Over the past 20 years, the role of low-grade inflammation has been increasingly recognized as a mechanism that participates in the progression of cardiovascular disease. Inflammatory and immune cells and macrophages can be found in the adventitia of blood vessels and in the kidney and heart. Blood vessels have enhanced expression of adhesion molecules (vascular cell adhesion molecule or VCAM-1 and intercellular cell adhesion molecule or ICAM-1), and there is increased leukocyte extravasation and production of cytokines. This leads to exaggerated oxidative stress and inflammation, which results in impaired function of the vascular wall. Dendritic cells (DC) are antigen-presenting cells activated by monocyte/macrophages, and they and natural killer (NK) cells accumulate in the perivascular fat.
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 forhead/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.

Effector T Lymphocytes: Role in Hypertension

Ang II stimulates the production of IFN-γ by spleen T-lymphocytes, and decreased production of IL-4, effects blocked by angiotensin receptor type 1 antagonists independently of BP lowering. Thus, Th1 cytokine production was enhanced and Th2 cytokines reduced by Ang II. Similar effects on cytokine messenger RNA in spleen and kidney were also reported.

Ang II and DOCA-salt hypertension were blunted in rag1−/− mice, which are deficient in T- and B-lymphocytes, and aortic and small artery remodelling and vascular oxidative stress produced in response to Ang II were decreased. Adoptive transfer of effector T cells from control mice restored BP rise induced by Ang II, in contrast to B-cell adoptive transfer that was ineffective. Ang II pressor responses were significantly blunted in Id2−/− mice lacking the gene for the inhibitor of differentiation 2 (Id2), which results in dysfunction of innate immune mechanisms through deficit of Langerhans and splenic CD8α+ DCs, decreased NK cells, and altered adaptive immunity through lack of CD8+ T memory lymphocytes. Ang II as well resulted in reduced BP rise, less T cells in perivascular fat, and superoxide generation in aortic rings of IL-17−/− mice, indicating participation of IL-17 in hypertensive responses to Ang II. More recently, it has been suggested that T effector cells that are mediating in part the hypertensive response to Ang II are actually CD8+ rather than CD4+.

When thrombosis was induced in cremaster arterioles of wild type, immunodeficient Rag-1−/−, CD8−/−, or CD4−/− lymphocyte-deficient or NADPH oxidase (gp91phox)-deficient mice infused with Ang II, arteriolar thrombosis was enhanced in wild type mice but not in Rag-1−/−, CD4−/−, T-cell-deficient, or gp91phox−/− mice, whereas CD8 T-cell−/− mice were less affected. Adoptive transfer of T cells from wild type or gp91phox−/− mice into Rag-1−/− restored the prothrombotic effects of Ang II. This demonstrated that CD4+ and to lesser degree CD8+ T lymphocytes contribute to the enhanced microvascular thrombosis found in Ang II-induced hypertension, in part via effects of NADPH oxidase-derived reactive oxygen species (ROS).

Part of the role that the brain plays in mechanisms of BP elevation involves Th1 lymphocytes. When the gene of extracellular superoxide dismutase was inactivated in circumventricular organs of the brain of mice, generation of ROS and elevation of BP occurred. This was accompanied by inflammatory infiltrates rich in Th1 lymphocytes in blood vessels and in the kidney. It was concluded that the brain through the sympathetic nervous system may raise BP, which induces development of neoantigens that in turn activate immune mechanisms. The latter effect may occur through stimulation of damage-associated molecular pattern (DAMP) receptors.

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, glomerulosclerosis, 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. 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. 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, TNF-α, 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. 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). 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, in order to evaluate genetic influences on inflammatory responses in hypertension. CD4⁺CD25⁺ and CD8⁺CD25⁺ lymphocytes and their activity and expression of Fopx3 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 Fopx3b 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.

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. Transfer of Treg also improved cardiac remodelling in Ang II-infused mice, albeit in absence of any lowering of BP. 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. 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. 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). 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, in order to evaluate genetic influences on inflammatory responses in hypertension. CD4⁺CD25⁺ and CD8⁺CD25⁺ lymphocytes and their activity and expression of Fopx3 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 Fopx3b 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. 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. Transfer of Treg also improved cardiac remodelling in Ang II-infused mice, albeit in absence of any lowering of BP. 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. 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.

**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. 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 remodeling 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 background \(^29\) 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 disease \(^41\) and in hypertension \(^42\) 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. \(^5\) 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 \(_A\) 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 of 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.
References


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