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.

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 CCL2/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.
mellitus are because alterations in the hematopoietic stem cell microenvironment and inflammatory cell phenotype. Based on these findings one could postulate that alterations in stem cell microenvironment and inflammatory cell phenotype could lead to alterations in neuroinflammation, contributing to the hypertension often seen in chronic inflammatory states and the associated increased risk of adverse cardiovascular events. This study highlights our growing understanding of the role of bone marrow stem cells in homeostasis and pathophysiology of disease. End-organ injury has been shown to induce a systemic stem cell response involving the bone marrow, spleen, and injured end organ. As outlined in the Figure, the bone marrow has been shown to have multiple roles in disease and tissue healing.

1. Bone marrow–derived stem cells have been shown to support tumor growth and metastases through the release of mesenchymal stem cells and endothelial progenitor cells.
2. As yet to be defined, bone marrow cells serve as the progenitor for end-organ cells. Cardiac stem cells, which have significant potential to improve cardiac function, are replenished after myocardial injury through proliferation and release of bone marrow–derived stem cells.
3. As highlighted by this study, genotypic or phenotypic differences in bone marrow stem cells can lead to the generation of inflammatory cells with varied activity leading to altered end-organ function, and in the case of SHR marked hypertension. The field eagerly awaits the findings of the on-going clinical trial to determine whether this is an active mechanism for disease in patients with drug-resistant hypertension.

Extending our understanding of the underlying physiology of bone marrow–derived stem cells, how their progeny of circulating stem cells or inflammatory cells contribute to tissue repair or alter end-organ physiology will lead to the development of novel strategies for the prevention or treatment of disease. Although confirmation of these findings by others and 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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