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T-cell involvement in sex differences in blood pressure control

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Abstract

Hypertension affects one-third of adults in the Western world and is the most common independent risk factor for cardiovascular disease, and the leading cause of premature death globally. Despite available therapeutic options, approximately half of the hypertensive population taking medication does not achieve adequate blood pressure (BP) control leaving them at increased risk of chronic kidney disease, renal failure, stroke, congestive heart failure, myocardial infarction, aneurysm and peripheral artery disease. New therapeutic options need to be identified for the treatment of hypertension in order to increase the percentage of individuals with controlled BP. There is a growing basic science literature regarding the role of T-cells in the pathogenesis of hypertension and BP control; however, the majority of this literature has been performed exclusively in males despite the fact that both men and women develop hypertension. This is especially problematic since hypertension is well recognized as having distinct sex differences in the prevalence, absolute BP values and molecular mechanisms contributing to the pathophysiology of the disease. The purpose of this article is to review the available literature regarding sex differences in T-cells in hypertension followed by highlighting the potential pathways that may result in sex-specific effects on T-cell activation and differentiation.

Keywords

angiotensin; blood pressure regulation; inflammation; sex differences; Th17 cell; T regulatory cell

INTRODUCTION

Hypertension affects one-third of adults in the Western world and is the most common condition seen by primary care physicians [1]. Uncontrolled hypertension leads to chronic kidney disease, renal failure, stroke, congestive heart failure, myocardial infarction, aneurysm and peripheral artery disease, and is associated with significant morbidity and mortality [2]. Despite the prevalence, negative impact on overall health and economic burden of hypertension, the pathogenesis of essential hypertension remains poorly understood. As a result, only ~36 million of the ~70 million American adults that have hypertension have adequate control of their hypertension [1]. New therapeutic options need to be identified for the treatment of hypertension in order to increase the percentage of

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individuals with controlled blood pressure (BP) and decrease premature death rates associated with cardiovascular disease.

Hypertension is now considered a state of low-grade inflammation. Elevations in BP are associated with the up-regulation of pro-inflammatory cytokines and the infiltration of immune cells into target organs both clinically and in experimental models of hypertension. Although early studies in the 1960s broadly implicated the immune system in hypertension, they did not directly identify the immune component responsible (for reviews see [3–7]). Significant advances in immunology research and technology have allowed for the identification and targeting of specific cells and components of the immune system allowing for the direct study of immune cells in BP control. As a result, more recent studies have significantly expanded our understanding of the role of the immune system in BP regulation and suggest a direct contribution of T-cells to the progression and development of hypertension.

SEX DIFFERENCES IN HYPERTENSION

Hypertension is well recognized as having distinct sex differences in the prevalence, absolute BP values and molecular mechanisms contributing to the pathophysiology of the disease (for reviews see [8,9]). Beginning in adolescence, males have higher BP than females and these trends persist into the sixth decade of life, after which point more women are hypertensive than men [1,10]. There are also sex differences in the relationship between elevations in BP and the degree of end-organ damage and severity of cardiovascular risk; comparable decreases in BP in men and women may not offer the same degree of cardiovascular benefit to both sexes. Decreasing BP to 125/80 in hypertensive women is required to offer comparable reductions in cardiovascular events as decreasing BP in hypertensive men to 135/85 mmHg [11]. This finding is consistent with the report that hypertensive women exhibit a steeper relationship between systolic BP and risk for cardiovascular events than men, and a 1 S.D. decrease in BP in women results in a greater cardiovascular risk reduction in women compared with men [12]. These studies become particularly important following the recent release of data from the SPRINT trial which compared the impact of traditional compared with intensive BP control in hypertensive patients on cardiovascular morbidity and mortality. More intensive BP control (target systolic BP < 120 mmHg) offered significantly greater overall cardiovascular benefit compared with achieving target BPs of 140 mmHg [13]. Approximately 35% of the participants in the SPRINT trial were women, yet the data were not presented separately by sex, therefore it remains unknown whether there were sex differences in the benefits of more aggressive BP control. Despite all of these findings, the most recent guidelines for BP control released in 2014 recommend the same approach for treating men and women with hypertension [14]. However, only ~55% of hypertensive patients achieve BP controlled to recommended levels [1] and women have been reported to have lower rates of BP control compared with men despite being more likely to take their prescribed medication [15]. These numbers highlight the need for more studies to identify the molecular mechanisms driving increases in BP in hypertension, especially in women.

T-cells have been suggested to link multiple organs in the control of BP, and based on the data discussed below we propose that T-cells may hold the key to explaining the basis of sex differences in hypertension. Unfortunately, the vast majority of the studies implicating T-cells in hypertension have been conducted exclusively using male experimental animals despite the fact that half of the hypertensive population is female. Therefore, understanding the role of T-cells in hypertensive females is an important, although understudied, area of research. Better understanding of the role of T-cells and the immune system in the development and maintenance of hypertension may also provide novel therapies to improve BP control rates in both sexes. This review will begin with a discussion of what is currently known regarding sex differences in T-cells in hypertension followed by highlighting the potential pathways and molecular mechanisms which may contribute to sex differences in the T-cell profile and BP responses to T-cells.

T-CELLS IN EXPERIMENTAL HYPERTENSION

Over the last decade there have been an increasing number of studies defining a critical role for T-cells in hypertension. Although the suppression of lymphocytes (both B- and T-cells) using the immunosuppressant, mycophenolate mofetil (MMF) significantly reduces BP in numerous experimental models of hypertension in male rats [16–19], it was not until the adoptive transfer studies by Guzik et al. [20] that T-cells were directly implicated in hypertension. Adoptive transfer of Pan $CD3^+$ T-cells, but not B-cells, restores hypertensive response to angiotensin (Ang) II and deoxycoticosterone acetate (DOCA) salt in male recombination-activating gene $(Rag)^{-/-}$ mice. These findings have been confirmed by additional studies in male severe combined immune deficiency (SCID) mice [21] and male Dahl salt-sensitive rats [22,23] and directly demonstrate that Pan $CD3^+$ T-cells are required to develop and maintain a hypertensive response in male experimental animals.

Pan $CD3^+$ T-cells can be separated into three different subpopulations: $CD1d^+$ natural killer T (NKT) cells, $CD8^+$ cytotoxic T-cells, and $CD4^+$ T helper (Th) cells, all of which have been implicated in BP control. Relatively little is known regarding the role of NKT cells in essential hypertension; however, Vinh et al. [24] showed that NKT cells do not play a role in Ang II-induced hypertension in male mice. NKT cells will not be further discussed in this review. There is growing interest in $CD8^+$ T-cells in hypertension [25,26]. Indeed, recent studies have shown that male $CD8^{-/-}$ mice, but not $CD4^{-/-}$ mice, exhibit a blunted hypertensive response to Ang II [27]. Moreover, adoptive transfer of $CD8^+$ T-cells resulted in greater Ang II-induced increases in BP in male $Rag^{-/-}$ mice than adoptive transfer of $CD4^+$ T-cells [27]. The authors concluded that renal $CD8^+$ T-cells contribute to experimental hypertension by contributing to sodium and volume retention and vascular rarefaction. In a separate study, $CD8^{-/-}$ mice (the sex of the mice was not specified) exhibited comparable increases in BP following 7 days of Ang II infusion compared with wild-type mice; however, the $CD8^{-/-}$ mice exhibited attenuated cardiac inflammation following Ang II infusion [26]. It should be noted that this second study employed a much higher dose of Ang II (1500 ng/kg per min) than the first study (490 ng/kg per min), raising the possibility that the role of $CD8^+$ T-cells in Ang II hypertension compared with Ang II-induced end-organ damage depends on the dose of Ang II; the higher dose may have resulted in a ceiling effect on BP masking a genotype effect. More studies need to be done to further examine the role

of $CD8^+$ T-cells in hypertension, as well as to examine $CD8^+$ T-cell subtypes in hypertension and BP control.

The majority of experimental studies examining T-cell subtypes in hypertension have focused on $CD4^+$ T-cells. $CD4^+$ T-cells are crucial for the functioning of an intact immune system and play diverse roles in immune surveillance and protection against foreign pathogens. Naïve $CD4^+$ T-cells differentiate into one of four main subtypes: Th1, Th2, Th17 or regulatory T-cells (Tregs); however, the most is known regarding the role of Th17 cells and Tregs in hypertension and related end-organ damage. For in-depth reviews on T-cell differentiation and T-cell subtypes see [28–32].

Th17 cells and hypertension

Th17 cells are pro-inflammatory T-cells that secrete the cytokines interleukin (IL)-17A, IL-17F, IL-21 and IL-22, and have been implicated in the pathogenesis of a number of autoimmune diseases (for reviews on Th17 cells see [33–35]). A role for Th17 cells in hypertension has been indirectly surmised based on studies manipulating IL-17 levels, a pro-inflammatory cytokine produced by Th17 cells. DOCA-salt increases BP, renal and cardiac IL-17 and Th17 cells in male Sprague–Dawley rats and treatment with an IL-17-neutralizing antibody attenuates increases in BP [36]. Moreover, Ang II-induced hypertension is not sustained on male $IL\text{-}17^{-/-}$ mice, supporting a pro-hypertensive role of Th17 cells [37]. However, DOCA-salt plus Ang II infusion results in comparable BP increases in male control (C57BL/6J mice), $IL\text{-}17^{-/-}$ and $IL\text{-}23p19^{-/-}$ mice (IL-23 is required for Th17 cell expansion) [38], calling into question the role of Th17 cells in mediating increases in BP. This may be related to the fact that, although Th17 cells are a primary source of IL-17, they are not the only immune cells to release IL-17. IL-17 is also produced by $\gamma\delta$T cells, NKT cells, neutrophils and eosinophils. Indeed, a recent study found that $\gamma\delta$T cells were responsible for Ang II-induced increases in cardiac IL-17A, and deletion of $\gamma\delta$T cell protected against Ang II-induced cardiac injury [38]. Additional studies using adoptive transfer of Th17 cells are needed to conclusively determine the impact of these cells on BP regulation.

Tregs and hypertension

Tregs suppress the function of other T-cells as well as macrophages and dendritic cells (DCs) to limit an immune response. As a result, Tregs are critical for maintaining immune homoeostasis, preventing autoimmune diseases and limiting chronic inflammatory diseases (for reviews on Tregs see [39,40]). In addition to indirect evidence linking Tregs to BP control [41], adoptive transfer studies have directly linked Tregs with improved cardiovascular outcomes and decreases in BP in male experimental animals. The first study to examine the direct impact of Tregs on BP and end-organ damage used male NMRI mice infused with Ang II [42]. Mice received 2×10^5 Tregs via intravenous injection on day 1 of Ang II infusion. Although Ang II-induced increases in BP were not altered by adoptive transfer of Tregs over the course of the 2 week study, Tregs attenuated Ang II-induced cardiac hypertrophy, fibrosis and electric remodelling. Consistent with this finding, intravenous injection of 1×10^6 Tregs 1 h after transaortic constriction attenuates cardiac fibrosis with no difference in BP between male mice that received Tregs or vehicle 14 days

later; BP was only measured at the end of the study so it is unknown whether Tregs altered the time course by which BP increased [43]. In contrast, intraperitoneal injection of 2×10^6 Tregs three times a week for 2 weeks attenuates Ang II hypertension in male C57Bl/6J mice and improves endothelium-dependent dilation compared with control mice [44,45]. Similarly, tail vein injection of $3{\times}10^5$ Tregs two to three times over a 2 week period attenuates Ang II and aldosterone induced-hypertension and vascular endothelial dysfunction in male C57Bl6 mice [46,47]. Treg supplementation also attenuates increases in BP in male athymic nude mice predisposed to develop pulmonary hypertension [48]. Therefore, there is consistent reporting of a cardiovascular protective role for Tregs, although adoptive transfer of more Tregs at more regular intervals may be required to observe a BP effect. Regardless, these data support the notion that Tregs would be an attractive therapeutic target to improve BP control and attenuate hypertension-induced end-organ damage.

Th17 cells and Tregs: is it all about balance?

The above discussion regarding the proposed roles of Th17 cells compared with Tregs on BP control suggests that the balance between these two T-cell subtypes is a critical determinant of the impact of T-cell activation on cardiovascular health. However, recent evidence suggests that it may not be this simple as additional populations of these T-cell subtypes are identified and characterized. High salt induces Tregs to produce the pro-inflammatory cytokine interferon (IFN)-γ both *in vivo* and *in vitro* [49] and there is a population of Tregs isolated from plasma that secrete IL-17 and IFN-γ in patients with multiple sclerosis [50], diabetes [51] and non-small-cell lung cancer [52]. Additional studies suggest that, in humans, IL-17^+ Tregs are generated in the periphery and contribute to antimicrobial defence, while also controlling autoimmunity and inflammation [53], however, how these cells affect cardiovascular health or BP control has not been examined. Moreover, the origin of these pro-inflammatory Tregs is in question. Th17 cells possess a high degree of plasticity [54], including the conversion of Th17 into Tregs [55,56]. Therefore, not only are there potentially pro-inflammatory Tregs, but also there are anti-inflammatory Th17 cells. Much more work needs to be done to define how these different subpopulations of Tregs and Th17 cells affect cardiovascular health in both sexes before a full understanding of their role in BP control can be achieved.

T-CELLS IN HUMAN HYPERTENSION

There is strong support for a role for T-cells in human hypertension. Immunosenescent $CD8^+$ T-cells are increased in human hypertension [57] and treatment of patients with psoriasis and rheumatoid arthritis with the lymphocyte suppressant MMF exhibit a significant decrease in BP that is maintained during treatment [58]. Moreover, BP returns to pre-treatment levels following the cessation of treatment, further supporting a direct effect of lymphocytes on BP. Treatment of hypertensive patients with carotid atherosclerosis with traditional BP-lowering drugs also decreases circulating Th17 cells and increases Tregs, providing additional indirect support for an impact of BP on T-cells in humans [59]. In addition, acute psychological stress increases $CD4^+$ T-cells and decrease Tregs in healthy men [60,61], and, although not assessed in the same study, acute mental stress also increases

BP [62]. These findings raise the possibility that chronic stress contributes to T-cell-mediated hypertension in humans. In addition to changes in T-cell number, there is also evidence for alterations in T-cell function in human hypertension. T-cells from hypertensive patients have been reported to have either suppressed proliferative responses [63] or greater T-cell activity *in vitro* [57]. T-cells have also been implicated in pulmonary arterial hypertension, patients with pulmonary arterial hypertension have an increase in circulating Th17 cells [64]. Taken together, these data provide a strong rationale for additional studies on the role of T-cells in human hypertension.

SEX AND T-CELLS IN HYPERTENSION

Experimental hypertension

All of the experimental studies above were performed exclusively in males, calling into question the role of T-cells in BP control in females. Although none of these initial studies establishing a role for T-cells in experimental hypertension included females, the immune system has been linked to increases in BP in females (for example lupus, pre-eclampsia [65–67]). However, no studies had directly compared either normotensive or hypertensive males or females to elucidate the impact of sex on T-cell differentiation, activation or infiltration which could contribute to sex differences in hypertension.

To this end, studies by our laboratory examined the impact of MMF on BP in male and female spontaneously hypertensive rats (SHR). Similar to what is observed in male SHR, BP in female SHR decreased with MMF, supporting a pro-hypertensive role for lymphocytes in females [19]. We further examined the renal T-cell profile in male and female SHR; male SHR have more $CD4^+$ cells and Th17 cells and females have more $CD8^+$ cells and Tregs. Based on the proposed roles for Th17 cells compared with Tregs on BP, our findings are consistent with males having a higher BP compared with females. Additional studies confirmed that, consistent with studies in males, increases in BP are associated with increases in renal T-cells in females. Female SHR have significantly more T-cells in their kidneys than normotensive Wistar–Kyoto rats and increasing BP in female SHR increases renal T-cell counts [68].

To more directly link increases in BP to the T-cell profile in SHR, our group further treated male and female SHR with the BP-lowering agents hydrochlorothiazide and reserpine from either 6–12 weeks of age to prevent age-related increases in BP, or 11–13 weeks of age to reverse established hypertension. Neither treatment significantly altered renal $CD3^+$, $CD4^+$ and $CD8^+$ T-cells or Th17 cells compared with same-sex vehicle controls. However, both attenuating age-related increases in BP and reversing established hypertension decreased renal Tregs only in female SHR abolishing the sex difference in Tregs [68]. The lack of a change in Th17 cells in either sex despite changes in BP calls into question the role of Th17 cells in BP control; however, our findings suggest a central role for Tregs in BP control especially in females. This conclusion is further supported by studies examining the impact of chronic Ang II infusion on renal T-cells in male and female Sprague–Dawley rats. Ang II infusion results in greater increases in $CD4^+$ T-cells and Th17 cells in males, whereas Tregs increase only in females [69]. Consistent with our findings, female C57Bl/6 mice display an increase in Tregs in adipose tissue in response to a high-fat diet not observed in males, and

females are protected from high-fat-diet-induced metabolic changes relative to males [70]. Based on the lower BP in multiple female experimental models of hypertension compared with males, including SHR and Ang II hypertension [8], we propose that the ability of females to increase Tregs in response to an increase in BP is a key compensatory mechanism to limit overall increases in BP. Likewise, the inability of males to increase BP may contribute to their higher overall BP and greater degree of end-organ damage seen in young males compared with age-matched females. More studies are needed to directly assess the role of Tregs on BP in females, and to determine the mechanisms by which Tregs are increased in females.

It is interesting to note that greater Tregs in female SHR as compared with male SHR are often mirrored by greater renal $CD8^+$ T-cells as well [19,68]. Although there are both effector and regulatory $CD8^+$ T-cells [71], to date there are no published studies that have further examined the $CD8^+$ T-cell subtypes in hypertension. Regulatory $CD8^+$ T-cells were the first identified subset of T-cells capable of inducing immune suppression [72]; however, difficulties in characterizing these cells have limited their study relative to Tregs. Based on recent studies described above indicating a key role for $CD8^+$ T-cells in hypertension in males, we postulate that females may selectively up-regulate regulatory $CD8^+$ T-cells as well as Tregs. Therefore, greater understanding of this novel T-cell subtype may provide new insight into role of T-cells in not only BP control, but overall cardiovascular health.

Three recent studies have greatly expanded our understanding of the impact of sex on T-cells and BP control using male and female $Rag^{-/-}$ mice. As has previously been demonstrated, adoptive transfer of $CD3^+$ T-cells from wild-type male mice to male $Rag^{-/-}$ mice restores the hypertensive response to Ang II [20,73,74]. However, adoptive transfer of $CD3^+$ T-cells from males did not increase BP responses to Ang II in female $Rag^{-/-}$ mice, and adoptive transfer of T-cells from female mice into male $Rag^{-/-}$ mice abrogated Ang II-induced increase in BP [73,74]. Additional studies further examined the role of $CD4^+$ and $CD8^+$ T-cells from males compared with females in mediating Ang II hypertension. Consistent with what was observed with total $CD3^+$ T-cells, both $CD4^+$ and $CD8^+$ T-cells from male donors restored Ang II hypertension in male $Rag^{-/-}$ mice, although T-cells from females prevented Ang II-induced increases in BP in male $Rag^{-/-}$ mice [9]. Furthermore, since male $Rag^{-/-}$ mice receiving T-cells from a female donor exhibited a lower BP than if the donor T-cells were from a male, these studies clearly illustrate that both the sex of the T-cell and sex of the animal are key determinants of the responsiveness to T-cell-mediated increases in BP.

It is important to note that these sex differences in BP responses were not due to a greater number of T-cells in males following adoptive transfer of male T-cells. Indeed, male $Rag^{-/-}$ mice tended to have more $CD3^+$, $CD4^+$ and $CD8^+$ T-cells both in the circulation and in perivascular fat following adoptive transfer of ‘female’ T-cells compared with ‘male’ T-cells, suggesting that the function of the T-cells is distinct in the recipient rat depending on the sex of the donor [74]. Consistent with this notion, male $Rag^{-/-}$ mice receiving $CD3^+$ T-cells from male donors had more T-cells producing pro-inflammatory cytokines (tumour necrosis factor (TNF) and IL-17) following 2 weeks of Ang II infusion than if the T-cells were from a female, whereas plasma IL-10 levels were significantly higher if the donor T-cells were of female origin [74]. In addition, male $Rag^{-/-}$ mice exhibit greater increases in TNF,

monocyte chemoattractant protein (MCP), and IL-2 than female $Rag^{-/-}$ mice following adoptive transfer of $CD3^+$ T-cells from a male donor and Ang II infusion [73]. These data suggest that not only are females able to limit the pro-hypertensive effects of T-cells from males in response to Ang II hypertension, but also T-cells from females have a more anti-inflammatory, anti-hypertensive immune cell phenotype than T-cells from males, which is consistent with data from our group. It should be noted that Tregs were not greater in female $Rag^{-/-}$ mice following adoptive transfer of male T-cells or in male $Rag^{-/-}$ mice following adoptive transfer of female T-cells. This finding potentially highlights the importance of the entire immune profile in dictating the physiological outcome of alterations in the immune system within each sex. The key papers reporting a sex difference in T-cells in hypertension are summarized in Table 1.

Human hypertension

The majority of the studies discussed above supporting a role for T-cells in human hypertension have included both men and women, although the data have not been analysed separately based on sex, preventing sex-based conclusions from being drawn. However, sex differences have been reported in T-cells in human hypertension. Healthy women have higher levels of circulating $CD4^+$ T-cells than men [75] and isolated $CD4^+$ T-cells from women produce more IFN-γ and proliferate more than $CD4^+$ T-cells from men, whereas $CD4^+$ T-cells from men have greater IL-17 production [76]. Unfortunately, $CD4^+$ T-cell subtypes were not assessed in these studies, therefore it is unknown whether differences in T-cell function are the result of greater Tregs in women or greater Th17 cells in men.

A sex-specific role for T-cells in human hypertension is also suggested by studies of autoimmune diseases, particularly systemic lupus erythaematosus (SLE). Women are more likely than men to develop SLE (9:1) and young women with SLE are approximately ten times more likely to develop hypertension than healthy young women [77,78]. Patients with SLE have an increase in circulating Th17 cells [79] and decreases in Tregs [80]. Moreover, pharmacological blockade of mammalian target of rapamycin (mTOR) using *N*-acetylcysteine (NAC) in patients with SLE (men and women) reported a decrease in total circulating $CD4^+$ and $CD8^+$ T-cells and increases in circulating Tregs and these alterations were accompanied by an improvement in patient health (BP was not reported) [81]. More women develop SLE than men, although disease severity is often worse in men; yet it is unknown whether men with SLE have greater T-cell activation. Due to the greater prevalence of SLE in women, the number of women represented in the studies above far outweighs the men and none of the data were presented separately for sex, leaving open the question of whether or not women with SLE maintain more Tregs than their male counterparts and whether this could affect the development and progression of hypertension. However, a study of 1979 lupus patients (157 men and 1822 women) reported that men are more likely than women to have disability, hypertension, thrombosis, and renal, haematological and serological manifestations of lupus [82]. Men were also more likely to exhibit end-organ damage including renal, cardiovascular, peripheral vascular disease and myocardial infarction – all of which are related to hypertension and linked to T-cell infiltration. Therefore, it is tempting to speculate that, consistent with experimental data in essential hypertension, females with SLE have enhanced Treg activation which attenuates

the pro-inflammatory effector T-cells relative to males. Dysregulation in the balance of Tregs and Th17 cells has also been implicated in BP control in women with pre-eclampsia. Women with pre-eclampsia have increased total circulating $CD4^+$ T-cells and Th17 cells and decreases in Tregs compared with women with healthy pregnancies [83–85]. Regardless, more clinical studies are needed to more fully define the T-cell phenotype and function in both healthy and hypertensive men and women to determine the likelihood of successfully targeting immune cells in a sex-dependent manner to increase BP control rates.

DOES SEX AFFECT T-CELL ACTIVATION IN HYPERTENSION?

With increasing support for the notion that T-cells play a critical role in BP control in hypertension, numerous studies have been initiated to understand how T-cells are activated in hypertension and identify the antigen(s) responsible. Current evidence suggests that T-cell activation occurs in response to increases in BP resulting in co-ordinated activation of innate and adaptive immune cells following the release and presentation of an endogenous antigen [6,7,86]. Although no studies to date have directly compared T-cell activation in hypertensive males and females, numerous steps along this pathway have been suggested to be differentially regulated in males compared with females. As a result, hypertensive stimuli may have sex-specific effects on T-cell activation and differentiation in hypertension.

Antigens: cell death and danger molecules

Vascular necrosis is a hallmark of malignant hypertension [87–89] and recent studies in male Dahl salt-sensitive rats indicate that renal injury in response to a high-salt diet, which is in part mediated by increases in T-cell infiltration, is dependent on increases in renal perfusion pressure and injury [90,91]. These studies suggest that elevated hydrostatic pressure in the kidney and vasculature in response to persistent hypertensive stimuli induces cellular necrosis. Necrosis is an uncontrolled pathological process characterized by loss of plasma membrane integrity resulting in the release of cellular material that is typically sequestered inside the cell. Matzinger [92] proposed the Danger Model of immunity in 1994 which suggested that the immune system is more concerned with damage than simply differentiating between ‘self’ and ‘non-self’. The Danger Model proposes that an immune response can be induced by either exogenous pathogen-associated molecular patterns (PAMPs) or endogenous damage-associated molecular patterns (DAMPs). As a result, cellular necrosis following injury results in the release of DAMPs into the extracellular space which are recognized by cells of the innate immune system leading to activation of the adaptive immune response. As a result, DAMPs may serve as antigens to induce T-cell activation in hypertension.

There is evidence in the literature to suggest that there are sex differences in the susceptibility of cells to undergo cell death. Isolated primary cortical neuron cultures from male rats more readily undergo autophagy and die, whereas neurons from females mobilize fatty acids, accumulate triacylglycerols, form lipid droplets and survive longer [93]. Similarly, cardiomyocytes from female mice exhibit greater survival in response to H_2O_2 (100 μmol/l) compared with cardiomyocytes from males [94]. These studies suggest an innate cellular difference in the cell death/cell survival machinery between the sexes, where

cells from females are better able to tolerate cellular stress to resist death. In support of this notion, key proteins involved in cellular death are differentially expressed in males and females in a sex-hormone-dependent manner [95,96]. Testosterone increases Fas, Fas ligand (FasL) and Fas-associated death domain (FADD) expression to promote apoptosis in vascular endothelial cells and renal tubular cells [97,98]. In contrast, Akt, an anti-apoptotic protein that promotes cell survival, expression is greater in kidneys from females than males [99]. Moreover, testosterone inhibits Akt expression whereas oestrogen increases Akt [99–101], and oestrogen-mediated increases in Akt are associated with decreased apoptosis following coronary artery ligation *in vivo* [102]. These data suggest that sex steroids are critical in determining which cell death pathway is activated in damaged tissue resulting in sex differences seen in the extent of injury and hypertension. This could explain the basis for sex differences observed in T-cell profiles in experimental animals in key organs associated with the regulation of BP. Additional studies are needed to determine the impact of sex on cell death *in vivo* in hypertension; greater cellular necrosis in males in response to hypertensive stimuli may explain greater effector T-cell activation compared with females. Greater necrotic cell death in males would result in greater release of DAMPs, which would result in more pro-inflammatory stimuli.

DAMPs are ideal candidates to act as antigens for T-cell activation in hypertension. Although there is very little known regarding sex differences in DAMPs, DAMPs are associated with numerous diseases and levels have been shown to be increased in hypertensive humans and experimental animals [103,104]. DAMPs can either be ‘normal’ proteins that are not typically found in the extracellular space in healthy tissues, or proteins that have been damaged, misfolded or otherwise modified by the oxidative extracellular environment. DAMPs include, but are not limited to, asymmetric dimethylarginine, biglycan, C-phosphate-G DNA/mitochondrial DNA, C-reactive protein, DNA, RNA, fibrinogen, high mobility group box-1, heat-shock proteins, hyaluronan, uric acid, serum amyloid A protein, ATP, uric acid and IL-1α [104,105]. Recent studies have shown that proteins oxidatively modified by highly reactive γ-ketoaldehydes (isoketals) are formed in experimental hypertension and accumulate in DCs leading to T-cell-induced hypertension [25]. Although these studies only included male experimental animals, it is well established that females have lower levels of oxidative stress relative to males [8,106], therefore we would speculate that females would exhibit less T-cell activation compared with males. Isoketal adducts have also been measured in hypertensive men (two) and women (ten) [25]. Isoketals are greater in circulating monocytes and $CD83^+$ cells (marker of human DCs) from humans with hypertension compared with healthy subjects. Moreover, the percentage of isoketal-positive cells was positively correlated with systolic BP, providing a potential link to human hypertension.

DAMPs activate T-cells via pattern recognition receptor (PRR) activation on cells of the innate immune system, including macrophages, leucocytes and DCs [107]. PRRs can be divided into four families including Toll-like receptors (TLRs), and TLRs have been linked to the development and progression of numerous cardiovascular disorders, including hypertension [103,104,108]. Although there are no studies to date that have directly compared the impact of TLR inhibition on BP in males and females, there is evidence to support sex differences in TLR expression and function. We have previously reported that

female SHR have greater TLR3, TLR5 and TLR6 mRNA expression in the renal cortex and greater TLR4 and TLR6 expression in mesenteric arteries compared with males [109]. Consistent with our data, women in the Framingham Heart Study have higher platelet TLR mRNA expression than men, although TLR expression in men is more commonly associated with circulating cytokines, whereas in women, TLR expression was associated with greater soluble P-selectin levels [110]. In addition, hypertensive women with an D299G polymorphism of TLR4 have lower left ventricular (LV) mass and reduced LV hypertrophy compared with women with the wild-type genotype, although this polymorphism had no effect on LV structure in men, further supporting sex-specific effects of TLR on cardiovascular function [111].

T-cell receptor activation and antigen-presenting cells

Women typically exhibit a more robust immune response post-infection than men [112], raising the possibility that there are sex differences in the ability of T-cells to be activated following presentation of an antigen. This could reflect a sex difference in either the antigen-presenting cell (APC) or the T-cell. T-cell activation requires both T-cell receptor ligation (signal 1) and co-stimulation (signal 2). Signal 1 is the binding of antigen in the major histocompatibility complex (MHC) of APCs to the T-cell antigen receptor. Signal 2 is provided by interaction of the T-cell co-receptor CD28 with the APC B7 ligands, CD80 or CD86. Although there are no studies to date that have directly examined whether sex differencs in APCs or T-cell activation contribute to sex differences in BP, there is evidence to suggest this as a promising line of investigation since blocking B7-dependent co-stimulation of T-cells attenuates Ang II and DOCA-induced hypertension in male mice [24]. In adddition, a functional T-cell receptor is required for male Dahl salt-sensitive rats to fully develop hypertension in response to a high-salt diet [23]. Although the same studies have not been performed in female experimental animals, B7 blockade more effectively treats B16 melanoma in C57/BL6 female mice compared with males [113] which is consistent with our finding that female SHR have greater CD80 and CD86 mRNA expression in the renal cortex than male SHR [109]. These data could explain why females typically mount a more robust immune response than males; however, this would not necessarily explain sex differences in the T-cell subtype activation.

Alternatively, a sex difference in APCs could contribute to sex differences in both T-cell activation and differentiation. The most efficient professional APCs are DCs and DCs from hypertensive male mice have increased surface expression of the B7 ligands CD80 and CD86 [24]. The use of adoptive transfer studies have further established that donor DCs from Ang II-infused mice promote T-cell proliferation and activation resulting in a hypertensive response to low-dose Ang II in recipient mice [25,114]. Although no studies to date have examined DC phenotype and function in hypertensive males compared with females, female sex hormones promote the differentiation of functional DCs [115,116]. Oestradiol acts via oestrogen receptor α to either induce DC differentiation, leading to the development of DCs with increased functional capacity, or decrease the number of differentiated DCs [117]. Therefore, female sex hormones have the capacity to affect the DC phenotype and function and it is not unreasonable to speculate that this may result in sex

differences in the differentiation and activation of distinct T-cell subtypes in females compared with males.

SUMMARY

There is an ever-expanding literature base supporting a causal role of T-cells in experimental hypertension. The challenge now is to fully understand the molecular mechanisms by which the immune system regulates BP in both sexes and how the different components of the immune system interact so that specific mechanisms can be targeted therapeutically without compromising natural immune defences. Although men and women both become hypertensive, many of the molecular pathways by which they become hypertensive differ and there is mounting evidence to suggest that the same will be the case for T-cells. Sex differences in BP control and cardiovascular disease have been known for over 60 years, and recent experimental studies in $Rag^{-/-}$ mice highlight the critical role of lymphocytes in mediating sex differences in basal BP control [73,74]. Therefore, based on the potential therapeutic application of Tregs, better understanding of how females are able to maintain higher numbers of Tregs will greatly aid in our ability to expand these T-cells *in vivo* to improve cardiovascular outcomes for all hypertensive patients.

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Abbreviations:

Ang	angiotensin
APC	antigen-presenting cell
BP	blood pressure
DAMP	damage-associated molecular pattern
DC	dendritic cell
DOCA	deoxycoticosterone acetate
IFN	interferon
IL	interleukin
LV	left ventricular
MMF	mycophenolate mofetil
NAC	*N*-acetylcysteine
NKT	natural killer T-cells
PRR	pattern recognition receptor

Rag	recombination-activating gene
SHR	spontaneously hypertensive rats
SLE	systemic lupus erythaematosus
Th	T helper
TLR	Toll-like receptor
TNF	tumour necrosis factor
Treg	regulatory T-cell

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Table 1

Sex differences in T-cell involvement with elevations in BP in animal models

Sex difference in T-cell involvement with BP control	Reference
T-cell population's origin of sex determines the effect on BP in Rag1$^{-/-}$ mice	Sandberg et al. [9]
Lymphocytes contribute to hypertension in SHR; the profile of circulating T-cells is sex-specific	Tipton et al. [19]
BP contributes to a sex-specific renal T-cell profile in SHR; elevations in BP increase renal Tregs in females	Tipton et al. [68]
Ang II infusion increases T-cells in SD rats; Treg levels increase only in females	Zimmerman et al. [69]
Tregs are increased in C57 high-fat-diet-fed mice exclusively in females which protect them from metabolic changes	Pettersson et al. [70]
Male CD3^{+} T-cells cause greater increases in BP and T-cell infiltration in male Rag1$^{-/-}$ mice than female	Pollow et al. [73]
Sex of the T-cell itself is distinct in its function BP control in Rag1$^{-/-}$ mice	Ji et al. [74]

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