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COMMENTARY

Hypertension: an autoimmune disease?

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In the current issue of *Hypertension Research*, Stumpf *et al.*[1] link T helper 1-mediated inflammation to essential hypertension. This study adds to the available evidence that the adaptive immune system contributes to hypertension.

The etiology of hypertension is still largely unknown. Although a pheochromocytoma, renal artery stenosis or Conn's disease can be detected in some patients with hypertension, in most such patients, no clear etiology can be found.

Some studies indicate that hypertension is a vascular disease, whereas others suggest that it is primarily a disease of sodium transport. Additionally, there is clear evidence that the central nervous system has a critical role in hypertension. In about half of hypertension patients, blood pressure remains high despite the use of antihypertensive therapy. Therefore, there is a clear need for therapeutic approaches based on new mechanistic insights.

Over the past three decades, studies have demonstrated that the immune system contributes to hypertension. First, increased blood pressure levels were found to be significant predictors of C-reactive protein levels (a nonspecific marker of inflammation).[2] Second, T cells were shown to have a role in experimental models of hypertension.[3–5] In addition, an increased incidence of hypertension has been found in immune-mediated diseases, such as rheumatoid arthritis and psoriasis.[6] Furthermore, immunosuppressive therapy with mycophenolate mofetil, and possibly other immunosuppressive drugs, lowers blood pressure in these diseases.[6,7] Finally, patients with acquired immune deficiency syndrome have a significantly lower incidence of hypertension when the disease is untreated (that is, with low numbers of CD4 T cells), but blood pressure increases during highly active antiretroviral therapy (that is, with reconstitution of CD4 T cells).[8] In 2007, a landmark study by Guzik *et al.*[4] presented convincing evidence supporting a pathophysiological role for T cells in the development of hypertension. Mice that lacked T cells had a blunted response to angiotensin II infusion or deoxycorticosterone acetate (DOCA) salt challenge. Adaptive transfer of T cells completely restored blood pressure elevation.

The antigen that is recognized by T cells has not yet been extensively studied. Elevated levels of autoantibodies against oxidatively modified low-density lipoproteins can be detected in patients with hypertension, suggesting that oxidized low-density lipoprotein might be the antigen.[9] Indeed, we recently demonstrated that immunoglobulin G antibodies to oxidized low-density lipoproteins were elevated in patients with cerebral small vessel disease as compared with patients with uncomplicated hypertension.[10] Interestingly, protective immunoglobulin M antibodies were lower in patients with cerebral small vessel disease as compared with uncomplicated hypertension patients.

Activated (probably antigen specific) T cells infiltrate the fat adjacent to blood vessels and kidneys, resulting in a local release of cytokines, endothelial dysfunction and, subsequently, renal retention of sodium. These factors may ultimately cause persistent blood pressure elevations.

T cells express not only the T-cell receptor that recognizes antigens but also many costimulatory molecules. Neurohumoral receptors are also present on T cells. Importantly, angiotensin type 1 receptors are expressed on T cells.[11] When stimulated by angiotensin II, skewing toward T helper 1 cells is observed. Stumpf *et al.*[1] found that hypertensive patients had significantly higher CXCL10/IP10 levels than controls and that plasma levels of CXCL10/IP10 correlated with systolic blood pressure. Previously, Antonelli *et al.*[12] had also demonstrated significantly higher CXCL10/IP10 levels in patients with hypertension as compared with controls. CXCL10/IP10 is a chemokine that promotes the migration of activated T helper 1 cells into tissues.[13]

T helper 1 cells primarily express interleukin (IL) 2, interferon-γ and tumor necrosis factor. By contrast, T helper 2 cells primarily express IL4, IL5, IL6 and IL13.

There is little evidence that T helper 2 cells also have a role in the pathogenesis of hypertension. However, Stumpf *et al.*[1] not only confirmed previous findings that CXCL10-/IP10 levels were elevated in hypertension (suggesting T helper 1 involvement) but also found elevated levels of T helper 2 cell cytokines, such as IL4 and IL13.[1]

T helper 2 cells are generally believed to be anti-inflammatory. However, experimental studies of atherosclerosis indicated that Th2 cells could accelerate the atherosclerotic process in certain conditions.[14]

In addition to T helper 1 and T helper 2 cells, T helper 17 cells were recently described. These cells have been implicated in the pathogenesis of many autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis.

Remarkably, Madhur *et al.*[15] recently demonstrated that patients with diabetes mellitus complicated by hypertension had significantly higher levels of IL17 (a marker of T helper 17 cells) than did diabetic patients who were normotensive. These findings suggest that, like T helper 1 and 2 cells, T helper 17 cells may be involved in the pathogenesis of hypertension. The fact that all these T-cell subsets might be activated indicates abnormal regulation of the immune system. Importantly, in the past decade, it became clear that several types of T cells are known to function as so-called regulatory T cells. In

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autoimmune diseases such as multiple sclerosis and rheumatoid arthritis, these regulatory T cells either are decreased in number or do not function correctly. Recently, Viel *et al.*[16] demonstrated in an experimental rat model of genetic salt-sensitive hypertension that dysfunctional regulatory T cells were related to hypertension.[16] These regulatory T cells should be further studied in patients with hypertension. Interestingly, vitamin D has recently received attention as a factor that may influence the function of regulatory T cells.[17] Vitamin D deficiency is associated with hypertension,[18] and a meta-analysis found that vitamin D supplementation resulted in a (small) reduction of systolic blood pressure.[19]

In conclusion, various T-cell subsets may have a role in hypertension. Clearly, more studies on the relationship between adaptive immune system and hypertension are needed to confirm the hypothesis that essential hypertension is an autoimmune disease.

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