Understanding mechanisms of hypertension in systemic lupus erythematosus

Erin B. Taylor and Michael J. Ryan

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***Abstract*:** Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that predominately affects women of reproductive age. Hypertension is an important cardiovascular risk factor that is prevalent in this patient population. Despite the high incidence of hypertension in women with SLE, the pathophysiological mechanisms underlying the development of hypertension remain poorly understood. This review will focus on disease-related factors, including inflammation, autoantibodies, and sex hormones that may contribute to hypertension in patients with SLE. In addition, we will highlight studies performed by our laboratory using the female NZBWF1 (F1 hybrid of New Zealand Black and New Zealand White strains) mouse model, a spontaneous model of SLE that mimics human disease and develops hypertension and renal injury. Specifically, using female NZBWF1 mice, we have demonstrated that multiple factors contribute to the pathogenesis of hypertension, including the inflammatory cytokine, tumor necrosis factor (TNF)-α, oxidative stress, as well as B-cell hyperactivity and autoantibody production.

Keywords: autoantibodies, cardiovascular disease, estrogens, hypertension, inflammation, systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disorder that can affect almost all organ systems including the kidneys, skin, joints, and central nervous system. Although the cause of SLE is unknown, genetic and environmental factors as well as sex hormones are likely to be involved in disease pathogenesis. SLE is predominantly a disease of women, since females of reproductive age are affected at a rate of nine females to one male, although the female predilection is less pronounced before menarche and after menopause [Tucker *et al.* 1995]. It is thought that the complex interaction between genetic, environmental, and hormonal components leads to a breach of immunological tolerance, and that this loss of tolerance results in the production of autoantibodies, most often to self-molecules in the nucleus, cytoplasm and on the cell surface. Antinuclear antibodies are found in ~95% of SLE patients and anti-dsDNA antibodies have been detected in 70% of patients [Reveille, 2004]. The presence of autoantibodies leads to the formation of immune complexes, which can deposit in virtually any tissue in the body. The classification criteria for SLE, as recently revised and validated by the Systemic Lupus International Collaborating Clinics (SLICC) in 2012, are outlined in Table 1. A person is diagnosed with SLE if they have had 4 or more of the 17 criteria outlined, including at least 1 clinical criterion and 1 immunological criterion; alternatively a patient can be diagnosed with biopsy-proven lupus nephritis and positive antinuclear or anti-dsDNA antibodies [Petri *et al.* 2012].

Survival has increased dramatically over the past 50 years for SLE patients, mostly through improved diagnosis and treatment, although 10% of patients still die within 5 years after diagnosis [Smolen, 2002]. Women who survive beyond the first 5 years after diagnosis are most likely to die from cardiovascular disease [Manzi *et al.* 1997]. The bimodal pattern of mortality in SLE was first described by Urowitz and colleagues in the Toronto lupus cohort: those who die in the first year after diagnosis have active lupus, and those who die later in the course of the disease have inactive lupus and a high incidence of atherosclerosis

Correspondence to:
Michael J. Ryan, PhD
Department of Physiology and Biophysics, University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216, USA
mjryan@umc.edu

Erin B. Taylor, PhD
Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS, USA

Table 1. Systemic Lupus International Collaborating Clinics (SLICC) criteria for the classification of SLE.

Clinical criteria	*Immunological criteria*
Acute cutaneous lupus (malar rash)	ANA above laboratory reference range
Chronic cutaneous lupus (discoid rash)	Anti-dsDNA above laboratory reference range
Oral ulcers	Anti-Sm
Nonscarring alopecia	Antiphospholipid antibody
Synovitis involving two or more joints	Low complement
Serositis	Direct Coombs test in the absence of hemolytic anemia
Renal	
Neurologic	
Hemolytic anemia	
Leukopenia or lymphopenia	
Thrombocytopenia	

ANA, antinuclear antibodies; SLE, systemic lupus erythematosus.

and myocardial infarction [Urowitz *et al.* 1976]. This bimodal pattern, as well as the high incidence of death due to cardiovascular disease, has been confirmed in subsequent studies [Mody *et al.* 1994; Abu-Shakra *et al.* 1995; Bernatsky *et al.* 2006]. In addition, women with SLE aged 35–44 were 50 times more likely to have a cardiac event (myocardial infarction or angina pectoris) compared with age-matched controls participating in the Framingham Offspring Study [Manzi *et al.* 1997]. Hypertension is an important, yet understudied, cardiovascular risk factor that is prevalent in this patient population. This review will discuss both clinical and experimental evidence for the increased prevalence of hypertension and potential underlying mechanisms.

Hypertension in SLE

Hypertension is a major risk factor for the development of cardiovascular disease and is prevalent in patients with SLE [Budman and Steinberg, 1976; Mandell, 1987; Petri, 2000; Selzer *et al.* 2001; Al-Herz *et al.* 2003; Sabio *et al.* 2011; Shaharir *et al.* 2015]. The incidence of hypertension is especially striking in women younger than 40: in one cohort 40% of women under 40 were hypertensive compared with 11% of the control subjects [Sabio *et al.* 2011]. While the pathogenesis of hypertension in SLE is not fully understood [Ryan, 2009], a combination of traditional (age, sex, obesity, ethnicity) and disease-related factors (immune system dysfunction, inflammation, renal involvement, drug side effects) may contribute to hypertension in SLE patients [Sabio *et al.* 2001; Chaiamnuay *et al.* 2007]. Specifically, renal function, the renin–angiotensin system (RAS), sex hormones, inflammatory cytokines, and autoantibodies will be discussed in this review.

Renal function

In ~50% of SLE patients, the kidneys are affected in the form of immune complex glomerulonephritis, and nearly all patients show evidence of kidney injury on biopsy [Boumpas *et al.* 1995; Guo *et al.* 2010]; however, SLE-associated hypertension can occur independently of nephritis [Ward and Studenski, 1992; Petrin *et al.* 1993]. For example, a recent study by Shaharir and colleagues revealed that 53% of SLE patients in one cohort were hypertensive despite the absence of nephritis [Shaharir *et al.* 2015]. Because of the importance of the kidney in the long-term control of blood pressure, impaired renal function is certain to contribute to the prevalent hypertension in SLE patients. Impaired renal hemodynamics and tubular function are likely contributors, since the ability of the kidney to excrete sodium and water in response to changes in pressure is critical for effective long-term control of blood pressure. Evidence suggests that both glomerular filtration rate (GFR) and renal plasma flow are impaired in SLE patients [Nakano *et al.* 1998], and tubular lesions are prevalent [Daniel *et al.* 2001]; however, whether these changes mechanistically promote SLE-associated hypertension has not been examined extensively. One factor that can promote impaired renal hemodynamics is renal vascular dysfunction. While there are no specific reports on renal vascular endothelial function in

SLE, the vascular endothelium is prominently affected in this patient population, as exhibited by the high rates of atherosclerosis in SLE patients [Alves and Ames, 2003; Bijl, 2003; Roman *et al.* 2003]. In addition, multiple studies have shown vascular endothelial dysfunction in SLE, as measured by brachial artery flow [Lima *et al.* 2002; Johnson *et al.* 2004; Piper *et al.* 2007], and both endothelial-dependent vasodilation and endothelial repair mechanisms are impaired in SLE patients. Therefore, studies designed to evaluate renal vascular function during SLE may yield important insight for understanding the prevalent hypertension.

Renin–angiotensin system

The RAS is critical for blood pressure and volume homeostasis; however, little is known about this system and its relationship to SLE and SLE hypertension. Multiple genetic studies have been conducted to link common angiotensin-converting enzyme (ACE) insertion and deletion polymorphisms and SLE disease; however, no definitive correlations have been made [Kaufman *et al.* 2001; Lee *et al.* 2006, 2013]. ACE inhibitors and angiotensin II (ANG II) receptor antagonists are commonly prescribed to SLE patients and have shown to be effective at controlling blood pressure, but mostly in patients with evidence of an activated RAS [Herlitz *et al.* 1984]. In addition to the RAS having an important role in blood pressure control, ANG II can stimulate the production of endothelin-1 (ET-1), a peptide whose role in blood pressure control results from a balance between vasoconstrictive actions and natriuretic actions in the renal medulla. Plasma ET-1 levels are increased in SLE patients [Julkunen *et al.* 1991] and serum from SLE patients can induce the production of ET-1 by endothelial cells *in vitro* [Yoshio *et al.* 1995].

Inflammatory cytokines

It is widely recognized that the immune dysregulation and low-grade inflammation has a role in the pathophysiology of hypertension [Harrison *et al.* 2010; Ryan, 2013]. This is supported by the fact that treatment with the immunosuppressive drug mycophenolate mofetil in both animal models and essential hypertensive patients reduces blood pressure [Rodriguez-Iturbe *et al.* 2002; Herrera *et al.* 2006; De Miguel *et al.* 2010; Ferro *et al.* 2011]. Various inflammatory cytokines, including interleukin (IL)-6, IL-17, IL-18, type I interferons, and tumor necrosis factor (TNF)-α have been implicated in the pathogenesis of SLE [Yap and Lai, 2013]. Similarly, studies report a correlation between cytokines such as IL-6, TNF-α, and C-reactive protein and blood pressure in patients with essential hypertension [Blake *et al.* 2003; Bautista *et al.* 2005; Vazquez-Oliva *et al.* 2005; Sesso *et al.* 2007]. Inflammatory cytokines interact with important blood pressure regulatory systems, such as the RAS [Brasier *et al.* 2002; Harrison *et al.* 2011; Capettini *et al.* 2012; Pacurari *et al.* 2014] and the sympathetic nervous system [Pongratz and Straub, 2014]. IL-6, which promotes B-cell hyperreactivity and increased autoantibody production [Cross and Benton, 1999], is elevated in the serum of patients with SLE and generally correlates with disease activity [Ripley *et al.* 2005]. While the role of IL-6 has not specifically been examined in SLE hypertension, it has been shown to contribute to ANG II-induced hypertension [Zhang *et al.* 2012]. TNF-α has also been shown to be elevated in the serum of SLE patients and can correlate with disease activity [Weckerle *et al.* 2012]. Studies report that blockade of TNF-α in SLE patients can decrease urinary protein but increase anti-dsDNA autoantibodies [Aringer *et al.* 2004]; nevertheless, the role of TNF-α in SLE hypertension remains unclear. The type I interferon IFN-α, which is elevated in the plasma of ~50% of patients with SLE [Baechler *et al.* 2004], plays a central role in mediating endothelial dysfunction by promoting endothelial progenitor cell (EPC) deletion [Lee *et al.* 2007]. In addition, there are elevated levels of circulating endothelial cells, which is a marker for vascular injury, in SLE patients [Clancy, 2000]. Whether or not elevated IFN-α impacts renal hemodynamic function as a mechanism to promote hypertension during SLE remains unclear.

Autoantibodies

Patients with essential hypertension or pregnancy-related hypertension have elevated circulating levels of immunoglobulin (Ig)G and IgM [Ebringer and Doyle, 1970; Suryaprabha *et al.* 1984; Hilme *et al.* 1989]. In addition, many studies have shown a correlation between the production of pathogenic autoantibodies and hypertension in humans [Gudbrandsson *et al.* 1981; Wenzel *et al.* 2008], and specific antibodies to a particular antigen are often increased and may have a role in the pathogenesis [Wallukat *et al.* 1999; Fu *et al.* 2000; Jahns *et al.* 2004].

For example, spontaneously hypertensive rats were previously shown to have autoantibodies in their serum that are cytotoxic to T cells, and transplantation of compatible thymus tissues was sufficient to reduce blood pressure in this model [Ba *et al.* 1982]. Also, women with preeclampsia reportedly produce activating ANG II type-1 receptor autoantibodies (AT1R-AA) and the antibody titer appears to correlate with disease severity [Siddiqui *et al.* 2010]. Administration of AT1R-AA isolated from humans to pregnant mice was shown to induce hypertension in those animals [Zhou *et al.* 2011]. A direct role of autoantibodies in humans was shown in patients with refractory hypertension, in which immunoadsorption of autoantibodies to the α1-adrenergic receptor was sufficient to lower mean arterial pressure [Wenzel *et al.* 2008]. Autoantibodies to nuclear components are a hallmark characteristic of SLE, and deposition of autoantibody immune complexes in the glomerular and tubular basement membranes are common in lupus nephritis. In addition, there is evidence that autoantibodies can bind directly to intrinsic glomerular antigens [Jang and Stollar, 2003]. Treatment with the B-cell depletion antibody anti-CD20 (Rituximab) has been shown to lower titers of anti-dsDNA antibodies in some studies [Anolik *et al.* 2004], but no study published to date has reported blood pressure in SLE patients on an anti-CD20 treatment regimen, and the role of specific autoantibodies in the pathogenesis of SLE-associated hypertension remains uncertain.

Sex hormones

Because of the striking female bias in SLE, a role for endogenous sex hormones in disease pathogenesis is likely. Nevertheless, there is conflicting evidence on whether women with SLE have increased estrogens: a meta-analysis of 20 studies found populations of women with SLE have increased, deceased or equivalent levels of 17-β-estradiol when compared with control subjects [McMurray and May, 2003]. While the levels of 17-β-estradiol may be in the normal physiological range, women with SLE do have abnormal estrogen metabolism, as evidenced by the increase in 16α-hydroxylation of estrone [Lahita *et al.* 1979]. These hydroxylated estrones are more potent and may have a role in increasing inflammatory cell numbers [Cutolo *et al.* 2004]. Furthermore, women with SLE may have low plasma androgens, including testosterone and dihydrotestosterone [Lahita *et al.* 1979; Jungers *et al.* 1982]. Because estrogens have diverse immunomodulatory functions [Lang, 2004; Straub, 2007], it is likely that altered estrogen metabolism in SLE influences multiple aspects of the immune system, including differences in inflammatory cytokine production and both B- and T-cell activation and function. Thus, both abnormal cytokine profiles and autoantibody production could be affected by estrogens and impact blood pressure, although the connection among these factors is not well studied in patients with SLE, particularly as it relates to cardiovascular risk factors such as hypertension.

Mouse models of SLE

In order to better understand the etiology of SLE-associated hypertension, experimental animal models are useful tools. Much has been learned about SLE disease pathogenesis using both spontaneous and induced murine models of SLE. For the purposes of this review, only the most commonly studied spontaneous models will be discussed. For a lengthier discussion of SLE mouse models, the reader is referred to [Theofilopoulos and Dixon, 1985; Perry *et al.* 2011]. The three most commonly studied spontaneous models are MRL/lpr, BXSB, and NZBWF1 (F1 hybrid of New Zealand Black [NZB] and New Zealand White [NZW] strains). While each of these mouse models varies in their utility, all three develop autoantibodies and immune complex-mediated glomerulonephritis, one of the hallmark characteristics of SLE. MRL/lpr mice have lymphoadenopathy due to an aberrant accumulation of $CD4^-$ $CD8^-$ T cells that express the B-cell marker B220. In addition, they have high levels of circulating Igs, and begin producing anti-dsDNA and anti-ssDNA antibodies by 12–16 weeks of age [Reilly and Gilkeson, 2002]. The lymphoproliferative phenotype is attributed to a recessive autosomal mutation on chromosome 19, which alters transcription of the Fas receptor [Watson *et al.* 1992]. MRL/lpr mice develop vasculitis and arthritis as well as severe lupus nephritis, but do not become hypertensive [Rudofsky *et al.* 1984]. Unlike lupus in humans, male and female MRL/lpr mice are affected at an equal rate. BXSB mice have a translocation of the telomeric end of the X chromosome to the Y chromosome, which results in gene duplications and upregulation of gene expression of many of the duplicated genes. One of the duplicated genes is Toll-like receptor 7 (*Tlr7*) [Pisitkun *et al.* 2006; Subramanian *et al.*

2006], which can bind to exogenous RNA ligands and lead to autoreactive B-cell activation [Leadbetter *et al.* 2002; Lau *et al.* 2005]. Because of the nature of the chromosomal translocation, only male BXSB mice develop a SLE-like disease, with symptoms ranging from secondary lymphoid tissue hyperplasia, immune complex mediated glomerulonephritis, monocytosis, and hypergammaglobulinemia. When BXSB mice are crossed with NZW mice, a severe coronary artery disease develops [Hang *et al.* 1981]. Although these mice are useful in studying coronary artery disease in the context of SLE, they do not have the same gender bias and do not develop hypertension.

The oldest and most extensively studied mouse model of SLE is the NZBWF1. Both NZW and NZB display limited autoimmunity; however the F1 cross of these two strains develops a severe lupus-like phenotype [Theofilopoulos and Dixon, 1985; Perry *et al.* 2011]. These mice exhibit many of the classic hallmarks of lupus disease, including lymphadenopathy, splenomegaly, elevated serum anti-dsDNA antibodies, and immune complex-mediated glomerulonephritis [Burnett *et al.* 2004]. NZBWF1 mice typically have a detectable anti-dsDNA autoantibody production by ~17–20 weeks of age [Bassi *et al.* 2015]. The glomerulonephritis becomes apparent between 5–6 months of age and ultimately leads to kidney failure and death between 10–12 months of age, which is less than half the expected lifespan of a mouse. Unlike the MRL/lpr mice, NZBWF1 mice do not develop arthritis or skin lesions. Importantly, NZBWF1 mice have been shown to develop hypertension [Rudofsky *et al.* 1984; Ryan *et al.* 2007]. Like patients with SLE, a strong gender bias exists in NZBWF1 mice and multiple genetic mutations contribute to the development of SLE. Multiple lupus susceptibility loci have been identified that are derived from either the NZB or NZW mice including Sle1, Sle2, and Sle3 [Kono and Theofilopoulos, 2006; Perry *et al.* 2011]. The Sle1 locus is associated with a selective loss of tolerance to chromatin, Sle2 results in B cells with a lowered cell activation threshold, and Sle3 mediates a dysregulation of $CD4^+$ T cells [Morel *et al.* 2000]. Contribution of these loci to cardiovascular risk in NZBWF1 mice is still not well understood.

Hypertension in NZBWF1 mice

Because of the strong gender bias and complex genetic component of SLE disease in NZBWF1 mice, this model most closely resembles human SLE, and is especially useful for understanding the pathophysiology of hypertension. Much of the work in our laboratory has made use of female NZBWF1 mice to elucidate the mechanisms of hypertension. NZBWF1 mice were first shown over 30 years ago to have elevated blood pressure using the tail cuff method [Rudofsky *et al.* 1984]. Our laboratory has shown that NZBWF1 mice have a ~10 mmHg increase in blood pressure, measured in conscious tethered mice *via* an indwelling carotid artery catheter, when compared to control NZW mice, by 30 weeks of age. This increase in pressure was evident in mice that had no evidence of renal disease as assessed by urinary albumin [Venegas-Pont *et al.* 2009]. However, by 36 weeks of age, the mice have an even higher mean arterial pressure (Figure 1), and the increase in blood pressure is accompanied by excretion of large amounts of albumin in the urine, indicative of glomerular injury [Ryan and McLemore, 2007]. Histological analyses of the kidneys of NZBWF1 mice also reveal the characteristic 'wire loop' glomerular pathology that is observed in human SLE patients with immune complex deposition in the glomerular basement membrane [Carlsoo and Ostberg, 1978; Lemoine *et al.* 1992]. In addition to immune complex deposition, there are increased numbers of monocytes and macrophages in the renal cortex (Figure 2), indicating that immune cells infiltrate the kidneys and raise the likelihood

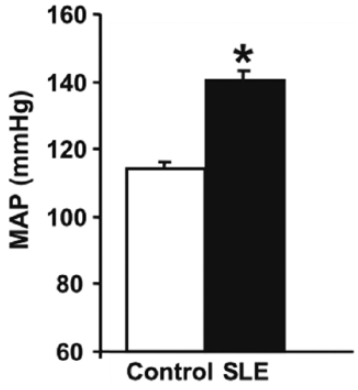

Figure 1. Mean arterial pressure is increased at 36 weeks of age in female NZBWF1 mice with SLE as compared with control NZW mice. Pressure was measured in conscious tethered mice *via* indwelling carotid artery catheters (*$p < 0.05$ *versus* control) [Adapted from Ryan *et al.* (2006)].
MAP, Mean arterial pressure; NZBWF1, F1 hybrid of NZB and NZW strains; NZW, New Zealand White; SLE, systemic lupus erythematosus.

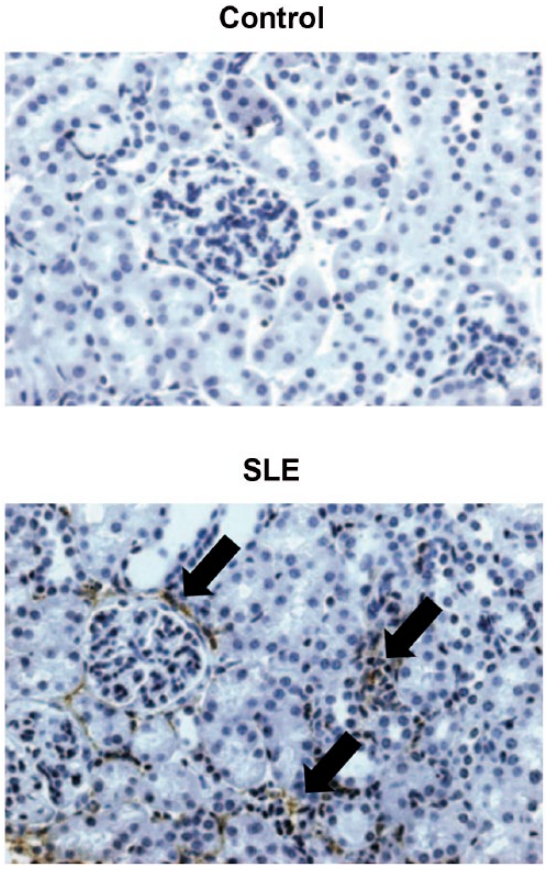

Figure 2. Renal cortices from female NZBWF1 mice have increased monocyte and macrophage infiltration as compared to control NZW mice, as assessed by staining with the monocyte/macrophage antibody F4/80 [Adapted from Ryan *et al.* (2006)].
NZBWF1, F1 hybrid of NZB and NZW strains; NZW, New Zealand White.

that they contribute to the pathogenesis of hypertension [Ryan *et al.* 2006]. Similar to humans, there is a disconnect between nephritis and arterial pressure in murine models of SLE: MRL/lpr, BXSB, and NZBWF1 mice all develop glomerulonephritis; however, only NZBWF1 mice develop hypertension. The hypertension in female NZBWF1 mice is associated with low plasma renin [Rudofsky *et al.* 1984] and is not sensitive to salt [Mathis *et al.* 2011]. This suggests that regulation of the RAS is largely intact in this model. Our laboratory has reported on several factors that contribute to hypertension in female NZBWF1 mice, including impaired renal hemodynamic function [Venegas-Pont *et al.* 2011], vascular endothelial dysfunction [Ryan and McLemore, 2007], altered inflammatory cytokine profiles [Venegas-Pont *et al.* 2010], oxidative stress [Mathis *et al.* 2012], adaptive immune system dysfunction [Mathis *et al.* 2014], and sex hormones [Gilbert *et al.* 2014; Gilbert and Ryan, 2014].

Because the kidneys have a central role in blood pressure regulation through long-term control of sodium and fluid balance, our laboratory has examined renal hemodynamic function as a contributing mechanism for the hypertension. In female NZBWF1 mice, there is a parallel rightward (hypertensive) shift in the pressure natriuresis relationship, demonstrating that at a given salt intake, greater arterial pressure is required to excrete the sodium. Therefore, renal excretory function is impaired in SLE and is an important mechanism for the development of hypertension. In further support of impaired renal hemodynamic function as a potential contributing mechanism for the hypertension, female NZBWF1 mice have an altered renal hemodynamic function as indicated by attenuated renal blood flow [Salvati *et al.* 1995; Venegas-Pont *et al.* 2011], increased vascular resistance [Venegas-Pont *et al.* 2011], and a lower GFR [Kiberd, 1991; Venegas-Pont *et al.* 2011] when compared to control mice. NZBWF1 mice also have increased blood urea nitrogen and plasma creatinine [Corna *et al.* 1997; Song *et al.* 1998]. While it has not been established in NZBWF1 mice whether they have renal vascular dysfunction, there is clear evidence of vascular endothelial dysfunction in these mice. Isolated carotid arteries from NZBWF1 mice displayed impaired relaxation to acetylcholine as compared with control mice at both 20 and 36 weeks of age [Ryan and McLemore, 2007]. NZBWF1 mice exhibit decreased numbers of EPCs in both the spleen and bone marrow at 36 weeks of age, and the EPCs have increased apoptosis and an impaired ability to differentiate into mature endothelial cells *in vitro* [Thacker *et al.* 2010]. These data indicate that vascular dysfunction corresponds with hypertension in SLE mice; however, a direct cause and effect relationship between these two has not been established.

While there is limited data on RAS components in mouse models of SLE, treatment of NZBWF1 mice with the ACE inhibitor captopril delays the onset of renal injury and proteinuria [Herlitz *et al.* 1988; De Albuquerque *et al.* 2004], and both captopril and enalapril were shown to reduce blood pressure [Herlitz *et al.* 1988]. However, NZBWF1 mice reportedly have low plasma renin activity [Rudofsky *et al.* 1984]. In studies by our laboratory, renal hemodynamic responses to an

acute infusion of ANG II were examined and NZBWF1 mice were shown to have a greater reduction in RBF after an ANG II infusion, suggesting that the kidneys of NZBWF1 mice have an enhanced sensitivity to ANG II [Venegas-Pont *et al.* 2011]. This enhanced sensitivity may contribute to the progression of renal disease and hypertension in NZBWF1 mice.

Because of the prominent immune dysregulation in NZBWF1 mice, it is reasonable to conclude that immune factors influence the development of hypertension in these animals. While some studies report lower circulating levels of TNF-α in NZBWF1 mice [Jacob and McDevitt, 1988; Kontoyiannis and Kollias, 2000], our laboratory and others routinely report increased levels of protein expression of renal TNF-α as compared with control mice. In addition, female NZBWF1 mice treated with the TNF-α antagonist etanercept had lower blood pressure and reduced glomerular injury when compared with vehicle-treated animals. Importantly, etanercept decreased monocyte and macrophage infiltration in the kidneys and lowered renal cortical levels of NADPH oxidase [Venegas-Pont *et al.* 2010]. These data suggest that a TNF-α blockade lowered blood pressure by reducing renal inflammation, which ultimately reduces renal oxidative stress, a recognized contributor to the development of hypertension [Wilcox, 2002; Reckelhoff and Romero, 2003]. The production of both reactive oxygen and nitrogen intermediates is increased in patients with SLE, and multiple studies have shown an increased production of nitric oxide (NO) in autoimmune animal models [Vladutiu, 1995; Oates and Gilkeson, 2006]. Specifically, the increased activity of inducible nitric oxide synthase (NOS2) in murine SLE models correlates with the increased production of pathogenic nitrogen intermediates such as peroxynitrite ($ONOO^-$) [Weinberg *et al.* 1994; Oates, 2010]. The production of reactive intermediates correlates with glomerular pathology and the onset of nephritis [Oates and Gilkeson, 2006; Oates, 2010]. Our laboratory treated NZBWF1 mice with a combination of tempol and apocynin to directly test whether renal oxidative stress impacted hypertension. This treatment resulted in lowered mean arterial pressures as well as reduced incidence of albuminuria and levels of renal cortical H_2O_2 and NADPH oxidase expression. Antioxidant therapy did not, however, impact the progression of SLE disease, as measured by anti-dsDNA levels [Mathis *et al.* 2012].

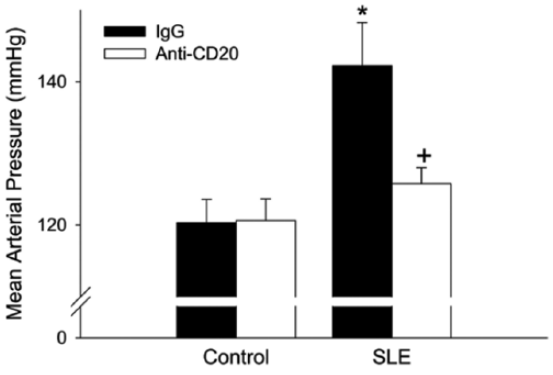

Figure 3. Mean arterial pressure measured in 34-week-old female NZBWF1 (SLE) and NZW (control) mice administered IgG or anti-CD20 for 14 weeks. * $p < 0.001$ *versus* control/IgG; + $p < 0.01$ *versus* SLE/IgG [Adapted from Mathis *et al.* (2014)].
IgG, immunoglobulin G; MAP, mean arterial pressure; NZB, New Zealand Black; NZBWF1, F1 hybrid of NZB and NZW strains; NZW, New Zealand White; SLE, systemic lupus erythematosus.

Recently, our laboratory also treated NZBWF1 mice with anti-CD20 antibody (mouse equivalent of rituximab). As indicated in Figure 3, a 14-week treatment prevented the development of hypertension in NZBWF1 mice. This treatment also lowered the percentage of $CD45R^+$ B cells in the spleen and the quantity of anti-dsDNA antibodies in the plasma. Importantly, this study revealed that a shorter (4-week) treatment with anti-CD20 did not significantly reduce blood pressure, which suggests that once autoantibodies are being produced and the inflammatory process has begun, anti-CD20 therapy may have limited efficacy on hypertension and renal injury [Mathis *et al.* 2014]. Nevertheless, this study highlights the importance of B cells in the progression of SLE hypertension in NZBWF1 mice.

Studies on the NZBWF1 mouse model have also revealed a complex role of estrogens in the pathogenesis of both SLE disease and the associated hypertension. Estrogens have multiple immunoregulatory functions, including modulating cytokines, cytokine receptor production, and effector cell activation [Cunningham and Gilkeson, 2011]. It has been demonstrated that NZBWF1 mice with a pharmacological blockade of estrogen early in life or genetic deletion of estrogen receptor (ER)-α exhibit reduced anti-dsDNA autoantibody levels, kidney damage, and mortality [Wu *et al.* 2000; Sthoeger *et al.* 2003; Bynote *et al.* 2008]. Consistent with these studies,

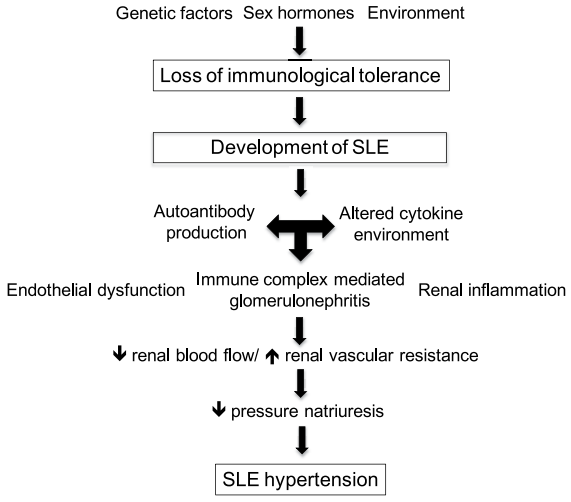

Figure 4. Proposed schematic for factors contributing to the pathogenesis of hypertension during SLE.
SLE, systemic lupus erythematosus.

our laboratory recently demonstrated that an early life ovariectomy (OVX) delayed the onset of albuminuria and autoantibody production and also caused an increase in body weight and fat mass. Early life OVX did not, however, alter blood pressure in adult NZBWF1 mice [Gilbert and Ryan, 2014]. Interestingly, the timing of estrogen removal (by OVX) appears to be important. In a recent study by our laboratory, Gilbert and colleagues found that performing OVX on adult (30 weeks) NZBWF1 mice exacerbates the hypertension and albuminuria as compared with sham-operated SLE mice without alterations in the production of anti-dsDNA autoantibodies. When the OVX mice were injected subcutaneously with 17-β-estradiol, the OVX-induced increase in blood pressure was prevented. OVX also caused an increase in renal TNF-α expression [Gilbert *et al.* 2014]. These data suggest that estrogens have important temporal roles in the pathogenesis of SLE and that while estrogens seem to promote SLE pathogenesis in early life, they may have a cardiovascular protective role in adulthood.

Conclusion

SLE is a chronic autoimmune disorder that predominately affects women of childbearing age. Because of the complex interaction between genes, sex hormones, and the environment, the pathogenesis of hypertension and development of cardiovascular disease is also likely to be multifactorial. Much of the work that has been published to date has focused on local mediators (such as cytokines and reactive oxygen species) that are likely to be downstream of the initial immune system dysregulation. These mediators contribute to local inflammation, which ultimately negatively affects renal function (Figure 4). The role of hyperactive T and B lymphocytes, both central to the development of autoimmune disorders, in the pathogenesis of hypertension remains unclear. Understanding SLE hypertension using NZBWF1 mice will be not only important for reducing cardiovascular risk in patients with SLE, but will also be important for elucidating mechanisms of human essential hypertension.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

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