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Themed Section: Immune Targets in Hypertension

REVIEW ARTICLE

Mechanisms of hypertension in autoimmune rheumatic diseases

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Patients with autoimmune rheumatic diseases including rheumatoid arthritis and systemic lupus erythematosus have an increased prevalence of hypertension. There is now a large body of evidence showing that the immune system is a key mediator in both human primary hypertension and experimental models. Many of the proposed immunological mechanisms leading to primary hypertension are paralleled in autoimmune rheumatic disorders. Therefore, examining the link between autoimmunity and hypertension can be informative for understanding primary hypertension. This review examines the prevalent hypertension, the immune mediators that contribute to the prevalent hypertension and their impact on renal function and how the risk of hypertension is potentially influenced by common hormonal changes that are associated with autoimmune rheumatic diseases.

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1 | INTRODUCTION

It is estimated that over 1 billion people worldwide have hypertension with disease complications contributing to 10 million largely preventable deaths each year (Collaborators, 2016). Despite improvements in treatment and the development of many classes of antihypertensive drugs over the past century, only about one quarter of patients who receive medication achieve blood pressure control (Mills et al., 2016). The burden of hypertension globally suggests that there is a continued need to understand the underlying mechanisms that contribute to its development. Increases in blood pressure are primarily attributed to perturbations in the kidney, vasculature, and CNS, but both clinical and experimental evidence implicate the immune system in the pathogenesis of essential hypertension (Rodriguez-Iturbe et al., 2014). In support of the connection between the immune system and hypertension, patients with autoimmune rheumatic diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and psoriatic arthritis/psoriasis (PsA) have prominent immune system dysfunction as well as high rates of hypertension (Al-Herz, Ensworth, Shojania, & Esdaile, 2003; Panoulas et al., 2008; Qureshi, Choi, Setty, & Curhan, 2009; Sabio et al., 2011). Recent evidence from our laboratory (Mathis et al., 2014; Taylor, Barati, Powell, Turbeville, & Ryan, 2018; Taylor & Ryan, 2017) and others (Rodriguez-Iturbe, 2016)

Abbreviations: CIA, collagen-induced arthritis; COC, combined-oral contraceptive; DAMP, damage assoicated molecular pattern; DC, dendritic cells; ET-1, endothelin-1; LN, lupus nephritis; NET, neutrophil extracellular trap; PAMP, pathogen assoicated molecular pattern; PsA, psoriatic arthritis/psoriasis; RA, rheumatoid arthritis; RAS, renin-angiotensin system; SSc, systemic sclerosis; SLE, systemic lupus erythematosus; SRC, scleroderma renal crisis

suggest that the prevalent immune system dysfunction in autoimmunity has a causative role in the development of hypertension. Hypertension is a major risk factor for the development of cardiovascular disease (CVD) in patients with autoimmune disorders. In fact, over 50% of premature deaths in RA are attributed to CVD (Symmons & Gabriel, 2011), and in SLE, patients who survive beyond the first 5 years most die from complications due to CVD (Manzi et al., 1997). While an association between autoimmunity and hypertension has been established, much remains unclear about the underlying pathways by which autoimmunity promotes hypertension. The purpose of this review is to discuss the link between autoimmunity and hypertension, with an emphasis on the role of immune system components in the development of autoimmune-associated hypertension. In addition, because of the prevalent renal disease in patients with autoimmune disorders and the general predilection of autoimmune disorders for women, consideration will be given to the effects of immune system activation on renal function and the potential role of sex hormones in cardiovascular risk during autoimmunity.

2 | IMMUNE SYSTEM DYSFUNCTION IN HUMAN HYPERTENSION

Studies over the past 40–50 years have provided evidence of inflammation, immune system dysfunction, and characteristics of autoimmunity in patients with essential hypertension. Cross-sectional studies reported a higher prevalence of hypertension in patients with increased levels of C reactive protein (Bautista et al., 2001; Bautista, Vera, Arenas, & Gamarra, 2005; Chul Sung et al., 2003), **IL-6** (Bautista et al., 2005; Chae, Lee, Rifai, & Ridker, 2001), and **TNF-α** (Bautista et al., 2005; Yu, Yang, & Yu, 2010) as well as elevated circulating leukocytes (Shankar, Klein, & Klein, 2004; Tatsukawa et al., 2008). However, due to the cross-sectional design of those studies, it could not be determined if the inflammatory marker or cells preceded the development of hypertension. Observational studies that recruited normotensive patients and evaluated inflammatory status and the development of de novo hypertension found that higher levels of C reactive protein at baseline were associated with an increased risk of developing hypertension (Sesso et al., 2003; Sesso, Wang, Buring, Ridker, & Gaziano, 2007). Consistent with essential hypertension, a variety of inflammatory cytokines, including TNF-α and IL-6, have been implicated in the pathogenesis of autoimmune diseases (Yap & Lai, 2013).

Although the initiation of the immune response remains elusive as it relates to hypertension, evidence suggests that physical injury of the vessel wall in response to increased pressure may be an important event (Anders, Baumann, Tripepi, & Mallamaci, 2015; Bartoloni, Alunno, & Gerli, 2018; Wenzel et al., 2016). In addition, it has been postulated that hypertensive factors such as **angiotensin II**, high salt, or **aldosterone** have direct effects on the innate immune system, by activating complement, **Toll-like receptors (TLRs)**, and the inflammasome. This ultimately leads to the formation of neoantigens and activation of the cells of both the innate and adaptive immune systems (Wenzel et al., 2016). It has been suggested that neoantigen formation leads to a loss of tolerance and the production of autoantibodies in hypertension (Rodriguez-Iturbe et al., 2014). Interestingly, this working hypothesis bearsa strong resemblance to the mechanisms involved in the development of autoimmune diseases. In support of this concept, patients with essential hypertension have been shown to have elevated levels of circulating IgG and IgM (Ebringer & Doyle, 1970; Hilme et al., 1989; Suryaprabha et al., 1984), and clinical studies have correlated the production of pathogenic autoantibodies and hypertension (Gudbrandsson, Herlitz, Hansson, Lindholm, & Nilsson, 1981). A study by Wallukat et al. first identified the presence of agonistic angiotensin **AT_1 receptor** autoantibodies in pregnancy-related hypertension, which were later identified in renal transplant associated hypertension and essential hypertension (Wallukat et al., 1999; Dragun et al., 2005; Liao et al., 2002). A direct blood pressure modulatory role for autoantibodies in humans was demonstrated by studies in patients with refractory hypertension in which immunoadsorption of **α_1-adrenoceptor** receptor autoantibodies was sufficient to lower mean arterial pressure (Wenzel et al., 2008). Therefore, the production of autoantibodies, as occurs in patients with autoimmune rheumatic diseases, points to a prominent role for B lymphocytes in the pathogenesis of hypertension and suggests a central role for autoantibodies in the prevalent hypertension during autoimmunity.

T lymphocytes, which are also important in the pathogenesis of autoimmune disorders, have been extensively studied in various experimental models such as angiotensin II and salt-sensitive hypertension (Zhang & Crowley, 2015). However, much less is known about T cells in human hypertension. Early studies showed that T cells infiltrated the kidneys in patients with essential hypertension (Heptinstall, 1954); however, the relative contributions of various **$CD4^+$** T_H subsets, $CD8^+$ cytotoxic T lymphocytes, γδ T cells, and NKT cells to the pathogenesis of human hypertension are still poorly understood. The potential importance of $CD8^+$ T cells was recently reported in a study of patients with essential hypertension. The authors concluded that hypertensive patients have more immuno-senescent $CD8^+$ T lymphocytes with increased expression of **CXCR3**, a receptor for chemokines, which recruit T cells to injured organs (Youn et al., 2013). Finally, Genome Wide Association Study (GWAS) studies suggest that gene variants expressed in T lymphocytes associate with hypertension. For example, variants in the gene encoding the T cell signalling component, the CD3ζ chain, associated with blood pressure in a study of 2,000 hypertensive subjects (Ehret, O'connor, Weder, Cooper, & Chakravarti, 2009), and a missense SNP in lymphocyte-specific adaptor protein (LNK or SH2B3) that is needed for T cell signalling segregated with diastolic blood pressure (Newton-Cheh et al., 2009).

While much of the attention has focused on the role of T and B lymphocytes in the pathogenesis of essential hypertension, it is increasingly appreciated that cells of the myeloid lineage may also play an important role. Neutrophils are the first line of defence against pathogens but have diverse roles in both B and T lymphocyte function. High neutrophil counts were found to be a predictor of hypertension in a Japanese cohort (Tatsukawa et al., 2008), and a recent study by Belen, Sungur, Sungur, and Erdoğan (2015) identified an increased neutrophil to lymphocyte ratio in patients with resistant hypertension. Circulating monocytes have also been isolated from hypertensive patients and shown to be "preactivated," indicating that they have enhanced secretion of inflammatory cytokines after stimulation with angiotensin II or LPS as compared to normotensive controls (Dörffel et al., 1999). Given that cytokines, complement,

lymphocytes, and myeloid cells are associated with hypertension in both humans and experimental models and their known roles in the pathogenesis of autoimmunity, their potential role in the autoimmune-associated hypertension will be reviewed in greater detail below.

3 | PREVALENCE OF HYPERTENSION IN AUTOIMMUNE RHEUMATIC DISEASES

Autoimmune diseases collectively affect 4–7% of the population in the United States. Each condition has a unique aetiology, with both genetic and environmental factors contributing to disease development and pathogenesis (Alzabin & Venables, 2012). Studies of both arthritic diseases such as RA and PsA; systemic autoimmune diseases, including SLE, Sjögren's syndrome, and systemic sclerosis (SSc); and several forms of vasculitis, including giant cell arteritis and antineutrophil cytoplasmic antibody-associated vasculitis, have reported increased prevalence of hypertension as compared to the general population, although large discrepancies are found in the published reports (Panoulas et al., 2008). Reasons for these discrepancies may include under-diagnosis of hypertension in autoimmune diseases, study design, and corticosteroid use (Bartoloni et al., 2018). In the case of RA, the prevalence of hypertension ranges from 52% to 73% in unselected, community-based RA populations (Chung et al., 2008; Gonzalez et al., 2008). The most convincing evidence of increased prevalence of hypertension in RA as compared to the general population is from a large population-based study in which the incidence of hypertension was 31%, as compared to 23% in the control population. This study also found increased prevalence of hypertension in patients with PsA and ankylosing spondylitis (Han et al., 2006). PsA, in particular, is associated with increased incidence of all traditional cardiovascular risk factors with one study reporting high blood pressure in up to 55% of PsA patients (Jamnitski et al., 2013). Many studies have reported an increased prevalence of hypertension in patients with SLE (Al-Herz et al., 2003; Budman & Steinberg, 1976; Mandell, 1987; Petri, 2000; Sabio et al., 2011; Selzer et al., 2001; Shaharir, Mustafar, Mohd, Said, & Gafor, 2015), although the prevalence varies widely depending on the cohort. The rates of hypertension are especially high in women with SLE younger than 40; Sabio et al. (2011) reported that 40% of SLE patients under the age of 40 had hypertension, compared to only 11% of age-matched controls. Sjögren's syndrome, a rare and poorly understood systemic autoimmune disease, affects the moisture-producing glands of the body. Similar to SLE, patients with Sjögren's syndrome frequently produce antinuclear antibodies and have high circulating immunoglobulins (Ramos-Casals, Tzioufas, & Font, 2005). While CVD has been infrequently studied in patients with Sjögren's, several studies reported a higher prevalence of both hypertension and dyslipidemia as well as cardiovascular events including myocardial infarction and stroke (Bartoloni et al., 2015; Juarez et al., 2014). Taken together, these clinical studies highlight the increased incidence of hypertension in autoimmune rheumatic diseases, but few studies have explored potential mechanisms that contribute to its development. In addition, there are scant data on the potential blood pressure lowering effects of various therapies currently prescribed to patients with autoimmune diseases.

4 | INFLAMMATION AND IMMUNE SYSTEM DYSFUNCTION

4.1 | Toll-like receptors

Both pathogen- and host-derived molecules can function as "danger" signals that stimulate inflammation. A variety of both immune and non-immune cells can become activated when they sense pathogen-associated molecular patterns (PAMP) or endogenous damage-associated molecular patterns (DAMP) using invariant immune receptors such as the TLRs. TLRs are Type I transmembrane glycoproteins that can either be cell surface molecules (TLR1, -2, -4, -5, and -6) or expressed on endosomal membranes (TLR3, -7, -8, and -9). Stimulation of TLRs can result in the production of pro-inflammatory cytokines and the activation of the adaptive immune system (Akira & Takeda, 2004). Aberrant TLR activation has been implicated in the pathogenesis of SLE, RA, PsA, and other autoimmune diseases (Mohammad Hosseini, Majidi, Baradaran, & Yousefi, 2015). While the link between TLR expression and hypertension has not been directly examined in autoimmune rheumatic diseases, the dysregulation of these receptors and their signalling could contribute to low-grade inflammation as well as the development of hypertension in autoimmunity. One clinical study evaluated TLR expression in kidney sections from patients with lupus nephritis (LN) and reported higher amounts of TLR3, TLR7, and TLR9 staining in LN patients. Regardless of the aetiology of primary hypertension, vascular damage-associated molecular patterns are likely to be present due to increased cell death and injury in response to increased pressure. Within the vasculature, TLRs have distinct profiles, with TLRs 2 and 4 being ubiquitously expressed (Pryshchep, Ma-Krupa, Younge, Goronzy, & Weyand, 2008). Several studies have illustrated the role of TLRs, specifically **TLR4,** in mediating vascular dysfunction and contributing to hypertension in the spontaneously hypertensive rat (Bomfim et al., 2012) and in obese mice (Liang, Liu, Wang, Xu, & Vanhoutte, 2013).

4.2 | Cytokines

Various pro- and anti-inflammatory cytokines play pivotal roles in the pathogenesis of autoimmune rheumatic diseases. While a full discussion of cytokine dysregulation in the context of autoimmunity is beyond the scope of this review, some of the cytokines increased in autoimmune diseases that may have a role in the pathogenesis of hypertension will be discussed here. In general, inflammatory cytokines can interact with important blood pressure regulatory systems such as the renin-angiotensin system (RAS; Brasier, Recinos, & Eledrisi, 2002; Capettini et al., 2012; Harrison et al., 2011) and the sympathetic nervous system (Pongratz & Straub, 2014). Furthermore, cytokines such as TNF-α can block the activation of **endothelial NOS** and can induce oxidative stress by increasing ROS production.

There are limited data on the role of cytokines in the development of RA-associated hypertension, from either clinical studies or animal models. The most commonly used experimental model of RA is a murine model of collagen-induced arthritis (CIA; Pietrosimone, Jin, Poston, & Liu, 2015), and while this model reproduces the joint inflammation present in RA, hypertension and other cardiovascular abnormalities do not occur. Nonetheless, several clinical studies have examined cytokines and hypertension in RA. One clinical study by Manavathongchai et al. (2013) measured inflammatory markers in RA patients with and without hypertension and found that increased serum **homocysteine** and **leptin** levels correlated with increased blood pressure, but the inflammatory cytokines TNF-α and IL-6 did not. Homocysteine and leptin can increase blood pressure by impairing pressure natriuresis, causing vascular endothelial dysfunction, and increasing renal sodium reabsorption (Beltowski, 2010; Lai & Kan, 2015). An additional clinical study performed 24-hr ambulatory blood pressure monitoring on RA patients taking the TNF-α inhibitor **infliximab** and found that systolic blood pressure was significantly lower in patients receiving the treatment. The reduction in blood pressure correlated with decreases in noradrenaline (Sandoo et al., 2011). **IL-17A** is associated with a more severe course of disease in patients with RA (Newton-Cheh et al., 2009) and is an attractive therapeutic target. In experimental models, the blockade of IL-17A in CIA suppresses arthritis and prevents joint damage. Whether cytokines can be a therapeutic target in RA patients with hypertension remains to be determined.

In SLE, high circulating concentrations of TNF-α correlate with disease activity (Davas et al., 1999; Maury & Teppo, 1989; Studnicka-Benke, Steiner, Petera, & Smolen, 1996), and TNF-α expression is increased in patients with LN (Herrera-Esparza, Barbosa-Cisneros, Villalobos-Hurtado, & Avalos-Diaz, 1998; Malide, Russo, & Bendayan, 1995), but there are limited data on the association between TNF-α and hypertension in patients. Our laboratory has examined the role of TNF-α in SLE-associated hypertension using the NZBWF1 (F1 hybrid of New Zealand Black and New Zealand White strains) mouse, a widely used and established experimental model of SLE. The NZBWF1 mouse exhibits many of the hallmark characteristics of SLE disease in humans, including lymphadenopathy, splenomegaly, elevated anti-dsDNA autoantibodies, and the development of immune-complex-mediated glomerulonephritis (Burnett, Ravel, & Descotes, 2004). As in patients with SLE, there is also a strong sex dimorphism in NZBWF1 mice. Importantly, our laboratory has established the NZBWF1 mouse as a model of autoimmunity with hypertension (Ryan & Mclemore, 2007). There are several other spontaneous models of SLE, including the MRL/*lpr* and BXSB models (Perry, Sang, Yin, Zheng, & Morel, 2011). While both of these animal models produce autoantibodies and develop immune complex-mediated glomerulonephritis, neither develop hypertension. Venegas-Pont et al. (2010) reported that administration of a TNF-α antagonist, **etanercept**, to NZBWF1 mice attenuated the hypertension and glomerular injury. Also, mice treated with etanercept had decreased monocyte infiltration to the kidneys and lowered NADPH expression in the renal cortex (Venegas-Pont et al., 2010). These data suggest that TNF-α may be an important factor contributing to the increased risk for hypertension during SLE, through a mechanism that involves renal inflammation and oxidative stress, both of which are implicated in the development of primary hypertension (Wilcox, 2002). Recent studies suggest that IL-17 plays a central role in the pathogenesis of LN, as it induces the production of other inflammatory cytokines and recruits inflammatory cells (Apostolidis, Crispín, & Tsokos, 2011; Zhang, Kyttaris, & Tsokos, 2009). Thus, it is likely that IL-17 plays a role in hypertension in SLE patients with renal involvement.

PsA is associated with pathogenic T cells that produce high levels of IL-17. Both IL-17 and TNF-α are targets for therapy in psoriasis, but the data are limited on the effect of these treatments on hypertension and CVD parameters. Piaserico et al. (2016) found that treatment of young patients with severe psoriasis with TNF-α inhibitors resulted in the restoration of coronary microvascular function. Studies are currently ongoing to evaluate the effects of the IL-17A inhibitor **secukinumab** on vascular inflammation and cardiovascular risk in patients with psoriasis (Lockshin et al., 2018). Several experimental models of psoriasis are utilized by researchers, such as **imiquimod** treatment (van der Fits et al., 2009), epidermal overexpression of molecules involved in pathogenesis (Schon, 2008), and more recently, the overexpression of IL-17 in keratinocytes (Croxford et al., 2014). The overexpression of IL-17 in keratinocytes leads to systemic vascular inflammation, endothelial dysfunction, and arterial hypertension, accompanied by increased numbers of neutrophils in the circulation (Karbach et al., 2014). In conclusion, various therapies that target cytokines are currently used in the treatment of autoimmune diseases, but the data are limited on the effects of therapies on blood pressure.

4.3 | Complement

The complement system is an evolutionarily ancient system consisting of secreted proteins synthesized primarily in the liver that mediate tissue damage and injury. Complement activation can occur by three pathways known as the classical, alternative, and lectin pathways. The classical pathway is initiated by IgG or IgM immune complex formation and binding of complement component C1q to the antibody site, the lectin pathway is initiated by the binding of mannose-binding lectin or ficolin to microbial components, and the alternative pathway involves direct activation by foreign pathogens (Vignesh, Rawat, Sharma, & Singh, 2017). Each of these pathways results in the cleavage of complement **component C3** and the formation of the membrane attack complex that can lyse pathogens and cells. Additionally, large numbers of activated complement proteins such as C3 and **C5** can bind and opsonize pathogens, targeting them for engulfment by phagocytes that express complement receptors. Overactivation of the complement system is an important mediator of tissue damage and injury in autoimmunity, but the absence of complement components is also linked to the development of autoimmune disease, probably due to an inability to clear debris and apoptotic cells (Ballanti et al., 2013; Lintner et al., 2016). The association between hypertension and excess complement activation has been investigated in both

humans and animal models. Elevated plasma levels of complement components C3 and **C4** in hypertensive patients has been previously reported by several groups (Bozzoli et al., 1992; Schaadt, Sørensen, & Krogsgaard, 1981). More recently Zhang et al. (2014) reported that hypertensive humans have increased levels of the complement protein C5a and that in a murine chronic angiotensin II infusion model, both C3a and C5a are increased in the circulation. The authors also showed that the absence of C5a or antagonism of the **C5a receptor** in mice chronically administered angiotensin II reduces cardiac remodelling and inflammation but does not affect blood pressure (Zhang, Li, Wang, Wu, Cui, et al., 2014; Zhang, Li, Wang, Wu, & Du, 2014). In addition, a link between T_{REG} and the complement receptors for C3a and C5a was recently identified. Aangiotensin II infusion elevates expression of these receptors on T_{REG}, and a loss of these receptors on T_{REG} prevents the development of hypertension in response to Ang II infusion (Chen et al., 2018). Taken together, these animal studies suggest that complement may be an important factor in the development of hypertension and end-organ damage. While the role of complement in autoimmune-associated hypertension has not yet been investigated, complement is likely to be an important factor in the development of hypertension, especially in those patients with renal involvement.

4.4 | Innate immune cells

In the context of autoimmune rheumatic diseases, several types of innate immune cells have been reported as being dysfunctional or having altered activity, including neutrophils, monocytes, macrophages, and dendritic cells (DC). For example, neutrophils are not only known mediators of tissue injury in autoimmune rheumatic diseases but are also likely to be important for the initiation and progression of autoimmune disease (Németh, Mócsai, & Lowell, 2016). Recent studies found abnormalities in various neutrophil functions in SLE, including increased levels of neutrophil aggregation, increased apoptosis, and abnormal clearance of apoptotic bodies (Kaplan, 2011). Also, neutrophils from SLE patients have increased levels of neutrophil extracellular trap (NET) formation, which is also called NETosis. NETosis results in the release of chromatin and other putative autoantigens from the cell, which may lead to increased autoantibody production (Gupta & Kaplan, 2016). Impaired NET degradation is associated with LN (Hakkim et al., 2010), suggesting that neutrophil dysfunction may have a role in SLE hypertension in patients with renal involvement. Similarly, neutrophils from RA patients have an activated phenotype and display delayed apoptosis, increased ROS production, and increased expression of high affinity FcR (Wright, Moots, & Edwards, 2014). To our knowledge, no clinical or basic science study has examined the relationship between neutrophils and autoimmune-associated hypertension; however, neutrophils have been examined in angiotensin II hypertension. Both neutrophils and monocytes infiltrate the vessel wall follwing infusion of angiotensin II, but only monocytes were shown to be essential for the hypertensive response to this peptide (Wenzel et al., 2011).

Circulating monocytes in both SLE and RA have been reported to have abnormalities in cell surface marker expression, antigen presentation, cytokine production, and phagocytosis (Davignon et al., 2013; Li, Lee, & Reeves, 2010). In the case of autoimmune diseases with immune complex formation, the binding of circulating autoantibody immune complexes to vascular walls may increase monocyte activation and promote a pro-inflammatory environment within the vasculature. The subsequent endothelial cell damage and endothelial dysfunction may be an important underlying risk factor for the prevalent hypertension and CVD in this patient population (Atehortúa, Rojas, Vásquez, & Castaño, 2017). Monocyte infiltration is increased in the kidney and periadventitial areas of peripheral vessels in many experimental models of hypertension, including the SHR (Rodríguez-Iturbe et al., 2002), Dahl salt-sensitive rat (De Miguel, Das, Lund, & Mattson, 2010), chronic angiotensin II infusion (Muller et al., 2002), and the NZBWF1 mouse model of SLE (Venegas-Pont et al., 2010). A reduction in macrophage infiltration is associated with lowered blood pressure, and depletion of circulating monocytes (Wenzel et al., 2011) or a deficiency in macrophage colony stimulating factor (De Ciuceis et al., 2005) results in protection from angiotensin II hypertension. Elegant studies by Steven Crowley's group identified a direct role for macrophages cells in the kidney during angiotensin II hypertension. The stimulation of the **IL-1R** suppresses the differentiation of $Ly6C^{+}Ly6G^{+}$ immature myeloid cells into mature $Ly6C^{+}Ly6G^{-}$ macrophages that can produce NO and limit **NKCC2**-mediated sodium resorption in the kidney. Thus, $IL\text{-}1R^{-/-}$ mice are protected from the angiotensin II hypertension, at least in part due to the elaboration of NO from intra-renal macrophages (Zhang et al., 2016).

DC are professional antigen presenting cells that play a pivotal role in $CD4^{+}$ and $CD8^{+}$ T lymphocyte activation. Under normal conditions, DC present self-antigens to maintain tolerance; however, DC dysfunction is implicated in the loss of peripheral tolerance to self-antigens in autoimmunity (Klarquist, Zhou, Shen, & Janssen, 2016). Multiple studies in experimental hypertension have demonstrated the importance of DC in the hypertensive response. A blockade of costimulatory molecules CD80 and CD86 expressed by DC using CTLA-Ig reduces T cell activation and blunts the hypertensive response to angiotensin II or DOCA-salt (Vinh et al., 2010). More recently, Kirabo et al. (2014) identified a novel pathway that implicates DC in angiotensin II hypertension: Proteins that are oxidatively modified by isoketals accumulate in DCs and activate them to produce the inflammatory cytokines IL-6, **IL-1β**, and **IL-23** and up-regulate costimulatory molecules CD80 and CD86. This leads to the proliferation of $CD8^{+}$ T cells and increased production of **IFN-γ** and IL-17A (Kirabo et al., 2014). The role that these innate immune cells have in the development of hypertension during autoimmunity has not been examined.

4.5 | T lymphocytes

The potential role of B and T cells in the pathogenesis of autoimmune-associated hypertension was demonstrated in studies by Herrera, Ferrebuz, MacGregor, and Rodriguez-Iturbe (2006), in which hypertensive patients with psoriasis or RA were treated with the

immunosuppressive drug mycophenolate mofetil, which depletes activated B and T lymphocytes. This small clinical study found that treatment with **mycophenolate mofetil** was sufficient to lower blood pressure in RA and psoriasis (Herrera et al., 2006). Autoimmune rheumatic diseases are characterized by aberrant T cell activation and alterations in multiple T_H cell subsets, including T_H1, T_H17, and T_{REG} (Cope, Schulze-Koops, & Aringer, 2007; Mak & Kow, 2014), but little is known about contributions of T cells to hypertension and cardiovascular complications in these diseases. Much of the work on immune system contributions to experimental models of hypertension, particularly angiotensin II and salt-sensitive hypertension, has focused on the importance of T cells. Studies by Harrison's group have shown that an oligoclonal population of $CD8^+$ T cells accumulate in the kidney, contribute to sodium and water retention, and are needed for the sustained hypertensive response to chronic angiotensin II infusion (Trott et al., 2014). The importance of T_H17 cells and T_{REG} have also been highlighted in this model as well (Zhang & Crowley, 2015). T_H17 cells primarily exert their effects by secreting IL-17A, and both the percentage of T_H17 cells and IL-17A production are elevated after Ang II infusion (Madhur et al., 2010). IL-17A has also been shown to induce the phosphorylation of endothelial NOS at the inhibitory site Thr^{495}, leading to impaired endothelium-dependent vasodilation (Nguyen et al., 2013). A recent study by our laboratory examined whether depletion of T cells using anti-CD3 therapy would attenuate hypertension in the NZBWF1 mouse with established renal disease. After 4 weeks of treatment with anti-CD3, mice had significantly lower mean arterial pressure as compared to the vehicle-treated mice. Despite the lowered blood pressure, their renal injury was unaffected by the treatment (Mathis, Taylor, & Ryan, 2017). Potential mechanisms for the lowered blood pressure include expansion of tolerogenic T_{REG} (Kuhn & Weiner, 2016), as T_{REG} dysfunction is an important contributor to the pathogenesis of SLE (Liu, Wang, Fung, & Wu, 2004; Valencia, Yarboro, Illei, & Lipsky, 2007). Adoptive transfer of T_{REG} has been reported to blunt the hypertensive response to chronic angiotensin II infusion (Barhoumi et al., 2011).

4.6 | B lymphocytes

B lymphocytes play important roles in autoimmune rheumatic diseases through the production of autoantibodies, antigen presentation, and cytokine secretion (Chan, Hannum, Haberman, Madaio, & Shlomchik, 1999; Lin et al., 1991; Mamula, Fatenejad, & Craft, 1994). The majority of patients with RA produce anti-cyclic citrullinated peptide antibodies as well as rheumatoid factor (anti-IgG). While there are limited data on autoantibodies and their contribution to hypertension in RA, several clinical studies have examined the association between anti-cyclic citrullinated peptide or rheumatoid factor with incidence of CVD in various cohorts, ultimately yielding conflicting evidence on the potential link (Ajeganova, Andersson, Frostegård, & Hafström, 2013; Barra et al., 2017; Mackey et al., 2015). Further studies are needed to correlate blood pressure data with autoantibody titers in RA. Autoantibodies to various nuclear components are found in ~95% of SLE patients, and anti-dsDNA antibodies have been detected in 70% of patients (Reveille, 2004). Various other autoantibodies, including those that bind to endothelial cells and could induce vascular damage, are also present in subsets of SLE patients. Because of the potential role of autoantibodies in essential hypertension discussed previously in this review, our laboratory has undertaken studies to elucidate the role of B cells and autoantibody production in the pathogenesis of SLE hypertension. We treated NZBWF1 mice with an anti-CD20 antibody to deplete B cells. Anti-CD20 is the mouse equivalent of **rituximab**, which has been used in treatment of SLE. A chronic, 14-week treatment with anti-CD20 was sufficient to prevent the development of hypertension in NZBWF1 mice, lower $CD45R^+$ B cell percentages in the spleen, and reduce the concentration of circulating anti-dsDNA autoantibodies. However, a short (4-week) treatment with anti-CD20 did not alter blood pressure, which suggests that once autoantibodies are being produced, B cell depletion is ineffective at lowering blood pressure (Mathis et al., 2014). A similar study was undertaken by Chan et al. (2015), who found that anti-CD20 treatment or the absence of B cells ($BAFF\text{-}R^{-/-}$ mice) prevents the development of hypertension in response to chronic angiotensin II infusion. The authors also noted increased aortic antibody deposits of IgG2b and IgG3 in mice receiving angiotensin II , which was ameliorated by the anti-CD20 treatment (Chan et al., 2015). Recently, we aimed to more specifically target autoantibody production by depleting plasma cells, which are differentiated B cells responsible for the majority of serum immunoglobulin production and SLE autoantibodies. After a 4-week treatment with the proteasome inhibitor **bortezomib**, NZBWF1 mice had significantly reduced IgG and anti-dsDNA levels in their plasma as well as attenuated hypertension (Taylor et al., 2018). Figure 1 depicts potential immune pathways that contribute to the development of hypertension in autoimmunity.

5 | RENAL HAEMODYNAMICS

Renal disease is one of the most common and severe manifestations of many rheumatic diseases, including SLE, RA, SSc, and PsA. Because of the important role of the kidneys in long-term blood pressure regulation and the fact that they are commonly affected in rheumatic diseases, it is important to consider how renal haemodynamic function changes during autoimmune diseases and how this function is affected by immune system activation and inflammation. SLE is characterized by immune-complex-mediated glomerulonephritis, tubular lesions, and glomerular and interstitial scarring (Moulton et al., 2017). It is estimated that at least 50% of patients with SLE have renal involvement, which markedly increases the risk of developing end stage renal disease (Boumpas et al., 1995). Studies have shown that both GFR and renal plasma flow are impaired in hospitalized SLE patients during active and inactive disease using urinary clearance methods (Nakano et al., 1998), but whether these changes promote SLE hypertension is unknown. However, studies in humans show that hypertension and nephritis are not necessarily linked. For example, Shaharir et al. (2015) reported that 53% of SLE patients were hypertensive in the

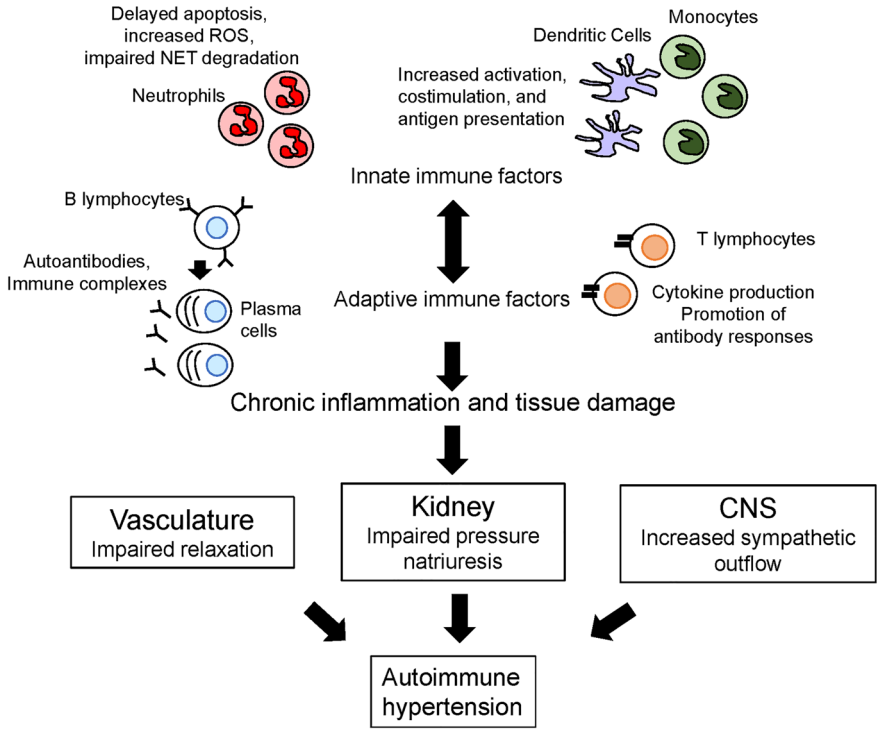

FIGURE 1 Immune system dysfunction in autoimmunity contributes to the development of hypertension. The crosstalk between the innate and adaptive immune systems leads to a chronic inflammatory state that affects the kidney, vasculature, and CNS, all promoting the development of autoimmune-associated hypertension

absence of nephritis. In addition, we recently reported that there is no relationship between hypertension and urinary albumin excretion or glomerulosclerosis scores in the NZBWF1 female mice with SLE (Taylor et al., 2018).

Patients with SSc experience renal impairment characterized by a reduction in renal functional reserve and lower renal blood flow leading to a reduction in GFR. Patients can also develop scleroderma renal crisis (SRC), which is an acute vascular manifestation characterized by hypertension (acute onset) and renal histological findings. However, SSc patients who are not in SRC may have the same histological findings, be normotensive, and have normal renal function. Nephrotoxic medications are thought to contribute to renal impairment in SSc along with renal vasculopathy and glomerulonephritis, which all likely contribute to hypertension in this patient population (Shanmugam & Steen, 2010). Overall, patients with SSc have an estimated 60–80% likelihood of developing slow progressive renal decline along with hypertension, increased serum creatinine, and proteinuria (Shanmugam & Steen, 2010). Patients with RA also have a wide range of renal disorders, with the prevalence of kidney disease ranging from 5% to 50% depending on the study (Hickson, Crowson, Gabriel, McCarthy, & Matteson, 2014). Reasons for the development of kidney disease in RA include drug toxicity and chronic inflammation, with glomerulonephritis being a common finding (Hickson et al., 2014). Thus, despite the known renal involvement across many autoimmune disorders that have an increased prevalence of hypertension, little is known about the mechanistic contribution of the kidneys to the pathogenesis of hypertension in this patient population.

In general, renal haemodynamic function has been sparsely studied in experimental models of autoimmunity. The NZBWF1 mouse model of SLE exhibits lower estimated renal plasma flow (Salvati et al., 1995) and GFR by 37 weeks of age (Kiberd, 1991). NZBWF1 mice also display increased plasma creatinine and blood urea nitrogen levels by 8 months of age (Corna et al., 1997; Song et al., 1998). In direct measures of renal haemodynamic function, we and others reported that female NZBWF1 mice have reduced renal blood flow (Salvati et al., 1995; Venegas-Pont et al., 2011) and increased renal vascular resistance (Venegas-Pont et al., 2011) when active renal disease is present. NZBWF1 mice have a parallel hypertensive rightward shift in the pressure natriuresis relationship, suggesting that impaired renal sodium handling is an important factor in autoimmune-associated hypertension (Mathis, Venegas-Pont, Masterson, Wasson, & Ryan, 2011). Importantly, the parallel shift in the pressure natriuresis relationship is consistent with a renal vascular contribution to the hypertension.

The role of the RAS and blood pressure control is well known (Ghazi & Drawz, 2017; Hall, 1991), but its role in autoimmune-associated hypertension is poorly understood despite the common use of ACE inhibitors to help control blood pressure and attenuate renal disease. Some patients with LN have been reported to display increased plasma renin activity (Herlitz, Edenö, Mulec, Westberg, & Aurell, 1984; Metsärinne, Nordström, Konttinen, Teppo, & Fyhrquist, 1992), and there is evidence suggesting that some patients with SLE or RA display increased serum levels of ACE (Sheikh & Kaplan, 1987). The increased ACE activity has the potential to contribute to hypertension by increasing angiotensin II , which can act both systemically and locally within the kidney to increase pressure. Elevated renin levels have also been reported in SRC in SSc (Shanmugam & Steen, 2010) and in PsA (Ena, Madeddu, Glorioso, Cerimele, & Rappelli, 1985). In many autoimmune rheumatic diseases, immune complex

deposition may be an important trigger causing increased inflammatory cells that lead to a local increase in ACE and angiotensin II production. Therefore, the local RAS activation has the potential to contribute to renal haemodynamic alterations and subsequently hypertension (Teplitsky, Shoenfeld, & Tanay, 2006). Another pathway by which angiotensin II could promote hypertension during SLE is via stimulating the production of endothelin-1 (ET-1), a peptide important for vasoconstrictive and natriuretic actions within the kidney. Patients with SLE, RA, and SSc have been reported to have higher plasma levels of ET-1 (Ena et al., 1985; Julkunen, Saijonmaa, Grönhagen-Riska, Teppo, & Fyhrquist, 1991; Pache et al., 2002) and studies in the NZBWF1 model show that **ET receptor** blockade lowers blood pressure, mortality, and prevents renal injury (Nakamura, Ebihara, Tomino, & Koide, 1995). Therefore, an increase in ET-1 may contribute to renal haemodynamic changes that could promote blood pressure increases.

The immunological changes that occur during autoimmunity are likely to be key mediators of renal haemodynamic function that could promote hypertension, although the role of different immune cells has not been fully elucidated. Renal leukocyte infiltration is directly associated with hypertension and renal injury and is likely to contribute mechanistically by promoting inflammatory cytokine production within the kidneys. Furthermore, inflammatory cytokines may directly change renal sodium excretion, renal blood flow, and GFR (Imig & Ryan, 2013). For example, TNF-α can not only cause both renal vasoconstriction and reduced GFR through a superoxide-mediated mechanism but also promote natriuresis in the kidney, suggesting that the localization of TNF-α in the kidney may have important implications in regulating renal function (Shahid, Francis, & Majid, 2008). Our laboratory previously showed that blockade of TNF-α biological activity in the NZBWF1 mouse model of SLE attenuated hypertension in association with reduced renal oxidative stress (Venegas-Pont et al., 2010).

Many other cytokines have been implicated in regulating renal function that are potentially involved in autoimmune disease processes. The cytokine **TGF-β** has been shown to impair afferent arteriolar autoregulatory responses (Sharma, Cook, Smith, Valancius, & Inscho, 2005) as well as drive fibrosis by increasing extracellular matrix deposition and inhibiting **MMP** activity (Border, 1994; Douthwaite, Johnson, Haylor, Watson, & El Nahas, 1999; Mozes, Böttinger, Jacot, & Kopp, 1999). Inflammatory cytokines including IL-17A, IFN-γ, and IL-1β can also affect renal sodium transporters. IL-1 can increase sodium excretion independent of GFR or renal blood flow (Beasley, Dinarello, & Cannon, 1988; Kohan, Merli, & Simon, 1989). Angiotensin II up-regulates the activity of the **sodium chloride symporter (NCC; SLC12A3)** in the distal nephron, and the expression of the **sodium hydrogen exchanger (NHE3)** in cultured proximal tubule cells. These changes do not occur in angiotensin II infused IL-17A$^{-/-}$ mice, suggesting an important renal mechanism by which IL-17 can promote hypertension (Norlander et al., 2016). IFN-γ also promotes sodium reabsorption via the NHE3 exchanger in the proximal tubule as well as the NKCC2 and sodium chloride symporter found in the distal portion of the nephron (Kamat et al., 2015). Despite reports pointing to important physiological roles for cytokines to regulate renal vascular and tubular function, the mechanistic contribution of these cytokines to autoimmune-associated hypertension are not clear.

Many cytokines promote the production of ROS leading to oxidative stress. The effects of ROS on renal vascular and tubular function have been well documented and are reviewed elsewhere (Araujo & Wilcox, 2014; Gonzalez-Vicente & Garvin, 2017; Harrison & Gongora, 2009). In general, ROS directly act on vascular smooth muscle cells and promote renal vasoconstriction (Wilcox, 2002). In the renal medulla, ROS generally promote increased sodium reabsorption. Thus, under pathological conditions, renal oxidative stress plays an important mechanistic role in promoting hypertension. Disease activity in patients with SLE directly correlates with circulating levels of ROS (Taysi, Gul, Sari, Akcay, & Bakan, 2002) making them a likely contributor to the prevalent hypertension. We previously reported that treatment of female NZBWF1 mice with antioxidants in the drinking water ameliorates the hypertension associated with SLE (Mathis et al., 2012). A summary of potential immune pathways involved in the alteration of renal haemodynamics is summarized in Figure 2.

6 | SEX HORMONES

A common feature of autoimmune diseases is the strong bias towards the female sex (Gleicher & Barad, 2007; Ngo, Steyn, & McCombe, 2014). However, the bias is not equally severe among all autoimmune diseases. The diseases with the strongest predilection (80–90% female) are Sjogren's syndrome, Addison's disease, SLE, and autoimmune thyroid disease. RA, multiple sclerosis, and myasthenia gravis, all displaying a strong female preference of 60–75%, while other autoimmune diseases, such as Type 1 diabetes, psoriasis, and Crohn's disease, affect males and females at similar rates (Berrih-Aknin, Panse, & Dragin, 2018). The sex differences in these diseases are likely to result from genes encoded on the sex chromosomes, gender-specific environmental influences, and the milieu of sex steroids. Prolonged exposure to treatment for severe manifestations of autoimmune disorders involving corticosteroids and **cyclophosphamide** is also known to modulate the gonadal hormone milieu in patients with SLE and SSc (Arnaud et al., 2017). Oestrogen, progesterone, and testosterone are all part of this hormonal milieu, and it is likely that a complex interaction between the hormones may influence autoimmune disease progression.

6.1 | Oestrogen

The fact that **oestrogen** is a powerful regulator of immune system function is supported by extensive evidence (Hughes & Choubey, 2014; Straub, 2007). For example, **oestrogen receptors** (ER-α and ER-β) have been identified in immune cell populations of both human and murine origin, including thymocytes, thymic epithelial cells, B cells residing within the bone marrow, T and B cells within the peripheral

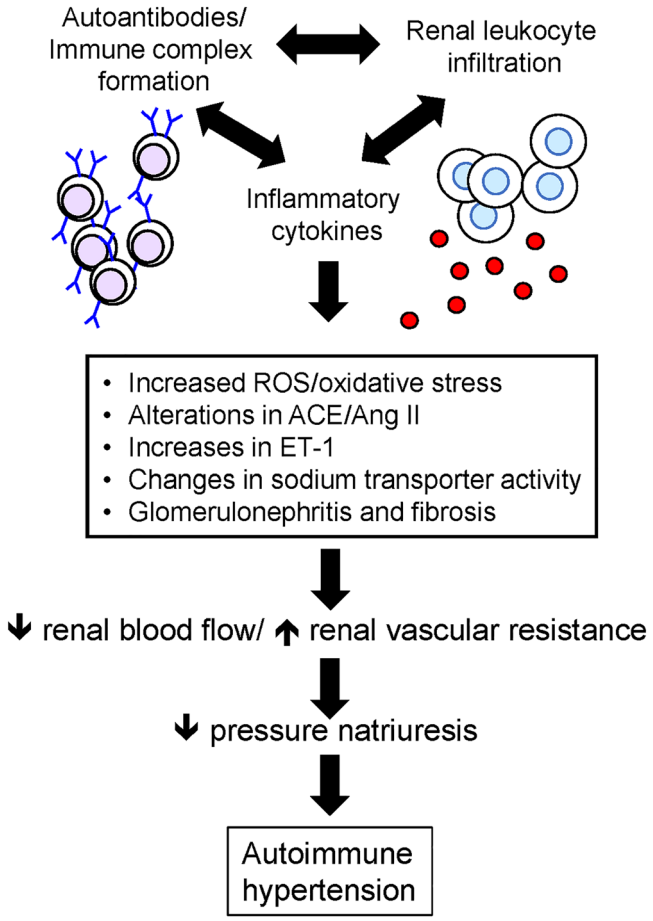

FIGURE 2 The role of the immune system in renal haemodynamic function. Autoantibodies and immune complexes, renal leukocytes, and inflammatory cytokines promote specific changes in the kidney leading to altered renal haemodynamics, impaired pressure natriuresis, and the development of hypertension.

blood, and macrophage and mononuclear cells (Straub, 2007). However, the role of oestrogens in the sex bias associated with autoimmune diseases and how it can influence disease progression remains surprisingly unclear. There has been speculation that the relapsing–remitting clinical course characteristic of many autoimmune diseases could correspond to fluctuations in sex hormones that occur throughout the female reproductive lifespan (Mcmurray & May, 2003). Some studies suggest that there is a decrease in the frequency of disease flares after menopause or ovarian failure in patients with SLE (Mok, Wong, & Lau, 1999; Urowitz, Ibañez, Jerome, & Gladman, 2006). However, the use of oestrogens in clinical trials as hormone replacement therapy or as combined oral contraceptive has shown no direct link to SLE disease activity (Buyon et al., 2005; Petri et al., 2005).

Much of what is known about oestrogens in SLE has come from studies in experimental models. The development of an SLE-like disease in NZBWF1 mice is strongly influenced by sex hormones; disease develops earlier leading to a significantly shortened lifespan in female compared to male NZBWF1 mice (Andrews et al., 1978; Howie & Helyer, 1968). The administration of exogenous oestrogen accelerates autoantibody production in female NZBWF1 mice and promotes autoantibody production in male NZBWF1 mice (Carlsten & Tarkowski, 1993; Roubinian, Talal, Greenspan, Goodman, & Siiteri, 1978; Roubinian, Talal, Siiteri, & Sadakian, 1979; Walker & Bole, 1973). Pharmacological blockade of oestrogen early in life results in reduced disease activity, as evidenced by lowered anti-dsDNA autoantibody levels, reduced renal injury, and decreased mortality (Sthoeger, Zinger, & Mozes, 2003; Wu, Lin, Su, Suen, & Chiang, 2000). The autoantibody production promoting effect of oestrogen appears to be mediated by **ER-α** rather than **ER-β** in this mouse model, as genetic deletion of ER-α results in amelioration of disease (Bynote et al., 2008). Conversely, propyl pyrazole triol, an ER-α selective agonist, promoted disease activity and increased albuminuria in young NZBWF1 female mice ovariectomized at 6 weeks of age. The treatment also increased serum concentrations of total IgG, anti-dsDNA, IgG3, IgG2a, and IgG2b compared to vehicle-treated ovariectomized NZBWF1 mice (Li & Mcmurray, 2007). Taken together with the link between elevated IgG or autoantibody production and the development of both essential hypertension and SLE associated hypertension in the NZBWF1 mouse, it is plausible that oestrogens may have a permissive role in the development of hypertension by increasing immunoglobulin production. However, data from our laboratory provide support for the concept that oestrogen might have distinct temporal effects on SLE and CVD progression. Early-life ovariectomy delayed the onset of autoantibody production and albuminuria but had no effect on blood pressure in the NZBWF1 mouse model of SLE (Gilbert & Ryan, 2014). Interestingly, ovariectomy during adulthood at 30 weeks of age exacerbated the hypertension in female NZBWF1 mice, and oestradiol repletion following ovariectomy in 30-week-old NZBWF1 mice prevented the rise in mean arterial pressure that was seen in vehicle-treated ovariectomized mice (Gilbert, Mathis, & Ryan, 2014).

Although hypertension and CVD does not develop in the CIA model of RA, examination of the oestrogen-mediated effects on arthritis revealed that treatment of mice with ethynyl estradiol before collagen immunization slows disease development in association with lower levels of anti-collagen Abs and decreased expression of pro-inflammatory factors by collagen peptide-specific T cells (Subramanian et al., 2005). Treatment of ovariectomized DBA/1 mice with 17β-estradiol in the CIA model of RA resulted in a decrease in Th17 cell migration to joints (Andersson et al., 2015). There is also some evidence to suggest that oestrogen may play a protective role in Sjogren's syndrome, as oestrogen replacement reversed an ovariectomy-induced increase in inflammation in the lacrimal glands in an adult female in a mouse model of Sjogren's syndrome (Brandt, Priori, Valesini, & Fairweather, 2015).

6.2 | Progesterone

Progesterone is a hormone required for pregnancy with known immunoregulatory properties, but its role in autoimmune diseases is not well understood (Hughes, 2012). Progesterone is a known vasoactive

hormone that has predominantly vasodilatory actions on several vascular beds, although there are some conflicting data (dos Santos, da Silva, Ribeiro, & Stefanon, 2014). One study suggests that administration of progesterone lowers blood pressure in humans (Rylance et al., 1985). Studies examining the effect of progesterone in the NZBWF1 mouse model of SLE have provided some conflicting results (Hughes, 2012). Keisler, Kier, and Walker (1991) saw no significant effect on either survival or serum anti-dsDNA reactivity in pre-morbid female NZBWF1 mice following treatment with any of the three synthetic progestins, including **medroxyprogesterone acetate**, a commonly used form of hormonal birth control used worldwide. Hughes et al. (2009), however, saw an increase in survival and a decrease in renal injury, along with suppressed renal and serum levels of pathogenic Th1-related anti-dsDNA IgG2a following treatment with continuous medroxyprogesterone acetate in pre-morbid female NZBWF1 mice. It is not clear whether progesterone might have unique temporal roles in SLE disease progression similar to that observed with oestrogen. Fewer studies have been conducted examining the effects of progesterone in other autoimmune rheumatic diseases. In a rat model of CIA, Ganesan et al. (2008) found that progesterone did not modify disease progression in this particular model and that if progesterone was administered in combination with oestrogen, the beneficial effects of oestrogen treatment were diminished. Little is known about how progestins affect autoimmune disease activity or blood pressure control in Sjogren's syndrome (Hughes, 2012). Additional studies are required to understand the significance of progesterone in autoimmune disease progression and the development of hypertension.

6.3 | Oral contraceptives and hormone therapy

The results from studies looking at cohorts designed to examine the effect of oestrogens and progesterones in patients with autoimmune diseases, or hormone therapy in patients with SLE, have thus far been inconclusive. For example, while oestrogen therapy may benefit postmenopausal women with SLE by alleviating symptoms of the perimenopausal transition (Cravioto et al., 2011), there is some concern that the use of exogenous oestrogens may exacerbate disease activity through increased autoantibody production, immune-complex formation, and further tissue damage. SLE patients might be at increased risk for disease flares or other adverse effects commonly associated with hormone therapy, such as an increased risk of venous thromboembolism or cerebrovascular thrombosis (Khafagy et al., 2015). Despite this potential risk, a recent review suggests that hormone therapy for post-menopausal women with SLE is well tolerated with no clear association between the use of exogenous oestrogens and instances of severe disease flares (Khafagy et al., 2015). In the largest randomized clinical trial to date, Buyon et al. (2005) examined the effect of hormone therapy on disease activity in patients with SLE as part of the Safety of Estrogens in Lupus Erythematosus National Assessment trial. This study included 350 patients with 173 patients receiving oestrogen daily plus medroxyprogesterone and 177 patients receiving placebo. The results of this clinical trial showed that mild to moderate flares were significantly increased in the hormone treatment group compared to placebo (P = 0.01); however, there was no significant difference in the rate of severe flares, as defined by the SLE-disease activity index composite (Buyon et al., 2005).

Data are limited concerning the safety of combined-oral contraceptive (COC) hormone therapy in women with RA (Drossaers-Bakker, Zwinderman, van Zeben, Breedveld, & Hazes, 2002), although the use of COC in RA appears to be considered safe. Some forms of progesterone-only contraception are also considered safe in RA and not associated with an increase in flares; however, the impact of these hormonal-based contraceptives on blood pressure has not been reported. The safety of COC and progesterone-only contraceptives in women with SLE is much more controversial.

6.4 | Testosterone

Generally, **testosterone** is considered to be anti-inflammatory. In support of this concept, animal models of SLE, RA, and multiple sclerosis showed increased disease activity following castration (Bebo et al., 1998; Ganesan et al., 2008; Panchanathan, Shen, Bupp, Gould, & Choubey, 2009). Testosterone decreases secretion of the pro-inflammatory cytokines IL-1β and IL-6 as well as TNF-α by monocytes and macrophages, increases T-cell production of anti-inflammatory **IL-10**, and inhibits NFκB activation of the gene promoter for IL-6 in human fibroblasts and T cell proliferation in animal models (Bove, 2013). Although relative androgen deficiency has been observed in some (Mok & Lau, 2000), this is not a consistent finding and there have been no reported trials examining the effects of testosterone therapy in men with SLE. In females with SLE, androgen levels are lower compared to their normal female counterparts (Lahita, 2016). One randomized, double-blind, single-centre, placebo-controlled trial was designed to administer a 150-μg testosterone patch to 34 women with mild to moderate SLE for 12 weeks. The results showed no increases in adverse events or changes in laboratory safety parameters (e.g., full blood count, erythrocyte sedimentation rate, creatinine, liver function tests, and cholesterol), but there was also no effect on SLE disease activity (Gordon et al., 2008). In addition, the adrenal androgen **dehydroepiandrosterone** was administered orally to women with SLE in three prospective studies that showed increases in testosterone levels and decreases in SLE disease activity and the occurrence of flares (Chang, Lan, Lin, & Luo, 2002; Petri et al., 2004; van Vollenhoven, Morabito, Engleman, & McGuire, 1998). However, a review of seven randomized control trials found that patients experienced little clinical benefit of dehydroepiandrosterone on disease activity in those with mild/moderate disease (as measured by SLE-disease activity index; Crosbie et al., 2007). No similar studies have been performed in women with RA, but testosterone therapy has been tested in males with RA (Hall et al., 1996). Men with RA have been shown to have low plasma serum testosterone (Martens et al., 1994), but this small clinical study found that monthly injections of testosterone enanthate did not improve disease activity (Hall et al., 1996). Although there are numerous studies that examine the role of androgens during autoimmune diseases, little is known about

testosterone in blood pressure control. This is a potentially important area to study because studies suggest that testosterone exerts beneficial effects on cardiovascular function by inducing rapid vasorelaxation of vascular smooth muscle (dos Santos et al., 2014).

7 | CONCLUSIONS AND PERSPECTIVES

Autoimmune disorders affect a significant proportion of the population, and many carry a significantly increased prevalence of hypertension leading to increased mortality due to CVD. Hypertension remains one of the most important modifiable cardiovascular and renal risk factors and has clear links to immune system activation and inflammation. Many patients with primary hypertension have increased circulating immunoglobulins, and extensive work in experimental animal models suggests the production of neoantigens leading to an immune response resembling that of autoimmune disorders. While there are many inflammatory and immunomodulatory pathways involved in the pathogenesis of both autoimmune disorders and hypertension, the specific mechanisms by which this occurs continue to be examined. Studies designed to understand the reasons behind the prevalence of hypertension in patients with autoimmune disease have proved and will continue to be informative.

7.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander, Christopoulos et al., 2017; Alexander, Cidlowski et al., 2017; Alexander, Fabbro et al., 2017a; Alexander, Fabbro et al., 2017b; Alexander, Kelly et al., 2017).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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