, these recent findings have stimulated renewed interest in earlier, pioneering studies that first hinted at a role for immunity in hypertension.

For example, work from the group of David Harrison has established that mice lacking functional lymphocytes have a muted blood pressure response to hypertensive stimuli that is restored by transfer of T but not of B lymphocytes (2). Preliminary experiments further indicate that CD8+ rather than CD4+ T cells are the key prohypertensive T cell subpopulation. These T cells may promote hypertension by potentiating vascular dysfunction and/or sodium retention in the kidney. Activated T cells appear to promote vascular dysfunction by potentiating local oxidative stress, a key function of inflammatory cells that protects the host in the setting of infection but becomes “autoimmune” in the setting of hypertension. Regarding renal mechanisms of hypertension, mice lacking functional T cells have enhanced expression in the kidney of cyclooxygenase-2, leading to exaggerated generation of the vasodilator prostaglandins E2 and I2 and preserved natriuresis in face of a hypertensive stimulus. Thus, activated T lymphocytes mediate blood pressure elevation by coordinate augmentation of vasoonstriction and renal sodium retention. The actions of T lymphocytes would imply that an adaptive immune response to a specific antigen promotes hypertension. Although no such putative antigen has been definitively established, the group of Rodriguez-Iturbe has put forth heat shock protein 70 as one possible candidate. Moreover, protection from hypertension in animals genetically deficient of key costimulatory receptors required to mobilize a full antigen-dependent T cell response represents further evidence of a directed antigen-mediated process. On the other hand, innate immunity that seeks to protect the host before it can identify and process a specific antigen may also play a role in hypertension. For example, monocytes are the precursors for the macrophages that can propagate broad inflammatory responses even in the absence of a processed antigen, and mice lacking monocytes have a muted blood pressure response to hypertensive stimuli. On the other hand, monocytes can also differentiate into dendritic cells that potently activate adaptive immune responses by presenting processed antigens to T cells, and inflammatory cytokines such as TNF-α that exacerbate blood pressure elevation can be produced by both innate and adaptive immune cell lineages. Thus, the relative participation of the innate versus adaptive immune response in the pathogenesis of hypertension will require further elucidation.

The clinical application of these new research findings also awaits further validation. Reports of reduced blood pressure levels in HIV-infected patients deficient in functional T cells and elevated blood pressure levels in patients suffering from autoimmune diseases such as psoriatic arthritis support a role for immune responses in human hypertension. Moreover, in kidney biopsies from patients with malignant hypertension, perivascular inflammatory cell clusters figure prominently. Nevertheless, particularly given the potential toxicities of broad immunosuppression, a more precise understanding of immune mechanisms in hypertension through additional preclinical studies will likely yield the greatest potential for the development of novel and safe immune-based therapies to limit blood pressure elevation and/or prevent the emergence of target organ damage in the setting of hypertension.

Steven Crowley, MD, is affiliated with the Division of Nephrology at Duke University Medical Center in Durham, NC.

References