EDITORIAL

When Memory Does Not Serve You Well

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Immune system activation is pivotal in the progression and maintenance of hypertension. The specific role of adaptive immunity has been demonstrated in severe combined immunodeficiency mice and Rag-1 (recombinase activating gene-1) knockout mice, 2 strains that lack T and B cells and that are protected from experimental hypertension. Further studies showed that adoptive transfer of T cells but not B cells into Rag-1 knockout mice eliminates this protection and increases blood pressure, suggesting an important role for T cells in the pathogenesis of the hypertension.

To dissect mechanisms responsible for T-cell–induced hypertension, we must recognize the potential role of T-cell subtypes. Trott et al demonstrated that while cytotoxic CD8+ T cells are involved in Ang II (angiotensin II)–induced hypertension in mice, CD4+ T helper cells are not as critical. Upon activation, CD8+ T cells increase the production and release of proinflammatory cytokines, such as TNF-α (tumor necrosis factor-α), IL-17 (interleukin-17), and IFN-γ (interferon-γ), as well as cytotoxic granules found in natural killer cells like perforin and granzymes. These inflammatory mediators promote chronic increases in blood pressure and end-organ damage. Once activated, CD8+ T cells can differentiate into effector memory (EM) cells that reside in peripheral tissues and help the immune system remember the previously encountered antigen or stimulus. This is detrimental in hypertension since intermittent and reoccurring stimuli force CD8+ T EM cells to generate a long-term immunity that, in turn, accelerate the response to a second antigen exposure, making the cells more effective and exacerbating the disease. Based on these findings, CD8+ T EM cells may be a target in hypertension; however, to determine new and effective therapies that combat these cells, the mechanisms involved in CD8+ T EM cell–induced hypertension must be elucidated.

Enhanced sympathetic nervous system activation is a hallmark of hypertension that includes increased vasomotor sympathetic tone to several organs such as heart, kidney, blood vessel, and bone marrow. In the bone marrow, the resultant increase in norepinephrine after sympathetic nervous system activation is what causes the increase in inflammatory cells and decrease in endothelial progenitor cells and evidence suggests that this mechanism likely involves β adrenergic receptors. Several animal studies confirm that infusion of angiotensin II increases activity of inflammatory cells like CD8+ T cells; however, it is not clear how the sympathetic nerves and β adrenergic receptors are involved in this process. In this issue of Circulation Research, Xiao et al performed a series of in vivo and in vitro and gain- and loss-of-function studies (eg, enhanced sympathetics using designer receptors exclusively activated by designer drugs and sympathectomy) to investigate the roles of sympathetic innervation and β adrenergic receptors in bone marrow and their control of T-cell homing in hypertension.

Xiao et al hypothesized that the sympathetic nervous system controls the homing, proliferation, and activation of CD8+ T EM cells in hypertension. One focus of the study was to confirm that sympathetic nerves have an effect on T-cell populations within the bone marrow in hypertension. Unilateral superior cervical ganglionectomy was used to probe this question and proved to be an effective tool because both innervated and denervated bone marrow cells were readily available. The investigators confirmed that sympathetic activity in Ang II–infused mice...
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Memory T-Cell Homing Requires β2-Adrenergic Receptors

increased tyrosine hydroxylase expression in forelimb bone marrow, and this response was blunted in animals subjected to superior cervical ganglionectomy. Innervated and denervated bone marrow cells from Ang II–infused mice were cocultured with splenic dendritic cells from Ang II–infused mice, resulting in the increased proliferation of CD8+ T cells in innervated but not denervated bone marrow. To further understand the mechanisms involved, the authors used unilateral injection of Gq-designer marrow. To further understand the mechanisms involved, the authors used unilateral injection of Gq-designer receptors exclusively activated by designer drugs into the SCG to enhance sympathetic nervous system activation and showed that this leads to homing of adoptively transferred CD8+ T EM cells mostly to the innervated bone marrow as opposed to the denervated bone marrow. A separate study showed that sympathetic innervation also increases CCL (C-C motif ligand) chemokines CCL19 and CCL21a, which are responsible for assisting with the migration and homing of the memory T cells. These data lead to a culminating in vivo study in which central inhibition of peripheral sympathetic nerve activity through Gq-coupled designer receptors exclusively activated by designer drugs injected bilaterally into the rostral ventrolateral medulla did not allow proper homing of adoptively transferred hypertensive CD8+ T EM cells, causing a failure to create memory in the bone marrow and importantly in the kidney. These same mice were protected from a repeated hypertensive challenge; there was no change in blood pressure after a subpressor dose of Ang II due to the lack of memory. Together, these experiments confirm that enhanced sympathetic nervous system activation is required for homing and proliferation of CD8+ T EM cells in the bone marrow in hypertension and that the absence of memory may protect from future hypertensive challenges.

Since norepinephrine released from sympathetic nerves innervating the bone marrow bind β2ARs (β2 adrenergic receptors) to elicit a response, the authors turned their focus toward these receptors. Ang II–infused mice were treated with a β2AR antagonist to inhibit peripheral activity of the sympathetic nerves and were subsequently challenged with a second hypertensive stimulus. The β2AR antagonist prevented proper homing and proliferation of CD8+ T EM cells; so when presented with a repeated challenge, the β2AR antagonist–induced reduction in memory blunted the response to a subpressor dose of Ang II. Other experiments even show that norepinephrine increased the migration of CD8+ T EM to bone marrow, probably through the increase in CCL19 and CCL 21 chemokines. This is important since an increase in the CD8+ T-cell population was also observed in hypertensive patients, and this correlated with an increase in other chemokines. The authors demonstrated how the migration of CD8+ T EM cells can be blocked by β2AR antagonist, and likewise, β2AR agonists enhance CD8+ T EM cell transmigration to the bone marrow cells; therefore, these results strengthen the hypothesis that β2ARs are required for memory T-cell homing in hypertension.

**Figure.** Enhanced sympathetic nervous system activity increases homing of CD8+ T cells via β-adrenergic receptors. Initial exposure to a hypertensive challenge enhances sympathetic nerve activity (SNA), which leads to increased activation of β2ARs (β2 adrenergic receptors) on immune cells in the bone marrow, specifically CD8+ T cells. The hypertensive stimulus also increases antigen presentation to these CD8+ T cells, promoting their activation and subsequent secretion of inflammatory mediators like proinflammatory cytokines (eg, TNF-α [tumor necrosis factor-α], IFN-γ [interferon-γ], and IL-17 [interleukin-17]) and cytotoxic granules. All of these mediate end-organ damage and long-term increases in blood pressure. Importantly, activation of CD8+ T cells also increases CCL (C-C chemokine ligands) like CCL19 and CCL21a that promote chemotaxis and homing of additional CD8+ T cells in the bone marrow and differentiation of these cells into effector memory (EM) cells. The sympathetic nerves are required to prime the environment of the bone marrow to maintain these CD8T EM cells. Upon repeated exposure to a hypertensive stimulus and antigens, the activated CD8+ T EM cells cause a heightened inflammatory response that is even larger than what occurred during the prior exposure. Taken together, the ability of CD8+ T cells to exert memory after the first exposure to a hypertensive challenge is detrimental and furthers the progression of the disease to severe hypertension. The sympathetic nerves and β2-adrenergic receptors are necessary for this process; therefore, therapeutic strategies that target these may benefit patients with hypertension. NE indicates norepinephrine; and SCG, superior celiac ganglion.
Collectively, the findings of the study by Xiao et al indicate sympathetic nerves are critical for CD8+ T EM T-cell homing and survival in hypertension (Figure). Enhanced release of norepinephrine activates β2ARs, and this nurtures the environment for CD8+ T EM cells in the bone marrow. Homing of additional memory cells to bone marrow can enhance the hypertensive response to a recurrent, sustained, or new stimuli. This process in the bone marrow may also be associated with impaired parasympathetic activity because a decrease of acetylcholine transferase and esterase was observed together with an increase in tyrosine hydroxylase and norepinephrine in the spontaneously hypertensive rat. Thus, a decrease in the parasympathetic tone may also contribute to the enhanced inflammatory response in hypertension and should be investigated in future studies.

The findings of this study by Xiao et al progress the field by expanding the knowledge of how sympathetic activity modulates memory T cells in hypertension through β2ARs. This is the first study to show that homing of CD8+ T EM cells require the sympathetic nerves and β2ARs. It is worth mentioning that there are AT1R (angiotensin type 1 receptors) in the bone marrow, and these receptors can also promote TNF-α release; therefore, the role of AT1R on the observed responses should be considered. Furthermore, we can also speculate that after superior cervical ganglionectomy, AT1R s would be decreased, and this decrease would support the results presented by the authors. Overall, this study provides evidence that repetitive hypertensive challenges can modify the system to have a quicker and more effective response with re-exposure to the same or similar hypertensive stimuli. This has already been shown in a study where the pressor response to Ang II was increased in animals that underwent a prior exposure to Ang II. In the same way, Xiao et al showed that memory T cells accumulate in the bone marrow in hypertension and that these memory cells are critical for future responses to a repeated hypertensive stimulus. Importantly, this study provides evidence that a paradigm shift in the therapy of hypertension may benefit some patients. Specifically, therapy with a β-blocker or β2AR antagonist would prevent sympathetic neurotransmission and homing of these hypertension-specific CD8+ T EM cells in the bone marrow and the kidneys, blunting the detrimental response of these immune cells in hypertension.

ARTICLE INFORMATION

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