The Good and the Bad
Immune Cells and Hypertension

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Hypertension continues to be a significant worldwide health challenge contributing to the rates of morbidity and mortality related to heart failure, ischemic stroke, renal disease, atherosclerosis, and cardiac hypertrophy. Contributions to hypertension include multiple organs including the kidneys, peripheral vasculature, and the central and autonomic nervous systems. One of the most recent advances in our understanding of underlying factors that influence the development and prevalence of hypertension is the role of the inflammation and the immune system. The role of T cells in the development and prevalence of hypertension is the role of the autonomic nervous systems. One of the most recent advances in our understanding of underlying factors that influence the development and prevalence of hypertension is the role of the inflammation and the immune system.

The role of T cells in the development of hypertension has been demonstrated in number of studies, and both hypertensive humans and male animals models of hypertension have shown T-cell accumulation in the kidneys and vasculature. Furthermore, T cells have been shown to be required for the development of some forms of hypertension. In initial studies using the angiotensin II (Ang II) infusion model of hypertension and a male mouse model lacking lymphocytes because of a deficiency in the recombination activating gene (Rag-1−/−), when these mice were infused with Ang II, the level of hypertension was significantly less than that observed in wild-type male mice. When the T cells from a male wild-type donor were given back to the male Rag-1−/− mice, the hypertensive effects of Ang II were restored, suggesting that Ang II–induced hypertension requires the adaptive immune system and T cells in particular. It should be noted, however, that this effect of T cells to induce hypertension is not present in female animal models and requires using T cells from male donors, suggesting that there are clear sex differences in the role of the immune system in hypertension.

A recent study by Shah et al9 aimed at further exposing the role of the immune system and inflammation in the development of hypertension focused on the role of myeloid-derived suppressor cells (MDSCs). The MDSCs are a heterogeneous population of immature myeloid cells that are known to suppress the effects of the adaptive immune system and T-cell responses in particular. The role of MDSCs in suppressing inflammation-related diseases has been demonstrated in patients with cancer, autoimmune disease, as well as chronic infection and inflammatory bowel disease. Given what we know about the role of inflammation and T cells in the development of hypertension, this new study offers important and timely insight for the role of MDSCs in the development of hypertension.

The study by Shah et al9 offers a comprehensive and through examination of the effect of MDSCs in 3 different forms of hypertension including Ang II infusion induced hypertension. hypertension induced by giving mice L-N-nitroarginine methyl ester (L-NAME) supplements and also a high-salt model of hypertension. Importantly, all of the mice used in the study were male and so the results can only be extrapolated to the role of MDSCs in males. The authors measured the numbers of peripheral CD11b+Gr1+ myeloid cells in all the models. In the Ang II hypertensive mice, increases in the circulation and spleen of CD11b+Gr1+ myeloid cells were reported when compared with normotensive controls. Importantly, this increase in CD11b+Gr1+ myeloid cells was not dependent on the Ang II because both the L-NAME–induced hypertensive mice and the high-salt–fed mice, which both exhibited significant increases in blood pressure, also had increases in circulating CD11b+Gr1+ myeloid cells. These results are the first to suggest that increases in circulating CD11b+Gr1+ myeloid cells are a general characteristic of hypertension in males.

However, if hypertension is now known to be related to activation of the immune system and T cells and increases in T-cell end-organ infiltration and MDSCs are thought to inhibit inflammatory responses and T-cell activation, why would MDSC cells be increased in hypertension? Could it be that hypertension-induced increases in MDSCs is a compensatory mechanism that occurs in concert with increases in T-cell activation and inflammation? Shah et al9 addressed this question directly by examining the effect of MDSC inhibition on the development of hypertension. In both the Ang II and the L-NAME models of hypertension, the authors reported an increase in the splenic T-cell expression of the proinflammatory cytokines IFN-γ and tumor necrosis factor-α and in T-cell interleukin (IL)-17. Both models of hypertension exhibited an increase of IFN-γ, tumor necrosis factor-α, and IL-17+ cells among both CD8+ and CD4+ T cells. When MDSCs were suppressed by 2-week treatment with anti-Gr1 antibody, there was a further increase in IFN-γ, tumor necrosis factor-α, and IL-17+ T cells. The depletion of MDSCs also resulted in a further increase in blood pressure and increases in T-cell infiltration of the kidney. These results show us that the role of the immune system in modulating hypertension involves not only activation of T cells and increases in inflammation, but also a
concomitant activation of MDSCs, which serve to buffer the pathological consequences of T-cell activation and the resulting hypertension.

The evidence for a protective role of MDSCs is broadened when these authors examined whether hypertensive mice that were given additional MDSCs via adoptive transfer exhibited any attenuation in the hypertension. These experiments used MDSCs from mice that were either hypertensive or normotensive. In the first set of experiments, the adoptive transfer with MDSCs was begun before the infusion of Ang II. In mice that received the MDSCs that had been primed in hypertensive mice, the Ang II–induced increases in blood pressure were significantly reduced. Furthermore, if mice were allowed to develop Ang II hypertension for 7 days and then received adoptive transfer of MDSC derived from bone marrow, the hypertension was resolved to control, nonhypertensive levels within 27 days. These results suggest that MDSCs may hold a clue for future development of new therapies to treat hypertension.

In summary, the study by Shah at al offers us insights as to the dual nature of the role of inflammatory cells in hypertension. These new data provide novel and interesting data on the role of MDSCs in hypertension and their potential to modulate the inflammation that is associated with hypertension. Key to translating these findings into understanding their role in hypertension in humans will require an in-depth evaluation of the types of MDSCs and T cells expressed in both men and women who are hypertensive. Unfortunately, the lack of inclusion of female animals in this study leaves us with no information, to date, on the role of MDSCs in hypertension in females. As to the potential for MDSCs as a therapeutic strategy in hypertension, this will most likely limited by the fact that these cells are known to suppress the host immune system and induce malignant tumor cell growth. Studies in cancer therapy have shown that the generation of MDSC is evoked by increases in granulocyte colony-stimulating factor, IL-6, granulocyte monocyte colony-stimulating factor, IL-1β, prostaglandin E2, tumor necrosis factor α and vascular endothelial growth factor ultimately leading to an inhibition of T-cell activation resulting in a suppressed immune environment that is permissive to tumor cell growth. Are these same factors responsible for the induction of MDSCs in cancer similar to the factors that induce MDSCs in hypertension? Additional studies are needed to elucidate the time course and cellular mechanisms involved in MDSC activation in hypertension. Furthermore, we know little about the specific mechanisms by which MDSCs inhibit T-cell activation in hypertension. Shah et al have shown that the antihypertensive effects of MDSCs are dependent on their ability to produce reactive oxygen species, but we also know that Ang II–dependent hypertension requires the production of reactive oxygen species in the brain and that inhibition of reactive oxygen species production in the brain prevents Ang II hypertension. Additional studies focused on furthering our understanding how MDSCs are induced in hypertension and the mechanisms by which they suppress T-cell activation in both males and females will be important for our understanding of the role of the immune system in the development of hypertension.

Disclosures

None.

References


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