Remarkable advances in our understanding of innate and adaptive immunity have shed light on why inflammation is centrally involved in the pathogenesis of many diseases traditionally not viewed as primarily inflammatory in nature. One key area of progress has been the discovery and study of innate immune receptors, referred to as pattern recognition receptors (PRRs), such as toll-like receptors and nod-like receptors. PRRs recognize molecules commonly produced by microbial pathogens, broadly defined as pathogen associated molecular patterns (PAMPs), but PRRs also recognize self molecules that are indicators of cell injury or death. These self molecules, called damage-associated molecular patterns (DAMPs), include reactive oxygen species, intracellular crystalline deposits, normal molecules in abnormal locations (ATP, heat shock proteins, nuclear proteins), and many others. DAMPs may be induced or change location because of cell injury or death by any number of causes (genetic, traumatic, toxic, metabolic), and their recognition by innate immune system receptors will initiate responses that include local and systemic inflammation. This is why diseases with just about any underlying cause may be expected to have an inflammatory component. Importantly, the innate immune system has evolved to amplify and modify responses to best combat diverse infections, but these amplified and specialized responses, if inappropriately targeted against self, may themselves become intrinsic to the progression of disease processes. One way this can occur is by innate immune stimulation of adaptive immune responses mediated by T lymphocytes. In fact, normal protective T cell-mediated immunity requires a kick-start by the innate immune system, a condition that ensures that we do not readily mount powerful and potentially harmful adaptive immune responses when there is no real damage or danger present.

Article see p 2529

One of major ways in which innate immunity promotes T cell-mediated immunity is through the activation of antigen-presenting cells such as dendritic cells (DCs). DCs process and present protein antigens, in the form of peptides bound to major histocompatibility (MHC) molecules, for recognition by the T cell antigen receptors. DCs express many pattern recognition receptors, and therefore become activated by PAMPs and DAMPs, leading to enhanced antigen processing capabilities, increased MHC expression, and migration from infected or damaged tissues into lymph nodes where naïve T cells are located. Importantly, pattern recognition receptor signaling in DCs also increases the expression of cell surface costimulatory molecules, which bind to different receptors on T cells. Concomitant signaling by the T cell antigen receptor and the costimulatory receptor are essential for activation of naïve T cells. The result is clonal expansion and differentiation into effector T cells capable of microbial defense and/or tissue injury. Several molecules possess costimulatory activity, but arguably the most important are CD80 (B7-1) and CD86 (B7-2) on activated DCs, which bind to CD28 on T cells. Our understanding of the essential role of CD80 and CD86-mediated costimulation for T cell activation has lead to the development of drugs for autoimmune diseases. For example, cytotoxic T lymphocyte antigen-Ig (CTLA4-Ig) (abatacept and belatacept) is a fusion protein blocker of CD80/CD86 approved for treatment of rheumatoid arthritis. In this issue of Circulation, Vinh and colleagues report that CTLA4-Ig treatment of mice prevents angiotensin or desoxycorticosterone acetate (DOCA)-salt-induced hypertension, and the drug effect is mimicked by genetic CD80/CD86 deficiency. These results support the concept that hypertension belongs in the list of cardiovascular diseases for which immunomodulatory therapy should be considered.

Considering that cell injury from many different causes can induce innate responses, and that innate immunity enhances the ability of antigen-presenting cells to activate T cells, it is not surprising that T cell responses may be found in the setting of many different disorders, including cardiovascular diseases. The participation of T cells in atherosclerosis was first described in the 1980s by Goran Hansson and colleagues, and there is now extensive literature describing how T cells contribute to atherosclerotic lesion growth and destabilization of advanced lesions. More recently, T cells have been shown to contribute to inflammatory processes within adipose tissues in the setting of metabolic syndrome. The possibility that T cells contribute to hypertension was addressed more than 25 years ago in studies of DOCA-salt-induced hypertension in control versus thymectomized mice. However, as recently reviewed elsewhere, there has only been modest attention paid to T cells in hypertension. Based on work from several laboratories, and in particular studies from David Harrison’s laboratory, T cells may now be taking on a larger role as culprits in hypertensive disease.

Setting the stage for Vinh and colleagues’ current article on costimulatory blockade, the Harrison group previously...
showed a requirement for T cells in angiotensin II or DOCA-salt-induced hypertension in mice.\textsuperscript{11} In wild-type mice, they saw a striking effect of angiotensin II infusion on T cell activation and on infiltration of T cells into periaortic fat. They used an adoptive transfer approach into lymphocyte-deficient (Rag-1\textsuperscript{-/-}) mice to demonstrate that T cells are required for development of full blown hypertension in either angiotensin II or DOCA-salt models. Furthermore, adoptive transfer of T cells lacking the angiotensin type I receptor or a functional nicotinamide adenine dinucleotide phosphate oxidase gene resulted in blunted angiotensin-II-dependent hypertension and decreased aortic superoxide production. In the current study, Vinh and colleagues addressed the potential involvement of the B7/CD28 pathway in mouse hypertension. They found that CTLA4-Ig ameliorated angiotensin II induced hypertension and reduced vascular superoxide production. CTLA4-Ig treatment blocked the ability of angiotensin II to increase numbers of circulating activated T cells, and the drug also inhibited T cell infiltration into periaortic fat. Moreover, CTLA4-Ig also blocked angiointestin-induced increases in T cell tumor necrosis factor-\alpha and IFN-\gamma production. Cognizant of the fact that costimulator expression on antigen presenting cells is critical for T cell activation, Vinh and colleagues examined secondary lymphoid tissue DCs and found that CD86 (but curiously not CD80 or class II MHC) was selectively increased in angiotensin-II-treated mice. All the effects of CTLA4-Ig treatment were also found in CD80/CD86-deficient mice as well as wild-type mice transplanted with CD80/CD86-deficient bone marrow. Remarkably, transplantation of wild-type bone marrow into CD80/CD86-deficient mice completely restored angiotensin-II-induced effects on hypertension and T cells. CTLA4-Ig also prevented DOCA-salt-induced hypertension and associated T cell activation and aortic infiltration. Finally, CTLA4-Ig could also reverse established angiotensin II and DOCA-salt-induced hypertension.

The findings from this study by Vinh et al and the previous study from the Harrison’s laboratory discussed above\textsuperscript{11} clearly establish that T cells contribute to hypertensive disease and vascular pathology in mouse models. Many questions are raised by this work, which will require additional investigation to fully understand how T cells contribute to the murine disease models and to determine if they contribute to human disease. The adaptive immune system has evolved to rely on exquisitely specific clonally distributed antigen receptors for lymphocyte antigen recognition and activation. Therefore, when T cells are implicated in a disease process, one of the first questions to arise is which antigens are being recognized? The authors emphasize that the requirement for
CD80/86-mediated costimulation in the mouse models indicates that antigen recognition by T cells is key, rather than nonspecific perivascular accumulation of previously activated/memory T cells of any specificity. A similar argument has been made for proatherogenic T cell responses, which are dependent on CD80/CD86-mediated costimulation.12 Nonetheless, the actual specificity of the pathogenic T cells in hypertension is important to know in order to understand the underlying mechanism of the disease process and also for the possible development of therapies based on antigen-induced tolerance, rather than nonspecific immunosuppression. This may not be an easy question to answer. For example, the identity of the relevant antigens recognized by proatherogenic T cells remains uncertain after decades of study, although there are strong candidates.13 There are multiple mechanisms for maintenance of T cell tolerance to self proteins, which kill off or inactivate self-reactive T cells during thymic development and in peripheral tissues. Therefore, barring the unlikely role of infection in the mouse models, the emergence of T cells that contribute to the development of hypertension is a failure of tolerance to normal self molecules or a reaction against altered self molecules, which accumulate because of the abnormal conditions that underlie disease (eg, injury to the vascular wall from direct or indirect effects of angiotensin).

The second major question raised by the work reported here and in previous articles is the mechanism by which T cell activation promotes hypertension. The presence of activated T cells in a perivascular distribution suggests a local effect of cytokines that may diffuse into arterial walls and alter vascular smooth muscle and/or endothelial function, but this has not been proven. In support of this idea, Harrison’s group has reported that interleukin (IL)-17 is required for sustained hypertension and vascular pathology, and they found increased IL-17-producing T cells in blood and IL-17 in the aortic media in angiotensin-IL-treated mice.14 Another group reported that aldosterone, a key mediator in hypertension, promotes differentiation of Th17 cells.15 Thus, T cells that produce IL-17 cells may play an important local role in this disease. The Harrison’s group has also reported that anterolateral cerebral ventricle lesions and hydralazine each prevented angiotensin-II-induced hypertension, T cell activation, and perivascular inflammation.16 They interpret these findings as evidence that modest hypertension, mediated through CNS-dependent mechanisms, occurs first in the angiotensin model, and this leads to T cell activation, which then induces perivascular inflammation and drives the progression to severe hypertension. This hypothetical sequence of events would be consistent with the concept that some initial vascular damage caused by mild hypertension is necessary to activate the innate immune system and upregulate costimulatory molecules expression, leading to loss of T cell tolerance to blood-vessel-associated self antigens or activation of T cell responses to altered-self antigens, possibly generated by oxidative stress. This paradigm (see Figure) is reminiscent of Svendsen’s thymectomy study7 mentioned earlier, which showed an initial thymus-independent (ie, T cell independent) phase of hypertension followed by a later long-lasting thymus-dependent phase in DOCA-salt-treated mice.

Are innate and T cell-mediated immune responses relevant to human hypertensive disease? Circumstantial evidence is consistent with the possibility. Recent studies have shown that plasma levels of inflammatory cytokines, such as tumor necrosis factor-α, IL-6, and IL-17 positively correlate with blood pressure in humans.14,17 In a small study of 8 patients with psoriasis, mycophenolate mofetil treatment, which mainly targets B and T cells, was shown to reduce blood pressure in essential hypertensive patients.18 Hypertension is a frequent comorbidity of rheumatoid arthritis.19,20 Nonetheless, there are no published studies that specifically investigate the effect of abatacept on hypertension in rheumatoid arthritis patients. Considering the compelling evidence from the work of Vinh et al on CTLA4-Ig in mice, it is worthwhile to further study hypertension in patients treated with CTLA4-Ig.

The pathogenesis of essential hypertension may be different in the setting of autoimmune disease, and therefore the experience of costimulatory blockade in rheumatoid arthritis patients may not predict efficacy in patients with essential hypertension but without autoimmune disease. Given the risks of infection that come with any immunosuppressive therapy, and the efficacy of current antihypertensive therapies, it is not yet clear which patients would be appropriate candidates for trials of costimulatory blockade. A reasonable starting place, as suggested by Vinh et al, may be to determine if CTLA4-Ig is effective as an adjuvant for short-term therapy of malignant hypertension. Certainly the evidence from animal models in support of a role for T cells in hypertension is currently very strong, warranting serious consideration of clinical trials of drugs targeting T cell activation or effector functions for high blood pressure.

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Disclosures
None.

References


