Complementing T Regulatory Cells to Combat Hypertension

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With the recent updates to the definition of hypertension,[1] it is expected that over half the adults in the United States will have elevated, stage 1 or stage 2 hypertension and may require blood pressure-lowering medication. Many of the current hypertension medications target the renin–angiotensin system and affect cells within the kidney and vasculature, but basic scientists are discovering new targets for the treatment of hypertension.

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There is now overwhelming evidence that inflammation and immunity promote the development and maintenance hypertension.[2,3] The immune system is divided into 2 branches: the innate, which spontaneously responds to danger signals presented by foreign invaders, and the adaptive, which involves specific cell-mediated responses. It is inevitable that innate and adaptive processes work together to defend the host from pathogens and harm. In this issue of *Circulation Research*, Chen et al[4] explains the intriguing relationship between complement activation (an innate response) and T regulatory (Tregs) cells (an important player in the adaptive response) and their roles in the pathogenesis of hypertension.

The complement system is an intricate mechanism consisting of 3 different pathways (ie, classical, mannan-binding lectin, and alternative pathways) that use >30 blood-bound proteins that are instinctively activated in response to pathogen- or danger-associated molecular patterns.[5–7] Within the classical pathway, complement activation products, C3a and C5a, are produced by immune cells and on release can bind to their receptors on other T cells, macrophages, and dendritic cells to initiate a local inflammatory response. Although this can serve as a protective mechanism to combat pathogens, too much of a good thing can be detrimental as we are discovering. For example, C3a and its receptor (C3aR), as well as C5a/C5aR are increased in the serum and kidneys in different models of hypertension suggesting an association that may be causative.[4,8,9] However, previous studies have shown that a single deficiency of C3aR (the C3aR$^{-/-}$) or C5aR (C5aR$^{-/-}$), did not alter the progression of angiotensin II–induced hypertension.[9] This suggests a compensatory response; in fact, Chen et al[4] demonstrated that as one component of complement is lacking in the animal the other component is present and remains detrimental. The next obvious question is what happens when both inflammatory mediators are removed from potentially pathogenic environments?

Chen et al[4] conducted eloquent studies where both C3aR and C5aR were deficient in mice subjected to angiotensin II–induced hypertension. These double knockout (DKO) mice were not only protected from hypertension, but also the accumulation of renal proinflammatory mediators (ie, IFN [interferon]-γ, IL [interleukin]-1β, IL-6, VCAM [vascular cell adhesion molecule]-1, and MCP [monocyte chemoattractant protein]-1), renal oxidative stress (ie, superoxide), and renal injury (ie, glomerular damage, collagen deposition, NGAL [neutrophil gelatinase-associated lipocalin], and osteopontin).[4] The effects were not only noted in the kidney, but the vascular dysfunction usually promoted by angiotensin II–induced hypertension, as well as the vascular oxidative stress and fibrosis, were attenuated by inhibiting C3a and C5a from interacting with their receptors in DKO mice.[4]

Renal Tregs were also elevated in DKO mice compared with wild-type mice after angiotensin II infusion, a finding that adds both mechanistic insight and translational promise to the Chen et al[4] study. C3aR and C5aR are indeed expressed by natural Tregs that are derived from the thymus, and activation of these receptors inhibit the known anti-inflammatory actions of Tregs.[7] Because renal Tregs containing a member of the FoxP3 (forkhead transcription factors) are reduced in angiotensin II–induced hypertension and other models of hypertension,[4,10,11] and because components of the classical complement pathway are enhanced systemically and specifically on these Tregs in hypertension,[4,8,9] it is thought that these responses would promote inflammation and that blockade of complement signaling would be immunosuppressive. In fact, the absence of complement signaling in DKO mice promoted the switch from CD4^{+}CD25^{-} T cells to anti-inflammatory CD4^{+}CD25^{+}FoxP3^{+} Tregs and enhanced the function of these cells. The importance of Tregs in this protection was recapitulated in studies where T regs were successfully depleted from the blood, spleen, and kidney of DKO mice by anti-CD25 antibody and the protective effect on blood pressure, renal, and vascular injury in these mice was abolished after Treg neutralization. Furthermore, Tregs from DKO mice lacking an active complement system adoptively transferred into wild-type mice effectively prevented angiotensin II–induced hypertension, confirming the power of these Tregs.

The results provoke the rhetorical question: what is the significance of these results in understanding essential hypertension? If enhancing Tregs can combat hypertension and eliminating the classical pathway of complement can enhance Tregs, can these findings be translated to produce a therapy that can be used in the clinics? The study by Chen et al[4] confirmed that C3a and C5a are increased in hypertensive patients and that

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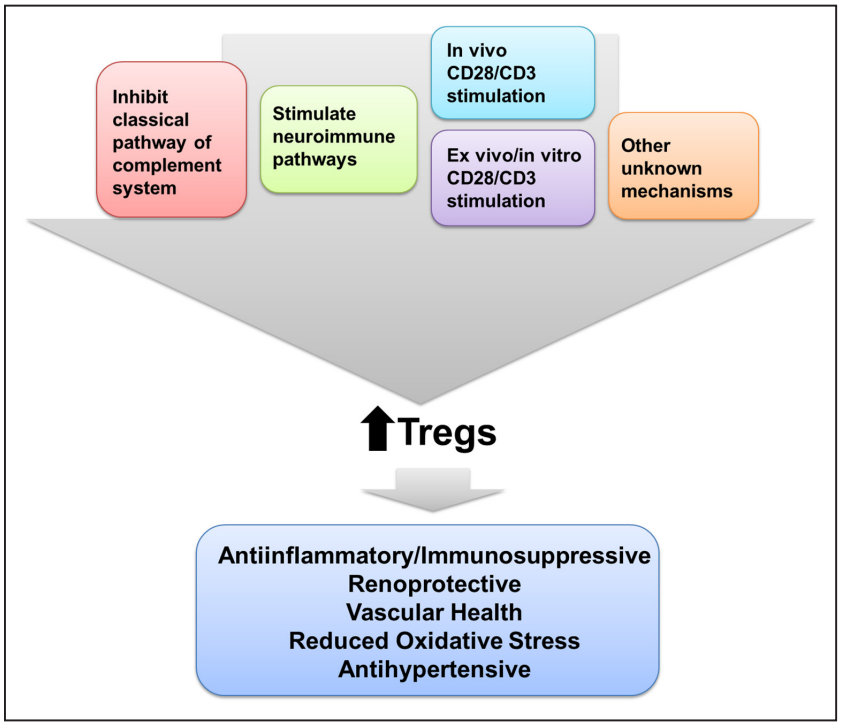

Figure. Therapeutic applicability of enhancing T regulatory (Tregs) cells. There is strong evidence that blockade of complement activation product signaling through the C3a receptor (C3aR) and C5aR enhances the anti-inflammatory function of Tregs. Other mechanisms have also been effective in augmenting Tregs. For example, activation of a particular neuroimmune axis (termed the cholinergic anti-inflammatory pathway) via vagus nerve stimulation increases Tregs. In addition, in vivo stimulation of Tregs using an anti-CD28 superagonistic monoclonal antibody, and ex vivo/in vitro stimulation via anti-CD28/CD3 monoclonal antibody-coated beads both are known to modulate Tregs. Because the reduction of Tregs is usually pathogenic and because adoptive transfer of Tregs has been shown to be therapeutic, it is important to effectively optimize methods to enhance Tregs to potentially combat chronic inflammatory disorders with oxidative stress including renal diseases, vascular diseases, and importantly, hypertension.

Tregs from these patients have increased C5aR, so blocking the complement system could indeed be protective and serve as a new therapeutic target for hypertension. Other studies have demonstrated effective mechanisms to enhance T regs in vivo or in vitro (Figure).[12,13] In addition, physiology teaches us that it is rare that a system works alone and indeed manipulation of Tregs by other mechanisms known to modulate these cells like neuroimmune pathways may provide a synergistic protective effect.[14] As critical components elucidating the association between immunity and hypertension continue to emerge, we should remain open to the idea that blood pressure-lowering therapies that target multisystem/multi-organ interactions will likely be most successful in the fight against hypertension.

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