Memories that last in hypertension

Hana A. Itani and David G. Harrison
Division of Clinical Pharmacology, Department of Medicine, School of Medicine, Vanderbilt University, Nashville, Tennessee
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Itani HA, Harrison DG. Memories that last in hypertension. Am J Physiol Renal Physiol 308: F1197–F1199, 2015. First published April 1, 2015; doi:10.1152/ajprenal.00633.2014.—In recent years, it has become clear that the immune system contributes to the genesis of hypertension. Hypertensive stimuli, such as angiotensin II, DOCA-salt, and norepinephrine, cause T cells and monocytes/macrophages to accumulate in the kidney and vasculature. These cells release inflammatory cytokines, such as IL-6, interferon-γ, and IL-17, that promote renal and vascular dysfunction. These cytokines also promote angiotensinogen production in the proximal tubule and Na+ retention in the distal nephron and contribute to renal fibrosis and glomerular damage. For several years, we have observed accumulation of memory T cells in the kidney and vasculature. Given the propensity for memory cells to produce cytokines such as interferon-γ and IL-17, interventions to prevent the formation or renal accumulation of specific memory T cell subsets could prevent end-organ damage and blood pressure elevation in response to hypertensive stimuli.

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HYPERTENSION affects more than one billion people worldwide and is an enormous healthcare burden in Western societies. It is a major risk factor for stroke, myocardial infarction, and heart failure (6, 8, 12). Perturbations of the central nervous system, vasculature, and kidney have all been implicated; however, the manner in which these interact remains poorly defined. During the past several years, research from our laboratory and others has shown that perturbations of the immune system play a major role in this disease (5). Hypertension is associated with the appearance of T cells in the kidney that release inflammatory cytokines, which promote Na+ retention and vascular dysfunction (16). Both ANG II and DOCA-salt challenge causes antigen-presenting cells, and in particular dendritic cells, to accumulate isoketal protein adducts. Recent studies have suggested that these oxidatively modified proteins serve as neoantigens and promote the release of cytokines, including IL-6, IL-1β, and IL-23 (7). These dendritic cells promote T cell proliferation and polarize T cells to an inflammatory phenotype. In keeping with this, mice lacking specific subsets of T cells are protected against the antidiuretic and antinatriuretic effects of ANG II (16).

The Concept of “Memory” in Hypertension

More than 50 years ago, Dickenson et al. (3) showed that normally suppressor doses of ANG II will ultimately elevate blood pressure when given for prolonged periods and termed this phenomenon “autopotentiation.” Recently, Xue et al. (17) showed that the central actions of ANG II have “memory.” During an initial exposure to a low dose (10 ng·kg⁻¹·min⁻¹) of ANG II, Xue et al. (17) showed induction of mRNA of ANG II type 1 and type 2 receptors, mineralocorticoid receptor, and aldosterone synthase in the lamina termina-1, which then potentiated the hypertensive response, induced by a second high dose of ANG II (120 ng·kg⁻¹·min⁻¹) (17). This augmented hypertension during the second exposure could be blocked by central administration of an ANG II type 1 receptor antagonist during the first exposure.

We propose that in addition to this central nervous system memory response, there is also a component of immunological memory. We have consistently observed an increase of memory T cells in the blood, vasculature, and kidneys of hypertensive mice. The precise role of these, compared with newly activated CD4+ and CD8+ T cells, is poorly understood. In this minireview, a novel aspect of immunity in hypertension and its role in end-organ damage will be discussed.

Molecular Basis of the Adaptive Immune Memory Response

Immunological memory is a cardinal feature of adaptive immunity, which provides protection against an antigen that has been encountered previously and is the basis for vaccination against infection. The classical adaptive T cell immune response is characterized by an initial expansion of T cells upon antigen presentation (Fig. 1) (14). The majority of these effector T cells ultimately die; however, a few remaining cells become long-lived memory T cells. Some of these return to secondary lymphoid organs, such as lymph nodes and the spleen, and are referred to as central memory cells. Others remain in the periphery, particularly in the bone marrow, skin and mucosa, and are referred to as resident memory cells. Upon a second exposure to the antigen, both central memory and resident memory cells can be activated to become effector memory cells. This activation involves a rapid expansion of cell numbers, the production of cytokines, and a change in surface markers. In the mouse, naïve T cells are CD44hi/CD62Lhi/CCR7+. Central memory cells are CD44hi/CD62Lhi/
Preliminary data indicate that this animal develops moderately severe hypertension upon dietary intervention. Another useful model is that similar to one used by Gonzalez-Villalobos et al. (4), which involves an initial challenge with the nitric oxide synthase inhibitor N-nitro-L-arginine methyl ester followed by a salt challenge. Another approach might involve adoptive transfer of memory T cells to naïve mice to determine if these worsen hypertension in response to generally subpressor stimuli. Another approach might involve adoptive transfer of dendritic cells from a hypertensive mouse to a naïve recipient. We have shown that this leads to marked hypertension in response to a generally subpressor dose of ANG II and that these cells preferentially activate memory cells from hypertensive mice (7). Finally, studies of mice lacking critical mediators such as CD70 and CD27 can prove useful.

**Concluding Remarks**

In summary, studies in mouse models of sustained hypertension will provide insights on the role and mechanism of action of immunological memory T cell formation. It is crucial to identify the tissue localization and longevity of antigen-specific memory T cells formed that could be major sources of potent inflammatory cytokines, such as IL-17A and interferon-γ. Accumulation of these cells over time in the kidney with repeated hypertensive challenges will promote renal damage. This is important because memory cells are very long lived and can sensitize individuals to repeated hypertensive stimuli, thus contributing to end-organ damage.

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AUTHOR CONTRIBUTIONS

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