**Novel Role of Bone Marrow Stem Cells in Systemic Disease**

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Identifying neural, hormonal, renal, and vascular mechanisms that cause systemic hypertension has led to the development of diagnostics, drugs, and devices for the treatment of hypertension during the past many decades. These successes have led to a decrease in the rate of stroke and contributed to the decrease in cardiovascular disease in the general population. However, in spite of the new discoveries, 20% of patients diagnosed with hypertension remain hypertensive with an increase in risk of cardiovascular disease. There is ample evidence that the central nervous system is altered by hypertension. The precise mechanisms of how all the various systems interact to cause hypertension still remain unclear.

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Organs most often associated with hypertension include the vasculature, the kidney, and the brain. Inflammatory cells are present in these organs with hypertension. In the vasculature, accumulation of inflammatory cells in the perivascular adipose tissue of the vessels is noted in hypertension. Sympathetic nerves innervate the perivascular adipose tissue which has confounded our ability to identify the link between the inflammation and sympathetic nerve activation. In and around glomeruli of the kidney, there is extensive perivascular infiltration of leukocytes in kidneys and hearts of transgenic rats harboring the human renin and angiotensinogen genes. Theuer et al demonstrated the role of nuclear factor-kB–mediated inflammation in blood pressure elevation and its effect on the end organ damage.

In this issue, Santisteban et al extend our understanding of the role of inflammatory cells in the genesis of hypertension. In an initial series of studies they demonstrate that the hypertension observed in spontaneously hypertensive rats (SHRs) can be imparted on the normotensive control Wistar-Kyoto rat through bone marrow transplantation of SHR bone marrow into Wistar-Kyoto recipients. They further show that the hypertension observed in SHR can be significantly lowered through the transplantation of Wistar-Kyoto bone marrow into SHR recipients. Those animals with bone marrow from SHR exhibited greater circulating inflammatory cells, regardless of the genetic background of the bone marrow recipient. The investigators demonstrate that this increase in inflammatory cells correlates with increased microglia activation in the paraventricular nucleus of hypothalamus. Animals with SHR bone marrow were shown to have increased sympathetic tone, whereas sympathetic tone was decreased in the presence of Wistar-Kyoto bone marrow transplantation regardless of the genetic background of the recipient.

The increased inflammatory cells and cytokines in SHR bone marrow resulted in increased neuroinflammation and sympathetic nerve activation. The investigators went on to show that hypertension induced by SHR bone marrow or chronic angiotensin II infusion could be inhibited by the oral administration of minocycline. Minocycline, an inhibitor of microglial activation, attenuated hypertension in animals with SHR bone marrow or chronic angiotensin II infusion.

Although the brain is a site of inflammation in hypertension, the mechanisms are not well understood. Ransohoff and Perry showed microglial cells in the brain function similar to activated macrophages. Consistent with what was shown in the study by Santisteban et al, chronic angiotensin II infusion activates microglial cells in the paraventricular nucleus of the forebrain and the efferent end effect is modulation of blood pressure. Minocycline not only prevents microglial activation but also reverses the cytokine production like interleukin-1β, tumor necrosis factor-α, and interleukin-6. Not investigated in this study, inflammatory cell recruitment and engraftment in hypertension have been shown to be mediated by junctional adhesion molecule-1 and its role in hypertension was demonstrated in a study done by Paton and coworkers. Junctional adhesion molecule-1 is known to be up-regulated in the brain stem of SHR and the overexpression of junctional adhesion molecule-1 in the nucleus tractus solitaries raises the blood pressure. In the study, the investigators observed increased levels of CCL2 (chemokine [C-C motif] ligand-2 [aka, monocyte chemoattractant protein-1]) in the hypertension rat models and the reduced level of CCL2 as a treatment response with minocycline, suggesting that the CCL2/CCR2 (C-C chemokine receptor) chemokine axis may have a major role in inflammatory cell extravasation into the central nervous system. This is consistent with studies that have linked the CCL/CCR2 axis in cellular recruitment into the central nervous system.

This study by Santisteban et al demonstrates that presumably genetic differences in hematopoietic stem cells within the bone marrow may be the link between the immune system and abnormalities of the central nervous system. The investigators demonstrate that minocycline has the potential to alter the abnormal physiology of inflammatory cells in SHR. Importantly, this strategy using minocycline is under investigation in patients with drug-resistant hypertension.

An important challenge going forward for the field is to determine whether the mechanisms described in this study by Santisteban et al are limited to specific causes of hypertension. It is possible that the mechanisms described could be present in multiple settings of hypertension, especially those associated with comorbidities such as aging, obesity, and diabetes.
on-going studies is necessary, this study serves as an excellent example of defining stem cell physiology and its potential translation to clinical populations at risk.

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**References**


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