The nerve of the spleen! Causing hypertension by placental growth factor

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This editorial refers to ‘Deoxycorticosterone acetate-salt hypertension activates placental growth factor in the spleen to couple sympathetic drive and immune system activation’ by M. Perrotta et al., pp. 456–467.

Excessive salt intake increases blood pressure in approximately one-half of hypertensive humans. Despite substantial investigation, the precise mechanisms underlying this salt sensitivity remain unclear. In this issue of Cardiovascular Research, Perrotta et al. demonstrate a critical role of sympathetic outflow to the spleen in the genesis of an experimental form of salt-dependent hypertension, the deoxycorticosterone acetate (DOCA)-salt model. They showed that either splenectomy or splenic denervation (by removal of the celiac ganglion) prevents the elevation of blood pressure caused by DOCA-salt challenge in mice. Traditionally, hypertension research has focused on the effects of sympathetic nerves on blood vessels and the kidney, where released norepinephrine causes vasoconstriction and promotes renin release and sodium reabsorption. But how could sympathetic innervation of the spleen affect blood pressure? Perrotta et al. illustrate an important role of the placental growth factor (PlGF) in this response. They show that DOCA-salt hypertension causes a striking increase in this factor in the marginal zone of the spleen, and that the hypertensive response to DOCA-salt is completely prevented in mice lacking PlGF. PlGF mice were also significantly protected from renal immune cell infiltration, and renal injury as reflected by decreases fibrosis and preserved creatinine clearance. This work follows on prior research from this group showing a critical role of PlGF in Ang II-induced hypertension, but shows for the first time how important this factor, and sympathetic activation of this factor is in salt-dependent hypertension.

This article adds to a growing body of evidence that the immune system, and in particular T cells, play crucial roles in hypertension. Perrotta et al. show that the T cell-rich region of the spleen (white pulp) decreases in normal mice upon DOCA-salt hypertension but not in PlGF-deficient mice. This finding is compatible with T cell egress from the spleen, and illustrate for the first time that sympathetic nerves and PlGF are needed for this response. Classically, T cells require three signals for activation. Signal 1 is detection of an antigenic peptide in the context of a major histocompatibility complex by a specific T cell receptor. Signal 2 co-stimulation, mediated by interaction between receptors on T cells and ligands of antigen-presenting cells. One of the best-characterized Signal 2 is mediated by the interaction of the B7 ligands CD80 and CD86 on antigen presenting cells with CD28 on T cells. We previously showed that deletion of B7 ligands or pharmacological inhibition of this interaction prevents both Ang II and DOCA-salt hypertension. Signals 1 and 2 occur in the immunological synapse, along with other ligands and receptors shared between the antigen-presenting cell and the T cell. Signal 3, in contrast, involves action of a variety of agonists on accessory receptors on T cells, including G-protein linked receptors, Toll-like receptors and others. Signal 3 can skew T cells to specific phenotypes. For example, IL12 promotes formation of Th1 cells, while IL-6 and TGFβ can skew cells to a Th17 phenotype. In addition to this complex signalling on T cells, many of these factors, like cytokines and Toll-like receptor ligands, can promote maturation of antigen-presenting cells, enhancing their ability to stimulate T cells, in part by increasing expression of co-stimulatory molecules, such as CD80 and CD86 and enhanced major histocompatibility complex surface expression and enhancing the ability to process antigens.

Given this background, one must ask what PlGF is doing, and by extension how sympathetic stimulation affects T cell activation in hypertension. The data from Perrotta et al. suggest that PlGF likely acts on antigen-presenting cells to increase expression of the co-stimulatory molecule CD86. The authors did not present data regarding CD80, another important B7 ligand but the expression of this molecule is less often up-regulated in the inflammatory setting. Although the authors localized PlGF to the marginal zone of the spleen, where macrophages and fibroblasts exist, it is possible that PlGF could provide a Signal 3 directly to T cells, because the investigators saw such a striking increase in egress of these cells from the spleen in the PlGF-deficient mice. Mobilization of T cells is dependent on a complex pathway involving the sphingosine 1-phosphate receptor 1, down-regulation of L-selectin, down-regulation of CCR7, and increases in surface expression of CCR5 and other chemokine receptors. How PlGF might affect these responses remains undefined.

Perrotta et al. suggest that noradrenaline released by sympathetic nerves stimulates PlGF release in the spleen. The precise adrenergic receptor(s) involved in this response have not been defined but potentially could be pharmacologically inhibited to prevent PlGF activation in humans. It is also possible that other neural mediators, including Neuropeptide Y or vasoactive intestinal peptide play a role in this response.
Finally, the article by Perrotta et al. raises the question of the importance of the spleen as a secondary lymphoid organ. In the mouse, it seems to be very important, because splenectomy completely prevented the hypertensive response to DOCA-salt. Likewise, the authors elegantly showed that transplant of PlGF-deficient spleens to wild type mice prevented DOCA-salt hypertension. In humans and in other larger animals, one wonders if peripheral lymph nodes might also contribute, due to their relatively larger size. Of note, Kalpaktsoglou et al. reported a compensatory increase in cellularity of the aortic and axillary lymph nodes following splenectomy in mice, suggesting that peripheral lymph nodes might have a compensatory role after splenectomy. Of note, we have also found that hypertension-specific memory T cells home to the bone marrow and can be reactivated by mild subsequent hypertensive challenges. Importantly, the bone marrow and lymph nodes receive substantial sympathetic innervation. Likewise, tertiary accessory lymphoid tissues have been observed in atherosclerosis and other inflammatory states and might have a role in the systemic T cell response. The action of PlGF in lymph nodes, the bone marrow, and accessory lymphoid tissues might mirror its effect in the spleen (Figure 1) but warrants further investigation.

In summary, the article of Perrotta et al. extends our understanding of how the sympathetic nervous system can signal the adaptive immune system in hypertension, particularly in salt-induced hypertension. As the authors point out, this axis involving sympathetic nerves, PlGF, antigen-presenting cells, and ultimately T cells is a potential target for therapeutic intervention and certainly invites further investigation.

**Figure 1** The role of PlGF in the pathogenesis of hypertension. Hypertensive stimuli such as salt, Angiotensin II, and cytokines/chemokines activates the sympathetic nervous system that innervates the spleen, secondary lymphoid organs, and the bone marrow. Activation of T cells occurs not only through the release of PlGF in the spleen but also possibly via analogous mechanisms in the lymph nodes and bone marrow. Activated T cells traffic to the kidney causing subsequent renal inflammation and end-organ damage, promoting the development of hypertension.

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**References**


**Conflict of interest:** none declared.

**Funding**

This work was supported by National Heart and Blood Institute of the National Institutes of Health grants (R01HL039006-27, R01HL125865-04 and P01HL129941), an American Heart Association Strategically Focused Research Network Grant (14SFRN20420046), and an National Institutes of Health institutional training grant award (T32HL069765) to J.V.B.