Is hypertension an autoimmune disease?

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T cells are required for significant blood pressure elevation in mouse models of hypertension. Recent evidence suggests that the treatments that raise blood pressure in these animal models also cause oxidation within DCs, resulting in formation of isoketal adducts of self-proteins, which activate antigen-presenting functions of these cells and serve as a source of modified self-antigens. T cells specific for these modified self-antigens then produce cytokines that promote blood pressure elevation, consistent with the idea that hypertension is an autoimmune response to altered self. Here, I will review the new evidence for this idea put forth by Kirabo and colleagues in this issue of the *JCI*, identify a number of as yet unanswered questions, and discuss some of the therapeutic implications.

T cells and hypertension

Hypertension is the major modifiable risk factor for death in individuals with cardiovascular disease (1); however, this complication cannot be controlled in 8% to 12% of patients (2). Therapies based on new pathogenetic insights into the development of hypertension could have significant clinical value. One possibility is that hypertension is a form of autoimmunity (3). David Harrison and coworkers first showed in 2007 an unanticipated role for T cells in two common models of hypertension in mice (4). Specifically, treatment either with angiotensin II or with deoxycorticosterone acetate plus NaCl (DOCA-salt) barely elevated blood pressure in RAG1-deficient mice, which lack T and B lymphocytes compared with WT mice; however, adoptive transfer of syngeneic T cells in RAG1-deficient animals restored treatment-induced blood pressure elevation. The initial Harrison study linked increased blood pressure to T cell production of TNF-α, and subsequent work revealed that T cell–derived IL-17A is also required to sustain hypertension in animals (5). IL-17A targets vascular smooth muscle cells (5–7), but it is not clear whether this results in hypertension. IL-17A–mediated injury to the kidney is an alternative mechanism for the development of hypertension. Angiotensin II can increase cytokine production by T cells but only when the T cells are first activated by cross-linking the T cell receptor (TCR) for antigen with anti-CD3 monoclonal antibody (4), a widely used experimental surrogate for antigen recognition. If T cells are actually activated by recognition of a specific antigen in hypertensive animals, what might this antigen be? The study by Kirabo et al. in this issue of the *JCI* now suggests an answer (8).

A primer on the T cell response to antigen

To put the findings of Kirabo and colleagues into context, it is important to consider how T cells respond to antigen. Each naive T cell (i.e., one that has emerged following thymic development but has not yet encountered a specific antigen) expresses a structurally unique TCR that differs from every other TCR and is specific for a small number of closely related short peptides in a noncovalent complex with one of a number of highly polymorphic membrane proteins encoded by genes within the MHC. During thymic maturation, the repertoire of developing T cells is purged to eliminate both T cells that cannot recognize peptides from self-proteins bound to self-MHC and T cells that recognize peptides derived from self-proteins with high affinity. This maturation process leaves only the T cells that react poorly to self-peptides but can recognize with higher affinity peptides derived from nonself-proteins, typically those from invading microbes that bind to self-MHC (9). However, naive T cells that recognize structurally modified peptides derived from self-proteins are not eliminated. For example, some individuals possess T cells that recognize self-peptides in which arginine residues have been enzymatically modified to citrulline and are then displayed by the allelic forms of a specific class II MHC molecule (HLA-DR4). This recognition of modified self can result in rheumatoid arthritis (RA) (10), explaining why there is a much stronger risk for developing RA in individuals who have inherited an HLA-DR4 allele. In general, a link to specific MHC alleles is a common feature of autoimmunity (11).

To initiate a T cell response, naive T cells must receive three distinct signals: specific antigen (the peptide bound to the MHC molecule that is recognized by its TCR); one or more antigen-independent boosters (costimulators) of T cell responses (such as CD80 or CD86, which engage CD28 on the T cell); and secreted cytokines that promote T cell expansion and differentiation (12). Specialized antigen-presenting cells, known as DCs, provide all three signals, but DCs must first be activated in order to elicit a response from naive T cells (13). DC-activating signals include molecules expressed by microbes, such as pathogen-associated molecular patterns (PAMPs), or molecules released from injured cells, known as damage-associated molecular patterns (DAMPs). Both PAMPs and DAMPs function to localize DC activation to sites of infection or tissue injury, at which DCs acquire antigens prior to migrating to sec-

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ondary lymphoid organs, in which the antigen is presented to naive T cells that express a relevant TCR. Antigen-activated T cells proliferate, producing a clone of daughter cells specific for the relevant antigen, and these differentiate into effector cells of various types. While there are very few naive T cells that can recognize a particular antigen, proliferation creates many effector cells that can do so. If the eliciting antigen is eliminated, most effector cells die off, but some become long-lived memory cells that can rapidly redifferentiate into new effector cells if the same antigen reappears, such as occurs during reinfection or in response to primary infection following vaccination. This expanded pool of memory T cells is the basis of immunological memory (14).

The role of isoketal-activated DCs in hypertension

This background provides context for the current findings of Kirabo and colleagues. First, infusion of angiotensin II or DOCA-salt to produce hypertension generated ROS in DCs through phagocyte oxidase. Importantly, it is the mediators of hypertension, not hypertension per se, that stimulates ROS production, as normalizing blood pressure with hydralazine did not prevent ROS formation. Second, ROS in DCs caused lipid oxidation, resulting in formation of isoketal adducts of various self-proteins. These isoketal-modified proteins were detectable by immunostaining, and the specific scavenger 2-hydroxybenzylamine prevented their formation. Third, isoketal-modified proteins behaved like DAMPs, activating DCs to upregulate MHC molecules, costimulators CD80 and CD86, and cytokines IL-1, IL-6, and IL-23, all of which was preventable by 2-hydroxybenzylamine. It should be noted that Kirabo and colleagues found that isoketal adducts unexpectedly reduce rather than activate the ability of DCs to present a model antigen, an unexplained observation. Fourth, DCs pulsed with isoketal-modified self-proteins were able to activate in vitro proliferation and cytokine production of memory T cells from hypertensive but not control animals. Finally, transfer of isoketal-activated DCs raised blood pressure in WT animals that have T cells but not in those lacking them. Cumulatively, the findings of Kirabo and colleagues (8) suggest that peptides derived from isoketal adducts of proteins behave as modified self-antigens, activating naive T cells to become IL-17A–producing effector cells. Thus, hypertension, like RA, may be an autoimmune disease to modified self.

Outstanding questions

While the report by Kirabo et al. greatly advances the understanding of how hypertension-inducing stimuli may activate T cells to produce IL-17A, several questions remain unanswered. First, what type(s) of DCs are relevant for initiating this T cell response? This issue is complicated, as monocytes, macrophages, and DCs are heterogeneous and plastic, and their relationship to each other is disputed (15). Still, this question could be addressed by separation of activated DCs prior to adoptive transfer. Second, which DC receptors recognize isoketal adducts as DAMPs? Most (if not all) of the relevant receptors for PAMPs and DAMPs are known, and mice are available in which these receptors and their adaptor molecules have been knocked out; therefore, this question should be readily addressable. Third, what is the actual antigen recognized by the activated T cells? Not all citrullinated peptides activate T cells of patients with RA. This issue may be approached by isolating peptides from the MHC molecules on activated DCs and/or by testing synthetic isoketal-modified peptides. Fourth, do these observations in mouse models apply to hypertensive humans? Kirabo et al. found that circulating myeloid cells in hypertensive individuals (both controlled and uncontrolled) have measurable levels of isoketal protein adducts, which are not present in normotensive individuals. Fifth, are these myeloid cells activated to present antigens, and do hypertensive individuals have circulating memory T cells that are responsive to isoketal-modified proteins or peptides? Finally, if human hypertension is an autoimmune disease, is there a link to a specific MHC allele? Remarkably, although the MHC was not identified in initial GWAS of hypertension, the most recent GWAS report noted an association between hypertension and the HLA-DQB1 allele; however, this must be independently validated (16). Future studies should be able to test the hypothesis that antigen-presenting cells expressing HLA-DQB1 may be especially effective at presenting isoketal peptide adducts to T cells that share this allele.

Conclusions

The most important implications of the study by Kirabo and colleagues relate to the possibility of potential therapies for hypertension. If the isoketal-stimulated adaptive immune response contributes to human hypertension, could targeting this pathway reduce the blood pressure of patients refractory to current antihypertensive drug therapies? Antioxidants have failed to provide clinical benefit in heart disease (17), but this may reflect the fact that ROS mediate both beneficial and pathological effects. The mouse data presented by Kirabo et al. suggest that a specific scavenger of isoketals could be protective without interfering with beneficial ROS functions. While global immunosuppression may be far too high a price to pay for reducing blood pressure, observational studies of blood pressure in patients on immunosuppression therapy for other reasons may be highly informative. Specific IL-17A or IL-17 receptor blockades with monoclonal antibodies have shown positive effects in clinical trials for psoriasis (18). Some of these patients were undoubtedly hypertensive, and the effects of inhibition of IL-17A and IL-17 on blood pressure could be examined. Interestingly, high dietary salt intake, which increases sodium ion concentration in the interstitium of the secondary lymphoid organs without increasing plasma concentration, favors the differentiation of autoreactive IL-17A–producing T cells (19). Thus, salt restriction, already recommended for hypertensive patients for hemodynamic effects, may also be an effective immunomodulatory strategy. Finally, tolerogenic therapies for autoimmunity (20), such as stimulating regulatory T cells with self-antigen plus low-dose IL-2, appear to be on the horizon. Now that we have candidate antigens, perhaps this is an approach that could be safely translated to patients with refractory hypertension.

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