In Search of the T Cell Involved in Hypertension and Target Organ Damage

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Inflammation significantly increases cardiovascular risk.1,2 This is manifested clinically by increased atherosclerosis in rheumatoid arthritis or systemic lupus erythematosus or by increased risk of myocardial infarction after infections. Importantly, recent evidence suggests that inflammation is important in the pathogenesis of hypertension and associated organ damage.1,2 Although the idea that inflammation caused by hypertension mediates target organ damage, including vascular stiffness, cardiac fibrosis, and kidney damage, is well accepted,1 the concept that immune activation may cause increased blood pressure is novel. We should, however, appreciate that already in the 1960s the first reports of immune dysfunction in hypertension had been published.1,2 More recently, we have shown that RAG1−/− mice, which lack mature T and B lymphocytes, are protected from severe angiotensin II–induced or deoxycorticosterone acetate-salt hypertension and vascular damage.4 Similar findings were confirmed in mice with severe combined immunodeficiency,3 and more recently in RAG1−/− Dahl salt-sensitive rats, which were protected from salt-sensitive hypertension, cardiovascular hypertrophy, and renal damage.6 These hypertensive phenotypes are dependent on T-cell activation.7,8 Interestingly, subsequent studies showed that the genetic removal of monocytes also protected mice from severe hypertension, in part, through the natural killer cell–dependent mechanisms.7,8 This demonstrates the complexity of the immune activation in hypertension, which is addressed by Li et al in the current issue of Hypertension. Understanding of these novel, immune mechanisms of hypertension will create the possibility of immunomodulatory approaches in the treatment of hypertension. For example, blockade of tumor necrosis factor-α can lower blood pressure.4 Similarly, mycophenolate mofetil, which primarily targets T and B cells, are protected from severe hypertension, in part, through the natural killer cell–dependent mechanisms.7,8 This demonstrates the complexity of the immune activation in hypertension, which is addressed by Li et al in the current issue of Hypertension. Understanding of these novel, immune mechanisms of hypertension will create the possibility of immunomodulatory approaches in the treatment of hypertension. For example, blockade of tumor necrosis factor-α can lower blood pressure.4 Similarly, mycophenolate mofetil, which primarily targets T and B cells, prevents the development of hypertension and urinary excretion of tumor necrosis factor-α in patients with psoriasis or rheumatoid arthritis.10

Although this creates a proof of concept that immunomodulation can aid in blood pressure control and can prevent target organ damage, the risk:benefit ratio needs to be taken into consideration. Thus, we need to identify the exact mechanisms of immune cell involvement in hypertension and should develop specific inhibitors of these mechanisms, possibly without affecting the antimicrobial immune defenses.

In the article published in the current issue of Hypertension, Li et al demonstrate that a specific subset of T cells, carrying the γδ T-cell receptor is a major source of interleukin-17 (IL-17), which not only participates in the development of long-term hypertension but is a key regulator of cardiac fibrosis associated with hypertension. γδ T cells represent a small subset of T cells, which are known to have a prominent role in the recognition of lipid antigens. They are of an invariant nature and may be triggered by alarm signals, such as heat shock proteins. These are best described in the gut mucosa and are a bridge between innate and adaptive responses. The increased presence of γδ T cells in hypertensive vessels was demonstrated previously, and Li et al focus on their presence in the myocardium. An interesting finding is that these cells produce large amounts of IL-17, much more than produced by any other subset of T cells. Li et al confirm that IL-17A is a key prohypertensive and demonstrate that it is a key profibrotic cytokine. This is in line with the findings by Madhur et al showing that angiotensin II–dependent hypertension is reduced in IL-17−/− mice, and patients with hypertension show higher IL-17 plasma levels. The role of IL-17 may be more complex, as recently a study has demonstrated that a deficiency of the IL-17/IL-23 axis accelerates renal injury in mice with deoxycorticosterone acetate+angiotensin II–induced hypertension.12 This complexity requires further elucidation, but it is possible that depending on the prohypertensive milieu and stage of hypertension, the role of IL-17–producing cells may differ. Li et al show that IL-17A production by local infiltrating γδ T cells, rather than classical CD4 or CD8 T cells, is critical for cardiac damage and fibrosis in response to angiotensin II infusion. This effect was in part dependent on IL-17A–induced acceleration of myofibroblast differentiation through the promotion of IL-6 production from cardiac fibroblasts (Figure). Mice lacking the T-cell–derived cytokine IL-17A were also protected against aortic stiffening, as IL-17A induced collagen 3a1 expression via the activation of p38 mitogen-activated protein kinase in angiotensin II hypertension.13 Moreover, treatment of deoxycorticosterone acetate-salt rats with anti–IL-17 antibody significantly reduced arterial hypertension, the expression of profibrotic and proinflammatory mediators and collagen deposits in the heart and kidney. Moreover, part of the protective effects of spironolactone in hypertension seems to be exerted through inhibition of the IL-17 axis.
Interestingly, Bellini et al. recently demonstrated that IL-17A increases proliferation of fibrocytes, the hematopoietic precursor cells involved in fibrosis (Figure). Angiotensin II signaling may contribute to the pathogenesis of renal fibrosis by recruitment of fibrocytes in the bone marrow and by activating these cells in the tissue. Although this aspect was not investigated by Li et al., it is interesting that T cells have been shown to mediate differentiation of monocytes into fibrocytes, which brings us back to immune mechanisms of hypertension.

In summary, an increasing body of evidence shows that IL-17 emerges as a key regulator of fibrosis in hypertension and is critical in the regulation of blood pressure increase. Furthermore, Li et al attribute its production in the heart to γδ T cells.

We now need to address the role of IL-17 in hypertension and cardiac/renal damage in clinical studies. Humanized anti–IL-17 monoclonal antibody, ixekizumab, is used in the treatment of psoriasis. However, further studies are required to demonstrate whether IL-17 antagonists may be effectively used in the treatment of severe hypertension, or at least psoriasis-related hypertension.

In addition, linking IL-17 with IL-6 in this process is crucial, as chronic angiotensin II infusion also stimulates IL-6 production and an increase of arterial pressure and this effect may be blocked in IL-6 knockout mice. Thus, IL-6 antagonists, such as tocilizumab, might provide yet another tool in modulating inflammation in hypertension.

Although γδ T cells seem to be important in cardiac fibrosis and damage, several other candidate T cells for hypertension remain. Youn et al. provided evidence that T-cell–derived inflammation contributes to human hypertension. They demonstrated an increased fraction of immunosenescent cytotoxic T cells (CD8+CD28nullCD57+) in the circulation of patients with hypertension. More importantly, these cells were preferentially targeted to the kidneys of hypertensive individuals. The link of these cells to IL-17 producing γδ T cells remains unclear.

This study by Li et al. brings another important point to our understanding of the immune mechanisms of hypertension. It brings to our attention an interaction between the monocyte and the T cell in this process (Figure), which could explain why removal of both cells separately would result in the protection from hypertension. Monocyte-secreted IL-1β, rather than cardiac fibroblast–secreted IL-6 or transforming growth factor-β, was required for IL-17A production from γδ T cell.

In summary, Li et al. show that a triangular positive feedback loop exists between monocytic-secreted IL-1β, γδ T cells in hypertensive cardiac damage
T-cell–derived IL-17A, and cardiac fibroblast–produced IL-6, which triggers cardiac fibrosis in hypertension. These results provide a possible mechanism for the development of fibrosis beyond myocardium, as IL-17 is also key in the development of arterial stiffness and renal damage. We now need studies to address the importance of IL-17 in human hypertension and we need to determine whether γδ T cells participate in fibrosis in other organs and conditions as these cells may provide a particularly valuable link in understanding the immunopathogenesis of hypertension.

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