The Immune System: Role in Hypertension

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ABSTRACT

Over the past 20 years it has become recognized that low-grade inflammation plays a role in cardiovascular disease. More recently, participation of the innate and the adaptive immune response in mechanisms that contribute to inflammation in cardiovascular disease has been reported in atherosclerosis and hypertension. Different subsets of lymphocytes and their cytokines are involved in vascular remodelling and hypertensive renal disease as well as heart disease. Effector T cells including T-helper (Th) 1 (interferon-γ-producing) and Th2 lymphocytes (interleukin-4 producing), as well as Th17 (which produce interleukin-17), and T suppressor lymphocytes such as T regulatory cells, which express the transcription factor forhead box P3, participate respectively as pro- and anti-inflammatory cells, and mediate effects of angiotensin II and mineralocorticoids. Involvement of immune mechanisms in cardiac, vascular, and renal changes in hypertension has been demonstrated in many experimental models, an example being the Dahl-salt sensitive rat and the spontaneously hypertensive rat. How activation of immunity is triggered remains unknown, but neoantigens could be generated by elevated blood pressure through damage-associated molecular pattern receptors or other mechanisms. When activated, Th1 may contribute to blood pressure elevation by affecting the kidney, vascular remodelling of blood vessels directly via effects of the cytokines produced, or through their effects on perivascular fat. T regulatory cells protect from blood pressure elevation acting on similar targets. These novel findings may open the way for new therapeutic approaches to improve outcomes in hypertension and cardiovascular disease in humans.

RÉSUMÉ

Au cours des 20 dernières années, il a été reconnu une inflammation de faible degré un rôle dans les maladies cardiovasculaires. Plus récemment, la participation de la réponse immunitaire innée et adaptative aux mécanismes qui contribuent à l’inflammation dans la maladie cardiovasculaire a été rapportée dans l’athérosclérose et l’hypertension artérielle. Différents sous-ensembles de lymphocytes et leurs cytokines sont impliqués dans le remodelage vasculaire et maladie rénale hypertensive aussi bien que dans les maladies cardiaques. Les cellules T effectrices incluant les cellules T auxiliaires (Th : T-helper) 1 (qui produisent d’interféron γ) et les lymphocytes Th2 (qui produisent d’interleukine 4), ainsi que les lymphocytes Th17 (lesquels produisent l’interleukine 17) et les lymphocytes T suppresseurs tels que les cellules T régulatrices, qui expriment le facteur de transcription FoxP3 (forkhead box P3), participent respectivement à titre de cellules pro-inflammatoires et anti-inflammatoires, et agissent comme médiateurs des effets de l’angiotensine II et des minéralocorticoïdes. L’implication des mécanismes immunitaires dans les changements cardiaques, vasculaires et rénaux de l’hypertension a été démontrée dans plusieurs modèles expérimentaux, par exemple, le rat Dahl sensible au sel et le rat spontanément hypertendu. La manière dont l’activation de l’immunité est déclenchée semble inconnue, mais des néoantigènes pourraient être générés par une pression artérielle élevée grâce aux récepteurs du modèle moléculaire associé à la lésion et à d’autres mécanismes. Lorsque les Th1 sont activés, ils peuvent contribuer à l’augmentation de la pression artérielle en affectant le rein, le remodelage vasculaire des vaisseaux sanguins directement par les effets des cytokines produites, ou par leurs effets sur la graisse périvasculaire. Les cellules T régulatrices protègent de l’augmentation de la pression artérielle en agissant sur des cibles similaires. Ces nouveaux résultats peuvent ouvrir la porte à de nouvelles approches thérapeutiques pour améliorer les résultats de l’hypertension et de la maladie cardiovasculaire chez les humains.
and adventitia of blood vessels as well as interstitium of the kidney and heart with activated B and T lymphocytes. Innate immune responses mediated by macrophages are triggered through toll-like receptors. Adaptive immune responses are represented by activated lymphocytes and interact with innate immunity to participate in the pathophysiology of cardiovascular disease and hypertension. In the osteopetrotic mouse, which has a mutation in the mcsf gene and accordingly is deficient in vascular macrophages, angiotensin (Ang) II and deoxycorticosterone acetate (DOCA)-salt did not raise blood pressure (BP) or induce vascular remodelling. A role of macrophages in remodelling of the vascular wall was demonstrated as well under the influence and through the action of reduced nicotinamide adenine dinucleotide (NADPH) oxidase. Early studies by a number of investigators suggested an implication of T lymphocytes, and changes in immune status in spontaneously hypertensive rats and other models of hypertension. Rodriguez-Iturbe et al. were among the first to demonstrate that immunity and T lymphocytes contribute to renal changes in SHR.6–8 The group of Croker et al. confirmed and extended these findings.12–14 In the osteopetrotic mouse, which has a mutation in the mcsf gene and accordingly is deficient in vascular macrophages, angiotensin (Ang) II and deoxycorticosterone acetate (DOCA)-salt did not raise blood pressure (BP) or induce vascular remodelling. A role of macrophages in the remodelling of the vascular wall was demonstrated as well under the influence and through the action of reduced nicotinamide adenine dinucleotide (NADPH) oxidase. Early studies by a number of investigators suggested an implication of T lymphocytes, and changes in immune status in spontaneously hypertensive rats and other models of hypertension. Rodriguez-Iturbe et al. were among the first to demonstrate that immunity and T lymphocytes contribute to renal changes in SHR.6–8 The group of Croker et al. confirmed and extended these findings.12–14

**T-Lymphocyte Subsets**

It is important to understand the complexity of lymphocyte subsets in order to comprehend how these cells participate in innate and adaptive immune mechanisms in cardiovascular disease and hypertension. NK cells are lymphocytes that belong to the innate immune system and express CD161 (NK1.1) but do not express the T-cell marker CD3, T-cell receptors, or immunoglobulin B cell receptors. They are activated by macrophage-derived cytokines, and play roles in autoimmunity and tumour rejection. NK T cells are a subset of CD1d-restricted T lymphocytes expressing T-cell receptors and CD4 or CD8, as well as CD161, which is the NK cell-associated marker. NK T lymphocytes, which should not be confused with NK cells, produce interferon (IFN)-γ and interleukin (IL)-2, IL-4, and tumour necrosis factor (TNF)-α. A particularly important subset comprises effector T lymphocytes, which include T helper (Th) 1, Th2, and Th17 subsets of lymphocytes. IL-12 triggers maturation of naïve T lymphocytes toward the Th1 lineage. Th1 cells typically produce IFN-γ and IL-2. They are involved in immunity against viruses, intracellular bacteria, and fungi. Th2 lymphocytes mature under the action of IL-4, and produce IL-4, IL-5, and IL-13. Th2 exert their effects on eosinophils to act upon parasites. Transforming growth factor (TGF)-β, IL-6, and IL-1, or TGF-β and IL-21 followed by IL-23 drive the commitment of naïve lymphocytes toward the Th17 lineage. Th17 produce IL-17A and F, IL-21, and IL-22. Th17 cells contribute to defense against extracellular bacteria and fungi, and are also involved in autoimmune diseases.

Opposing the actions of T-effector lymphocytes are T regulatory or suppressor lymphocytes (Treg), which are CD45+ or CD8+ lymphocytes that are also CD25+. They are involved in self-tolerance and maintain immune homeostasis. CD4+ T lymphocytes become Treg under the influence of transcription factor X-linked forkhead/winged helix (Foxp3). As mentioned, some Treg may express CD8 rather than CD4. Treg effects are mediated by IL-10 or TGF-β (see below) that exert anti-inflammatory actions, although other mechanisms such as direct cell-cell contact or effects mediated by cytotoxic T-lymphocyte antigen-4 may also play a role. TGF-β exerts dual actions depending on the concentrations of IL-6. When IL-6 is low, TGF-β drive T cells to become Treg, whereas in presence of elevated concentrations of IL-6, cells of Th17 belonging to the lymphocyte subset are the result.

**Effect of lymphocytes on kidney injury**

The role of the immune system on kidney injury contributing to Ang II-induced hypertension was studied in scid mice, that lack lymphocyte responses, by examining effects in mice of...
the immunosuppressive agent mycophenolate mofetil (MMF) on the course of hypertension and kidney disease induced by chronic infusion of Ang II. Although MMF did not affect BP or cardiac hypertrophy, atherosclerosis, lymphocyte infiltration into the renal interstitium, and proteinuria were reduced, as well as messenger RNA expression of IFN-γ, TNFα, and TGFβ. Splenic lymphocytes exposed in vitro to Ang II caused p kinase-dependent cytoskeletal remodelling, which may lead to activation of the former.12 The same authors studied kidney injury contributing to Ang II-induced hypertension in scid mice, which lack lymphocyte responses, and showed that these mice had blunted hypertensive responses to Ang II infusion.25 Moreover, lymphocyte deficiency led to significant reduction in injury to the kidney, associated with increased sodium excretion. Although renal expression for IFN-γ, IL-1β, and IL-6 was unaffected, TNFα, endothelial nitric oxide synthase, and cyclooxygenase-2 expression in the kidney were enhanced, and accordingly there was increased generation of natriuretic agents such as nitric oxide, prostaglandin E2, and prostacyclin. Lymphocyte deficiency thus protected the kidney and blunted BP elevation via endothelial nitric oxide synthase and cyclooxygenase-2-mediated natriuresis. Dahl salt-sensitive (SS) rats that were fed isocaloric diets with elevated amounts of protein and salt developed the highest BP and proteinuria, and had more T lymphocytes infiltrating the kidneys.26 Treatment of SS rats fed the high-protein diet with MMF reduced BP, proteinuria, and renal T cells infiltration. Thus, in Dahl SS rats fed a high-protein diet, immune cells play a pathophysiological role in kidney damage and BP elevation, which is affected by sodium and protein intake.

Regulatory T Lymphocytes in Vascular Remodelling and Hypertension

Genetic predisposition may lead to enhanced adaptive immune responses that favour development of inflammation as a result of blunted immune surveillance. The latter may be the result of abnormal Treg number or function and participate thus in the pathophysiology of hypertension. Chromosome 2 bears several proinflammatory genes (vascular cell adhesion molecule-1, IL-2, IL-6 receptor, fibroblast growth factor 2, and the angiotensin AT1 receptor).27 Accordingly, we investigated consomic rats (SSBN2) that had chromosome 2 from Brown Norway rats (normotensive strain) introgressed into the genetic background of hypertensive Dahl SS rats,28 in order to evaluate genetic influences on inflammatory responses in hypertension.29 CD4+CD25+ and CD8+CD25+ lymphocytes and their activity and expression of Foxp3 were enhanced in SSBN2. The consomic strain also presented exaggerated production by Treg of anti-inflammatory IL-10 and TGFβ. Treg expressing low levels of Foxp3β and producing little TGF-β and IL-10 were detected in blood vessels of Dahl SS rats. The vasculature of Dahl SS rats was remodelled and dysfunctional, with upregulated inflammatory responses. In addition, proinflammatory cytokines such as IL-1β, IL-2, IL-6, TNFα, and IFN-γ were produced in excess by vessels from Dahl SS rats in comparison with consomic rats, contributing to the inflammation of blood vessels in the former. Thus, there was a chromosome 2-dependent imbalance of pro- and anti-inflammatory and immune responses favouring inflammation in SS genetic hypertension, and an anti-inflammatory phenotype in rats bearing chromosome 2 from Brown Norway on the Dahl SS genetic background. This imbalance of pro- and anti-inflammatory cytokine responses was also found in vitro with cultured T cells, indicating that at least in part there might be independence from BP levels.29

Adoptive transfer of Treg to Ang II-infused mice resulted in lower telemetric systolic BP and reduction of small artery stiffness, generation of superoxide, and immune cell infiltration in blood vessels and perivascular tissue, and enhanced production of inflammatory mediators and immune cells in the cortex of the kidney.30 Transfer of Treg also improved cardiac remodelling in Ang II-infused mice, albeit in absence of any lowering of BP.31 We recently showed that aldosterone-infused mice respond to adoptive transfer of Treg with reduced small artery remodelling and oxidative stress and immune cell infiltration in blood vessels and kidney, although without change in BP.32 Thus Treg as well as T effector lymphocytes appear to participate in pathophysiology of hypertension as they do in the progression of other forms of cardiovascular disease.1,33-37 Treg likely induce actions via the anti-inflammatory effects of IL-10, although other mechanisms may also participate.16,37,38 Indeed, carotid arteries from IL-10-deficient mice (IL-10−/−) incubated with Ang II produced a 50% reduction of acetylcholine-induced relaxation and doubling of superoxide generation in the vascular wall, whereas effects were minor in vessels from wild type mice. Ang II infusion induced mild endothelial dysfunction in wild type mice but significantly impaired acetylcholine-induced relaxation in IL-10−/− mice by increasing superoxide, suggesting that Treg-derived IL-10 blunts ROS generation in the vascular wall.33 In studies from another group of investigators, incubation of arteries from Ang II-infused IL-10−/− mice with conditioned media of cultured Treg from control mice reduced NADPH oxidase activity and improved endothelium-dependent relaxation, effects which could be reversed by an IL-10 antibody or receptor antagonist.39 Adoptive transfer of cultured Treg from control mice to Ang II-infused IL-10−/− mice reduced systolic BP and NADPH oxidase activity and improved endothelial dysfunction. In vivo IL-10 infusion into Ang II-treated mice reduced BP and NADPH oxidase activity and improved endothelial dysfunction. Thus it can be concluded that IL-10 from Treg attenuates NADPH oxidase activity leading to improvement of endothelial function and BP control.

Discussion

The data reported above is mostly restricted to animal models. Two questions remain to be discussed: how is the immune system activated in cardiovascular disease in these experimental models, and does the immune system participate in hypertension in humans?

We and others have proposed that activation of the immune system in cardiovascular disease depends on neoantigen generation that would lead to DC activation.4,5 Elevated BP may exert its effects through DAMP receptors or other mechanisms (Figure 1). As well, infection inducing low-grade inflammation via stimulation of pathogen-activated molecular patterns could play a role, although more recently the role of periodontitis that was considered one of the culprits has been debunked. When activated, antigen presentation by macrophages would result in DC activation, and migration of DCs to peripheral lymph...
nodes, where activation of Th1 would occur.4 Th1 may contribute to BP elevation by affecting the kidney, vascular remodelling of blood vessels directly or via effects of the cytokines produced, or through effects on perivascular fat. Treg could protect from BP elevation by acting on similar targets.29 Although some evidence supports these hypotheses, evidence is not final. In our study of Dahl SS rats and consomic rats bearing chromosome 2 from Brown-Norway on a Dahl SS genetic background29 we did not show either that Treg numbers are reduced relative to effector or cytotoxic T lymphocytes, but rather that potentially the mechanism leading to this condition is more dependent on the Treg phenotype and reduced anti-inflammatory cytokines (ie, IL-10) with enhanced NADPH oxidase activity and excess proinflammatory mediators generated as discussed in that publication. In consomic rats, IL-10 production would be protective as suggested by other authors.40

Although low-grade inflammation is well demonstrated in cardiovascular disease41 and in hypertension42 as depicted by elevation of serum concentrations of C-reactive protein and cytokines, evidence of involvement of the immune system in cardiovascular disease is only starting to appear in the literature. Indeed, it has been documented that patients with coronary artery disease may exhibit excess circulating Th17 lymphocytes.3 Interestingly, in immune-suppressed patients with human immune deficiency virus-associated disease, although cardiovascular disease may occur in part as a result of side effects of antiviral agents used in the treatment of the disease, there is no excess prevalence of hypertension that has been noted. Some immune suppressant drugs such as cyclosporine are associated with BP elevation. However, this seems independent of the immune system and related rather to upregulation of endothelin (ET)-1 and ET receptor expression and activity, and to increased calcium influx into vascular smooth muscle cells, as well as associated endothelial dysfunction.43

**Conclusion**

A role of the immune system and T lymphocytes in hypertension and other cardiovascular diseases is increasingly recognized on the basis of rodent research of which much has been cited in this review, and some initial human studies that suggest a role of Th17.20 Will it be possible to harness the power of immune mechanisms to control BP and target organ damage? This remains a matter of speculation. However, it can be hoped that the current studies implicating immunity in the pathophysiology of hypertension and cardiovascular disease are only the beginning of unraveling the role of these potent endogenous mediators and protectors from cardiovascular injury, and will lead to novel discoveries that may allow new treatments to be developed that can help improve outcomes for hypertensive patients.

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**Figure 1.** In normotensive conditions, when innate immunity is not activated, macrophages are not stimulated and will not produce tumour necrosis factor (TNF). Accordingly, antigen-presenting cells (APCs, dendritic cells [DCs]) have an anti-inflammatory or immune suppressant phenotype, and stimulate the commitment of naïve T lymphocytes to the T regulatory cell (Treg) lineage. These T lymphocytes will produce the anti-inflammatory interleukin (IL)-10 and transforming growth factor (TGF)β, which will suppress vascular, cardiac or renal inflammation. As a result of stimulation of damage-activated molecular pattern (DAMP) receptors, which could be a consequence for example of blood pressure elevation, or stimulation of pathogen-activated molecular pattern receptors, the latter in response to periodontitis (now considered a controversial cause) or other forms of low-grade infection, or other conditions resulting in elevated TNFα, consequence of genetic predisposition, high salt intake, increased endothelin (ET)-1, or activation of the renin-angiotensin II (Ang II)-aldosterone system, APC or DCs adopt a proinflammatory phenotype, migrate to secondary lymphoid organs and stimulate the maturation of T effector lymphocytes such as T helper (Th)1 which produce interferon (IFN)γ and IL-6, or Th17 which produce IL-17, leading to a vascular, cardiac, or renal inflammatory response. Formation of neoantigens, which needs to be demonstrated, could also be a cause of activation of T effector lymphocytes leading to a role in low-grade inflammation in cardiovascular disease. HTN, hypertension; Foxp3, forkhead box P3; PAMP, pathogen-activated molecular pattern.
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