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Autoimmune heart disease: role of sex hormones and autoantibodies in disease pathogenesis

DeLisa Fairweather^{1,*}, Michelle A Petri², Michael J Coronado¹, and Leslie T Cooper Jr³

¹Johns Hopkins University Bloomberg School of Public Health, Department of Environmental Health Sciences, 615 N. Wolfe Street, Baltimore, MD 21205, USA

²Johns Hopkins University School of Medicine, Division of Rheumatology, 1830 East Monument Street, Baltimore, MD 21205, USA

³Mayo Clinic, Department of Medicine, 200 First Street SW, Rochester, MN 55905, USA

Abstract

Cardiovascular disease (CVD) and autoimmune diseases (ADs) are the first and third highest causes of death in the USA, respectively. Men have an increased incidence of the majority of CVDs, including atherosclerosis, myocarditis, dilated cardiomyopathy and heart failure. By contrast, nearly 80% of all ADs occur in women. However, in one category of ADs, rheumatic diseases, CVD is the main cause of death. Factors that link rheumatic ADs to CVD are inflammation and the presence of autoantibodies. In this review we will examine recent findings regarding sex differences in the immunopathogenesis of CVD and ADs, explore possible reasons for the increased occurrence of CVD within rheumatic ADs and discuss whether autoantibodies, including rheumatoid factor, could be involved in disease pathogenesis.

Keywords

autoimmune disease; cardiovascular disease; pathogenesis; rheumatic disease; sex differences

Cardiovascular diseases (CVDs) and autoimmune diseases (ADs) are two of the highest causes of death in the USA [1,2]. Men have an increased incidence and severity of most CVDs, including atherosclerosis, myocardial infarction (MI), myocarditis, dilated cardiomyopathy (DCM) and heart failure, with the exception of hypertension, which is higher in women [1,3,4]. By contrast, nearly 80% of all ADs occur in women [2,5]. Although CVD occurs more frequently in women with rheumatic ADs such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis, myositis, Sjögren's syndrome (SS) and antiphospholipid syndrome (APS) as compared with women without disease [6–8], several recent studies have shown that men with SLE are more likely to develop atherosclerosis [9–11]. Additionally, men with SLE develop more severe disease (increased lupus nephritis) and have a worse outcome (increased renal failure, MI and death) than women with SLE [12,13]. In RA, overall mortality due to CVD appears to increase in both sexes, yet male sex predicts cardiovascular events and death [11,14–16]. There is

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*Author for correspondence: Tel.: +1 410 955 4712, Fax: +1 410 955 0116, dfairwea@jhsph.edu.

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increasing evidence that autoimmunity plays an important role in the pathogenesis of inflammatory heart diseases such as atherosclerosis, myocarditis and DCM [6,17]. Both cell and antibody (Ab)-mediated pathology contribute to disease progression in ADs and CVDs [18]. In this review we will examine recent findings regarding sex differences in the immunopathogenesis of CVD and AD, and explore possible reasons for the increased occurrence of CVD within rheumatic ADs, including the pathogenic role for autoantibodies (autoAbs).

CVD is more prevalent in men

Sex hormones play a major role in the pathogenesis of CVD, as reflected by a higher incidence and severity of CVD in men than women across all age groups [1,19]. Estrogens are protective for heart physiology and prevent or delay CVD [19–21]. Evidence that the incidence of CVD increases in women as estrogen declines with age and menopause, further supports a protective role for estrogens in the heart. Sex differences in the incidence of CVD are also influenced by gender differences in cardiovascular risk factors and presentation of disease [22,23]. Although CVD occurs more frequently in men, it is also the leading cause of death in women, just as it is for men. For this reason it is critical that researchers and clinicians gain a better understanding of the factors that contribute to CVD in both men and women [24].

Sex differences in normal cardiovascular physiology

Sex differences exist in normal heart physiology and function. For example, men have larger hearts (left ventricular mass), cardiac contractility is greater in healthy women than age-matched men, myocardial mass is better preserved in women as they age, cardiac apoptosis is threefold higher in men compared with women as they age, women have smaller coronary vessels than men and pre-menopausal women have lower blood pressure but a faster resting heart rate than men [25,26]. Many other sex-specific differences exist in the hearts of apparently normal men and women according to microarray and proteomic analyses [27]. For example, in the aging female heart, hypertrophy, apoptosis and fibrosis are less pronounced than in the aging male heart [20]. These underlying sex differences in cardiac function directly influence the immune response to infection and injury in the heart.

Sex differences in the immune response

The immune system under normal and pathological conditions is extensively regulated by sex hormones [28]. Sex steroid hormone receptors such as estrogen receptor (ER)- α , ER- β rogen receptor and aromatase, the enzyme that converts androgens to estrogens, are expressed in vascular endothelial cells, vascular smooth muscle cells, cardiac fibroblasts and cardiomyocytes in humans and rodents [29]. Steroid receptors regulate gene expression by classic genomic actions as well as membrane-associated receptor signaling. Surface expression of sex steroid receptors in particular is likely to be important in influencing the immune response.

Estrogen is known to stimulate the immune system while androgens are recognized to be immunosuppressive [28,30]. However, descriptions of the role of androgens and estrogens on the immune response often do not take into account differences in the effect of sex hormones on the innate and adaptive arms of the immune response. This distinction between innate and adaptive immunity is critical in providing a framework for understanding how CVDs can be increased in men while ADs are increased in women [18]. Other important considerations include dose, timing and target organ effects of sex hormones [31]. Estrogen is well known to activate B cells, resulting in increased Ab and autoAb responses to infection, vaccines and autoantigens [5,28,31,32]. By contrast, androgens decrease B-cell

maturation, reduce B-cell synthesis of Ab, and suppress autoAb production in humans with SLE [28]. Estrogen has been shown both in culture and in animal models to induce differentiation of CD11b⁺ dendritic cells (DCs) [33] and to increase Th1 and/ or Th17 responses, increasing inflammation via transcriptional activation of NF- κ B [31,34,35]. Estrogens are also able to increase the regulatory arm of the adaptive immune response by enhancing tolerogenic DCs, IL-4-driven Th2 responses, TGF- β , PD-1 receptor expression on immune cells, Treg populations, and alternatively activated macrophages [5,31,36–40]. The capacity of estrogen to decrease cell-mediated immune responses by increasing regulatory mechanisms is probably due to its ability to inhibit components of the innate immune response including Toll-like receptors (TLRs) [18,28,37,41]. Far less research has been conducted on the role of androgens on immunity, but generally androgens have been found to increase Th1 responses [18,28,42]. Collectively, these data support the idea that the ability of estrogen to increase adaptive immune responses (e.g., autoAbs, autoreactive B and T cells) could increase ADs in women, while the ability of androgen to increase innate immune responses (e.g., TLRs, mast cells, macrophages) could increase inflammatory heart disease (Figure 1) [5,38,41,43–45]. Additionally, women may be particularly sensitive to lower circulating vitamin D levels, which may counteract some of the protective effects of estrogen and therefore increase AD in women [39].

Sex differences in autoimmune heart disease

Autoimmune disease occurs when cell and Ab-mediated immune responses develop against self antigens, resulting in systemic or organ-specific damage [6,18]. For some time it has been appreciated that both genetic background and the environment contribute to the development of ADs [2]. A recent understanding of the interaction of genes with the environment has revealed the importance of epigenetic mechanisms and the influence of the X and Y chromosomes on disease pathogenesis (reviewed in [46–52]). Research in this area is progressing rapidly and will provide critical insight into the role of sex in determining the development of AD and CVD. The following sections focus on the influence of sex hormones on the immunopathology of disease.

Atherosclerosis

Approximately half of all deaths worldwide can be attributed to CVD and atherosclerosis, or coronary artery disease (CAD) in particular [1]. The pathology of atherosclerosis is characterized by atheromas or fibro-fatty plaques that protrude into and obstruct vessels and compromise blood flow to the heart (and other organs), resulting in ischemic heart disease [53,54]. MI (heart attack), cerebral infarction (stroke), aortic aneurysms and peripheral vascular disease are the major consequences of atherosclerosis. MI alone accounts for approximately 20–25% of all deaths in the USA [55]. The key processes in atherosclerosis are inflammation, lipid accumulation, intimal thickening and fibrosis [53]. Macrophages are the main inflammatory cell type in atherosclerotic plaques, with a 4:1 to 10:1 ratio of macrophages to T cells in human atherosclerotic lesions [53,54]. When macrophages engulf lipoprotein particles they become foam cells. The atherosclerotic plaque evolves to include a core of apoptotic and necrotic cells, cell debris and cholesterol crystals surrounded by inflammatory cells that include T cells and mast cells in addition to foam cells, vascular smooth muscle cells and a fibrous cap composed mostly of collagen [53]. Plaque growth can narrow the arterial lumen, but thrombosis at the site of plaque rupture is the proximal cause of MI. Deposition of autoAbs and/or immune complexes (ICs) at the plaque site may precipitate thromboembolism [6,56].

The presence of autoAbs and autoreactive T cells against oxidized low-density lipoprotein (oxLDL)/ low-density lipoprotein (LDL), Hsp60/65, β 2-glycoprotein-I and/ or collagen suggest that atherosclerosis may be considered an AD [6,57,58]. T-cell clones reactive to

oxLDL have been isolated from human plaques and LDL autoAbs are abundant in atherosclerosis patients [53,56,59]. In one study, autoAbs against oxLDL discriminated between atherosclerotic and control patients better than other lipoproteins such as total cholesterol or LDL levels [59]. A correlation exists between oxLDL–autoAb titer and the extent of atherosclerosis, cardiovascular complications and the risk of restenosis following angioplasty [6]. Elevated oxLDL/ β 2-glycoprotein-I autoAb complexes are associated with more severe CAD and predict a 3.5-fold increased risk for adverse outcomes, including arterial thrombosis [60]. Further evidence that atherosclerosis could be an AD comes from animal studies where atherosclerosis is accelerated after immunization with the autoantigens Hsp65 or β 2-glycoprotein- I, or following transfer of β 2-glycoprotein-I-autoreactive T cells [6]. Additionally, regulatory B and T cells, as well as intravenous administration of total IgG (IVIg), have been found to protect against atherosclerosis in mice, similar to their role in inhibiting ‘conventional’ ADs [6,61,62]. These findings indicate that autoAbs and autoreactive T cells participate in the pathogenesis of disease.

The innate immune response plays a major role in the initiation and development of atherosclerosis [45]. Macrophages and the endothelium of normal and atherosclerotic arteries express a broad range of TLRs including TLR1, 2, 3, 4, 5, 7 and 9. Signaling via the major TLR signaling adaptor protein, MyD88, is critically important for atherosclerosis development in mouse models of disease [63]. For example, oxLDL binds TLR2 and TLR4 resulting in activation of the inflammasome and IL-1 β and IL-18 production, which generates a Th1 response (IL-18 is a potent inducer of IFN- γ) [53,64–67]. Thus, autoAb-ICs such as oxLDL/ β 2-glycoprotein-I activate macrophages to form foam cells, stimulate an innate proinflammatory response, and promote thromboembolism.

The prevalence and severity of atherosclerosis among individuals and groups is related to a number of major risk factors including age, sex, tobacco use and genetics. Men are at a far greater risk for developing atherosclerosis than women [1,19,68,69]. Although the increased incidence of CVD in men has been partially attributed to gender differences in smoking habits, recent studies on the effect of sex hormones on CVD indicate that testosterone may directly increase inflammation and cholesterol levels in men [19].

Human monocytes and macrophages express ER- α and ER- β , but in mice ER- α appears to only be expressed in macrophages [70]. Females are reported to have higher levels of ERs in their arteries than males, which decrease with age/menopause [19]. Similarly, androgen receptors are expressed at higher levels on/in macrophages in men than in women [71], and are present in mouse macrophages [70]. The androgen receptor was found to increase lipid loading in human macrophages [71], while estrogen prevented cholesterol accumulation in macrophages by reducing expression of the LDL scavenger receptor, CD36 [72,73]. Estrogen via ER- β signaling has been shown to regulate artery tone and blood pressure, while ER- α has been shown to mediate protection against vascular injury and atherosclerosis [19,74]. Additionally, estrogen has been found to decrease lipopolysaccharide-/TLR4-induced IL-1 β , IL-6 and TNF- α production and NF- κ B activation from splenic murine macrophages [75,76]. Studies examining whether sex differences exist in autoAbs during atherosclerosis are lacking. One study found that there were no sex differences in oxLDL levels in the sera of men and women that did not have CVD [77].

Males develop atherosclerotic plaques earlier and more extensively than females, suggesting that testosterone increases atherosclerosis in males [19,21]. This was confirmed in a study where treatment of atherosclerosis-prone male mice with testosterone increased atherosclerosis, while suppression of testosterone decreased atherosclerosis in male but not female mice [78]. However, men with CAD have lower circulating levels of testosterone than normal controls, suggesting that higher testosterone levels may be cardioprotective

[79]. There could be several explanations for these findings. Higher concentrations of testosterone may be converted to cardioprotective estrogens by aromatase, circulating testosterone levels may not reflect cardiac level or function, or low testosterone may increase other cardiovascular risk factors. In support of this idea, low testosterone levels in men have been found to predict insulin resistance and the development of Type 2 diabetes and to be associated with high blood pressure [19], all of which are risk factors for CVD. However, studies to date suggest that estrogen protects against atherosclerosis, while androgens increase disease.

Myocarditis & dilated cardiomyopathy

Myocarditis, or inflammation of the myocardium, leads to a significant minority of DCM cases in the US [1,80–82]. DCM is the most common form of cardiomyopathy requiring a heart transplant [3,80]. Between 4 and 20% of sudden cardiovascular deaths among young adults, the military and athletes are due to myocarditis [82]. However, the true incidence and prevalence of myocarditis are unknown due to the lack of widely available, safe and accurate noninvasive diagnostic tests [83]. Viral infection is the most commonly identified cause of myocarditis in developed countries (Box 1), and other rare etiologies include bacteria, protozoa, toxins, drug reactions and sarcoidosis [82,84]. Most cases of suspected myocarditis are not linked to a specific cause [85]. Coxsackievirus B3 (CVB3) infection, a common cause of myocarditis, has recently been implicated in up to 40% of patients who died suddenly of MI [86], suggesting a possible etiologic link between myocarditis and MI. Infections are believed to induce or trigger autoimmunity [87–89]. Similar to atherosclerosis, myocarditis and DCM occur more frequently in men than women [3,4]. A recent study of myocarditis/acute DCM patients found that myocardial recovery and transplant-free survival were significantly worse in men – driven by a marked difference in survival [4].

Myocarditis by definition is inflammation of the myocardium. However, in most clinical cases and animal models, myocardial inflammation also involves the pericardium. Similar to findings in clinical biopsies of myocarditis patients [3], the primary infiltrate found in mouse models of myocarditis consists of macrophages and neutrophils with lower levels of T cells, B cells, mast cells and DCs [41,90,91]. Interestingly, the cellular composition during acute myocarditis is similar to the infiltrate of atherosclerotic plaques. NK cells, CD8⁺ T cells and $\gamma\delta$ T cells, needed for antiviral defense, are also important in the early cellular response in viral animal models of myocarditis [92–94]. Regulatory mechanisms such as Tim-3⁺ CD4⁺ T cells, alternatively activated macrophages and Tregs are elevated at the later stage of acute myocarditis, resulting in dispersion of acute inflammation [41,94–96]. Several weeks later, in susceptible strains of mice, a low-level inflammation re-emerges that is associated with myocyte necrosis, fibrosis and DCM [88]. Acute myocarditis is characterized by a predominantly Th1 and/or Th17 response [97–100]. However, only mice that respond to infection or self antigen with a Th2 response, such as BALB/c and A/J strains, develop the chronic stage of myocarditis associated with fibrosis and DCM [18,88,101].

The innate immune response to infection is critical to the development of CVDs, including myocarditis, DCM, heart failure and atherosclerosis [102]. Activation of innate sensors such as TLRs and the inflammasome result in distinct cytokine profiles that drive the adaptive immune response. TNF- α , IL-1 β and IL-18 have all been shown to play an important role in myocarditis by inducing myocyte hypertrophy, contractile dysfunction, myocyte apoptosis, and contributing to extracellular matrix (ECM) remodeling – a critical step in the progression from myocarditis to DCM [103–106]. Out of all the TLRs that have been described so far in humans and mice, TLR4 is unique in its ability to work with the inflammasome to produce bioactive IL-1 β and IL-18 in the heart [104,107]. TLR2 and TLR4 signaling increase TNF levels and TLR2 can act with TLR4 to increase IL-1 β levels

[107]. TLR2 and TLR4, in particular, are able to induce an immune response to damaged self proteins including cardiac myosin [102,108]. *Tlr4* mRNA expression has been found to be higher in patients with myocarditis than controls and to correlate with viral RNA levels in the heart [109]. Myocarditis patients with active viral replication had higher levels of TLR4 that was associated with lower systolic function. We found that TLR4-deficient mice develop reduced inflammation and lower IL-1 β and IL-18 levels in the heart during acute CVB3 myocarditis [104]. IL-1 β is known to induce cardiac remodeling that leads to fibrosis, DCM and heart failure following acute myocarditis [103,106,110,111]. The importance of TLR4 signaling in a strictly autoimmune model of myocarditis was demonstrated by Nishikubo *et al.* where TLR4 signaling was found to be necessary to mount a Th1-type immune response [112]. We have shown that TLR4 is upregulated in macrophages and mast cells during the innate immune response to CVB3 as early as 12 h after infection and during acute CVB3 myocarditis [41]. A number of TLRs important in the response to viral infections (e.g., TLR3, TLR7, TLR9) and their downstream adaptors, MyD88 and TRIF, have been shown to be important in protecting against myocarditis in animal models of viral myocarditis [101,102,113–116]. The data so far suggests that viral-specific TLRs, such as TLR3 and TLR9, protect against myocarditis while TLR2 and TLR4, which are activated by infection and damaged self, increase disease.

Huber and colleagues were the first to describe that male mice have increased CVB3-induced myocarditis compared with females [117]. The amplified inflammatory response in males is not due to increased viral replication, which is similar between the sexes [41,118]. Innate immune responses to CVB3 are critical to sex differences in acute CVB3 myocarditis. In a mouse model of CVB3 myocarditis using purified CVB3, males had a higher cardiac infiltration of $\gamma\delta$ T cells, macrophages and T cells than female mice and an increased Th1 response [119]. By contrast, female mice had a higher protective Th2 response and more Tregs [119–121]. Similarly, in a mouse model where CVB3 and heart proteins were injected, males experienced increased cardiac TLR4⁺ CD11b⁺ inflammation including macrophages, neutrophils, mast cells and DCs and a predominant Th1 response, while females had increased B cells, inhibitory Tim-3⁺ CD4⁺ T cells, Tregs and a Th2 response [41,95]. We demonstrated that the predominant Th1 response in male mice was due to TLR4-derived IL-18, originally named IFN- γ -inducing factor, rather than to a classical IL-12/ STAT4-induced Th1 response [122]. Gonadectomy reduces CD11b⁺ inflammation, and specifically macrophages, in the heart of male mice during acute myocarditis and causes a reversal of the Th1 response in males to a Th2 response with increased Tim-3⁺ T cells and Treg [43]. To our surprise, TLR4 was only expressed on alternatively activated macrophages, cells that require IL-4 or a Th2 response [43,96]. These findings suggest that IL-1 β produced by TLR4⁺ alternatively activated macrophages in males in susceptible Th2-responding BALB/c and A/J mouse strains is critical for the induction of fibrosis that leads to DCM.

TLR4 expression is significantly elevated on macrophages and mast cells in the spleen and peritoneum of male BALB/c mice compared with females as early as 12 h after infection with CVB3 and remains elevated in the heart of males with myocarditis [41]. We recently showed that, 12 h after CVB3 infection, male BALB/c mice upregulate genes in the spleen that are associated with the development of CVD and heart failure [44], indicating the importance of the innate inflammatory response in the progression of disease. This idea is supported by a clinical study that found that inflammation was the best predictor of progression from myocarditis to DCM in patients [123]. Additionally, in patients with acute myocarditis, men have been found to have more myocardial fibrosis than women [124]. In mice, testosterone administration was able to increase myocardial inflammation and fibrosis in males but not females in a MI model [125].

Although the role of inflammation in the pathogenesis of myocarditis and DCM is clear, the role for autoAbs in the pathogenesis of disease is less clear. AutoAbs are produced in response to cardiac injury and/or molecular mimicry to pathogens and thus serve as markers of injury [126,127]. Additionally, autoAbs may stimulate the immune response via ICs or directly alter cardiac or immune function by stimulating receptors including the β -adrenergic receptor or the M2 muscarinic receptor [128–130]. Circulating antimyosin autoAbs are found in patients with myocarditis, DCM, Chagas disease, Kawasaki disease, rheumatic fever and following MI [129]. In myocarditis/DCM patients, antimyosin Abs were found to bind to the S2 region of cardiac myosin and to activate β -adrenergic receptors, which control heart rate and contractility [131,132]. Overstimulation of this receptor can lead to cardiomyocyte death, ECM remodeling and heart failure in animal models [133]. These data suggest that autoAbs contribute to disease progression; however, whether sex differences exist in autoAbs or antimyosin isotypes is yet to be investigated. The majority of research on sex differences in CVD has centered on the role of sex hormones in heart failure.

Heart failure

Heart failure is the end consequence of a number of inflammatory cardiovascular conditions including atherosclerosis, myocarditis and chronic DCM. Most cases of heart failure are caused by reduced myocardial contractile function (systolic dysfunction), which occurs during ischemic injury, pressure or volume overload and during DCM. However, heart failure can also occur because of an inability to relax or fill the ventricle during diastole, in part due to myocardial fibrosis in the setting of preserved systolic function. Patients with chronic heart failure who have elevated levels of inflammatory mediators have a worse prognosis [134]. Antiviral treatments such as IFN- β may reduce myocarditis and heart failure in animal models and possibly patients, implying that viral infections are an important cause of myocarditis cases that lead to DCM and heart failure [123,135]. Male sex is an important risk factor for developing inflammatory DCM and heart failure, just as it is a risk factor for atherosclerosis and myocarditis.

Men with heart failure have a worse prognosis than women and a higher mortality [20]. The incidence of heart failure increases dramatically in women postmenopause, with the strongest predictor of mortality in women being age, whereas in men it is New York Heart Association (NYHA) classification [20]. Men and women with heart failure present with different clinical manifestations. In the Euro Heart Survey, men were found to develop systolic heart failure whereas more often women had preserved ejection fraction and diastolic heart failure [136]. Hypertension, obesity and diabetes are more likely to be risk factors in women, while CAD and DCM are risk factors in men [20,68]. In animal models of heart failure and in end-stage failing human hearts, gene-expression profiles reveal an increase in ECM remodeling genes in males compared with females [124,125,137], similar to myocarditis and DCM.

Thus, a common theme in all autoimmune heart diseases is the importance of innate activation of the immune response via TLRs (e.g., TLR2 and TLR4), the induction of proinflammatory and profibrotic cytokines (e.g., Th1 and IL-1 β) and remodeling that leads to fibrosis, dilation and heart failure. Testosterone has been associated with, or shown to increase, all of these factors in clinical studies and/or animal models of disease.

Why are ADs more prevalent in women?

ADs affect approximately 8% of the population, and of those individuals approximately 78% are women [2,138]. There are a number of hypotheses to explain this gender difference, including the effect of sex hormones, microchimerism, genes on X or Y chromosomes, X chromosome inactivation and differing responses to environmental factors (reviewed in

[5,18,46–48,139–141]). Estrogen may directly increase ADs in women by elevating autoAbs and amplifying autoreactive T- and B-cell responses [18]. One unanswered question is why CVD is increased in rheumatic diseases including SLE, RA, systemic sclerosis and SS. These are more prevalent in women; SLE has an incidence of 9:1, SS 9:1, systemic sclerosis 4:1, RA 2–3:1, and myositis 2:1 in women versus men [6,7,9,14,18,139,142,143]. A better understanding of how sex hormones influence disease pathogenesis may provide clues to help answer these questions.

Systemic lupus erythematosus

SLE is a common multisystem autoimmune disease of unknown etiology that often presents as a photosensitive rash, polyarthritis, and/or renal disease. SLE occurs more frequently in women than men, at a ratio of 9:1, with an onset of disease at 20–30 years of age [12,18,144–146]. Infections such as Epstein–Barr virus, parvovirus B19 (PVB19) and CMV have been associated with the development of SLE [146,147]. SLE is a disease of multiple immune system abnormalities (Box 2). Factors involved in disease pathogenesis include defects in antigen presentation (e.g., HLA DR/DQ), poor clearance of ICs and/or apoptotic material by macrophages because of complement defects (e.g., CD11b, C1q, CRP, MBL, FcRs), transcriptional regulation of interferons (e.g., TLR7, TLR8, TLR9, IRF3, IRF5), elevated proinflammatory cytokines such as TNF, IL-6, and IFN- α/β , dysregulated B cells (e.g., BLyS), and elevated autoAbs (e.g., antinuclear Abs) [145–147].

Some studies suggest that women with SLE have abnormally high levels of active estrogen metabolites that could increase disease [146,148]. Recently, Wang *et al.* showed that polymorphisms in ER genes were associated with SLE, providing a mechanism for how estrogen metabolites could increase the risk for SLE in women [149]. Estrogen has been found to increase autoAbs and IC deposition in animal models of lupus [144,150]. Many lines of evidence also link elevated type I interferons IFN- α and IFN- β with worse SLE pathogenesis and women with SLE have higher levels of IFN- α than men [145,151]. TLR7, TLR8 and TLR9 are important in protection from viral infections, but are also activated by nucleic acid (i.e., nuclear antigens) and ICs, critical components of the elevated Ab response to damaged self found in SLE patients [152]. Interestingly, the genes for TLR7 and TLR8 are located on the X chromosome in humans and mice, which could contribute to elevated interferons in women with SLE [145]. Additionally, estrogen has been shown to activate DCs, which in the context of activation of TLRs by infections, may release interferons and activate macrophages [151–153]. Osteopontin is a cytokine involved in immune cell signaling and ECM remodeling that has been found to be overexpressed in biopsies from SLE patients [145] and is also elevated in heart diseases including CAD, MI, hypertrophy and myocarditis [154]. Interestingly, analysis by sex revealed that the relationship between osteopontin and SLE occurs only in men and not women with disease [155]. A summary of some of the known sex differences in SLE are listed in Box 3.

The major CVD found in SLE patients is atherosclerosis/vascular thrombosis. The risk of developing atherosclerosis/CAD in SLE patients is four- to eight-fold higher than in controls, and in young women the risk of MI is increased 50-fold [156]. However, in a recent study of 14,829 SLE patients, male SLE patients (10% of patients) were more likely to have cardiovascular and renal comorbidities compared with females [157]. Although SLE patients who develop atherosclerosis are more likely to be male and have classical CAD risk factors such as hypertension and obesity [9,158], recent studies suggest that increased CVD risk in SLE patients cannot be fully explained by CVD risk factors alone and that SLE disease-specific factors also play a role [159,160]. Rarely, patients with SLE develop pericarditis, myocarditis, endocarditis or valvular disease (Box 4) [156,161]. The major cause of death in SLE patients is premature atherosclerosis [156,162]. Very rarely, myocarditis associated with fibrosis in SLE patients may progress to DCM and heart failure.

One post-mortem study of SLE patients revealed a high prevalence of pericarditis of 63% [161]. Vascular occlusion in SLE may be due to vasculitis (i.e., IC deposition), vasculopathy, atherosclerosis and/or thrombosis due to APS (Box 4). APS is associated with the presence of antiphospholipid autoAbs that induce vascular thrombosis and pregnancy loss. Although APS is most frequently associated with SLE, it can occur as an independent clinical entity [142]. Lupus anticoagulant is the antiphospholipid Ab that confers the greatest risk of thrombosis. In a prospective study, the presence of lupus anticoagulant was associated with thrombotic events (i.e., MI), but was not associated with subclinical atherosclerosis (i.e., carotid plaques) [163]. IC deposition may drive a local inflammatory response involving the vascular tissue, pericardium and/or myocardium, resulting in thrombosis [156,161]. oxLDL autoAbs may also be present in APS patients and antiphospholipid autoAbs have been found to accelerate the influx of oxLDL into macrophages further promoting atherosclerosis. Thus, the ability of autoAb/ICs in SLE to increase inflammation and trigger thromboembolic events may increase CVDs in women (Figure 1).

Rheumatoid arthritis

RA is a common inflammatory form of arthritis affecting approximately 1–2% of the population. The incidence of RA is two- to three-fold higher in females than males [18]. Anticyclic citrullinated protein Abs are an early biomarker of RA. Abs directed against peptides and proteins containing citrulline, a modified form of the amino acid arginine, are highly specific for RA [164]. Citrullination is a normal physiological process that occurs within cells undergoing cell death and citrullinated proteins are only released for recognition by the immune response if poor clearance of apoptotic or necrotic cells occurs [164]. RA patients also have elevated levels of oxLDL autoAbs in their sera [165]. Inflammation in the synovium during RA includes CD4⁺ T cells, macrophages, and mast cells with increased levels of TNF, IL-1 β and IL-6 [166], a composition similar to that observed in atherosclerosis and myocarditis patients. Elevated levels of proinflammatory and profibrotic cytokines in RA patients contribute to increased inflammation and fibrosis. Unregulated autoAb production from B cells leads to IC deposition, which along with proinflammatory cytokines, recruits more inflammation and promotes ECM remodeling of the joint.

RA is more prevalent in women before age 50, but disease severity is greater in women after 50 years of age [31]. AutoAbs are known to increase with age, and so may contribute to increased IC deposition and damage in older women. The increased autoAb and IC response in women compared with men suggests a role for estrogen in the pathology of disease. However, many investigators have reported that estrogen protects against arthritis in animal models of RA [18,167]. Based on results found in animal models, recent clinical studies examined the effect of ER- α or ER- β agonists on RA. In two separate studies ER agonists were found to be ineffective at reducing the inflammatory response during RA [168,169]. What could account for the discrepancy between animal models and clinical RA? One possibility is that the acute inflammation induced by adjuvants in animal models may be effectively inhibited by estrogen, particularly if estrogen is administered during initiation of the innate immune response [18]. Evidence in support of a role for estrogen in promoting disease comes from a study that found that free estrogen levels in the synovial fluid of men with RA were increased twofold compared with control men, but were similar to estrogen levels in women with RA [170]. In addition, incidence rates of RA in men increase with age as androgen levels decrease and Th2 responses and autoAbs increase [171]. Overall, these findings suggest that estrogen increases RA-mediated pathology.

Numerous studies have shown that RA patients exhibit many of the traditional CVD risk factors, such as hypertension and hyperlipidemia, although several studies found no relationship [11,172]. For this reason it is not surprising that RA is associated with an

increased cardiovascular morbidity and mortality compared with the normal population, which accounts for 30–50% of RA deaths [14,172]. There is a two- to three-fold increased risk for MI, congestive heart failure, sudden death and stroke in RA patients [166]. Several studies found that overall mortality and death due to CVD and ischemic heart disease in RA patients were increased in both sexes, but that male sex predicts cardiovascular events and death [14,15]. Although several studies have reported CVD is increased in both sexes with RA, few studies examined sex differences; a meta-analysis of RA patients found that only three out of 24 studies examined sex differences [15]. RA is likely to increase the risk of developing CVD by elevating vascular and myocardial inflammation and dyslipidemia. Similar to SLE, RA patients develop atherosclerosis and vascular thrombosis, and more rarely, pericarditis, myocarditis or endocarditis/valvular disease (Box 4). Evidence of the important role for elevated proinflammatory cytokines in disease pathogenesis comes from studies finding that treatment of RA patients with anti-TNF drugs reduces the chance of developing heart failure by 50% [134,173]. The inflammatory infiltrate in the joint of RA patients closely resembles the infiltrate in the atherosclerotic plaque and myocardium in inflammatory autoimmune diseases such as atherosclerosis and myocarditis. Importantly, the same pathogenic mechanisms that increase inflammation in the joint are likely to increase CVD in RA patients.

Sjögren's syndrome

SS is characterized by chronic inflammation of the exocrine salivary and lacrimal glands, resulting in dry mouth and eyes [174]. SS can be considered a heterogeneous AD possessing both organ-specific and systemic features [175]. SS can occur as a primary condition or in association with other ADs such as RA and SLE. AutoAbs in SS include antinuclear Abs (ANA), particularly against ribonuclear proteins (e.g., anti-Ro/SSA), and rheumatoid factor (RF). The double name Ro/SSA derives from the description of these autoAbs by two different research groups – one to define a SLE patient ('Ro') and the other in association with SS (SS-A) [176]. Abs against Ro/SSA antigens have been detected in patients with SS, SLE, RA and fetal–maternal autoimmune syndromes, but their precise role in the pathogenesis of disease is unclear [176]. In humans and mouse models of the disease, the salivary gland infiltrate is composed of T cells, B cells, macrophages and DCs [174,177]. Similar to SLE, SS has a female predominance of 9:1. In the mouse model, females were found to have greater salivary gland inflammation and a more predominant Th2 and Th17 response and more B cells [174]. However, there are no studies that have specifically examined the role of sex hormones in disease pathogenesis. The true incidence of CVD among SS patients is not known but one study found a higher prevalence of subclinical atherosclerosis in patients compared with controls [178]. In this study, the presence of anti-Ro/SSA autoAbs, but not alterations in lipid profiles, was associated with subclinical atherosclerosis, suggesting a role for Abs in disease progression [142,178]. These data suggest that a similar increased CVD risk may exist for SS patients as occurs for other rheumatic ADs.

Systemic sclerosis

Systemic sclerosis (also called scleroderma) is considered the prototypic multisystem fibrotic disease that commonly affects the skin, lungs and kidneys [18,142]. Pathological characteristics of the human disease and animal models include overexpression of the profibrotic cytokine TGF- β and elevated numbers of mast cells, eosinophils and basophils – all of which are associated with Th2 responses. The role for autoAbs in the pathogenesis of disease is unknown, but approximately 95% of scleroderma patients are positive for ANA [179]. Although a relatively uncommon disease, it has the highest case-specific mortality of any of the autoimmune rheumatic diseases because of vascular and fibrotic complications. Patients with systemic sclerosis have a fourfold increase in mortality compared with the

general population, with approximately a third of deaths due to CVDs, including atherosclerosis [142,180]. Patients with systemic sclerosis may rarely develop vasculitis or myocarditis (Box 4). A recent study found that systemic sclerosis was an independent risk factor for coronary calcification, in addition to the conventional risk factors for atherosclerosis [181]. Systemic sclerosis patients also have higher levels of lipoprotein (Lp[a]) and oxLDL autoAbs [142]. Although female predominance in systemic sclerosis patients ranges from 4:1 to 14:1, male gender is considered a factor determining poor prognosis [182]. Men with the disease were found to have more inflammatory myopathy, greater pulmonary artery pressure as assessed by echocardiography, and fewer anticentromere autoAbs than women [182]. Although more research is needed, the presence of mast cells, basophils, eosinophils and autoAbs strongly suggests a Th2-skewed immune response.

A role for RF?

The rheumatic diseases SLE, RA, myositis, SS, and systemic sclerosis are a group of inflammatory autoimmune disorders where autoAb and IC deposition induce tissue damage, inflammation and fibrosis [183]. Historically, RF was considered a primary pathogenic autoAb needed for the formation of ICs in RA [184]. RFs are autoAbs against the Fc region of Abs (e.g., IgM, IgG, IgA). As part of the normal immune response to infection, RF promotes complement fixation, clearance of ICs by macrophages, enhances antigen presentation and amplifies the avidity of IgG [185–187]. But RF can also participate in AD pathology by its ability to form ICs. RF occurs in 70–90% of RA, 60–80% of SS, 30% of SLE, 20% of myositis and 20% of systemic sclerosis patients [186,187]. When RF is present in RA patients, its presence predicts a more aggressive, destructive disease course [184]. RF levels also correlate with the severity of salivary gland damage in SS [186]. These data suggest that RF may contribute to the pathogenesis of rheumatic ADs, although the precise mechanisms involved remain unclear.

Many infections are known to transiently induce RF (Box 5) [186,187]. Interestingly, many of these infections are also associated with inflammatory heart diseases such as myocarditis (Box 1 & 5). The presence of RF may be useful and beneficial early in the course of a bacterial or viral infection [186–188]. RF levels are higher in secondary (e.g., 23%) compared with primary infections (e.g., 8%), and even higher in the sera of latently infected individuals (e.g., 37%) suggesting that individuals with higher RF may not be clearing infections [186]. Increased Th2 responses in females may inhibit clearance of bacterial or viral infections. Numerous infections, particularly viral and bacterial infections, have been associated with rheumatic ADs (Box 6) [189]. There is a considerable overlap in the infections that induce RF (Box 5), rheumatic ADs (Box 6) and myocarditis (Box 1). It would be interesting to determine whether RF could be a biomarker for infections that induce or promote autoimmune and CVDs.

Considering the importance of infections and innate TLR activation in the pathogenesis of cardiovascular and rheumatic ADs [45,53,102,190], it is perhaps not surprising that several studies have found that RF is associated with increased all-cause mortality and CVD mortality in RA patients (although a stronger relationship may exist for CVD mortality and anticyclic citrullinated protein autoAbs) [11,191,192]. Goodson *et al.* found that after adjusting for age and sex, CVD mortality association in newly diagnosed patients with inflammatory polyarthritis was strongest in the subgroup of patients who were RF-positive at baseline [193]. In recent-onset inflammatory polyarthritis patients, male sex and RF positivity were predictors of early and later mortality [194]. It has been known for some time that ICs not only increase autoimmune heart disease but also serve as an independent risk factor for MI [195]. Importantly, a recent study found that elevated RF increased the

risk for ischemic heart disease in men from the general population, but not women [196]. More men than women were positive for RF (23.9% men vs 11% women, mutually adjusted odds ratio: 2.9 [95% CI: 1.6–5.3] vs 1.3 [95% CI: 0.6–2.8]; $p < 0.001$, respectively) [196]. RF autoAb titers have also been found to be higher in men versus women with RA and SS even though these diseases are more prevalent in women [186–198]. The relatively higher levels of RF in rheumatic ADs such as RA and SS, where RF occurs in 80% of patients, may predispose women to develop CVD and/or indicate that drivers of disease, such as infection, are elevated. More studies are needed to determine whether sex hormones directly influence RF levels and whether RF is involved in the pathogenesis of autoimmune and/or CVDs.

Expert commentary

This review has focused on the role of sex hormones in regulating immune function during AD and CVD. TLRs are activated by infections and damaged self. In men, testosterone promotes a proinflammatory Th1/Th17 response that leads to cardiac remodeling and fibrosis (Figure 1). In men, autoAbs including RF and ICs contribute to atherosclerosis and thrombosis and promote the progression to DCM and heart failure following myocarditis. By contrast, estrogen promotes a regulatory Th2 response in women that leads to increased autoAbs following infection and/or tissue damage (Figure 1). IC deposition in females promotes inflammation and fibrosis that leads to AD. Additionally, Th2-skewed responses in females may allow infections to persist resulting in increased RF, ICs and inflammation that predisposes women to premature atherosclerosis.

Although the question of why CVDs occur more often in men is somewhat easier to address, the answer to why ADs are increased in women remains controversial. Even though estrogen has a well-established ability to activate B cells and increase Ab/autoAb levels that require a Th2-type immune response, few studies have examined the role of sex hormones on autoAb levels or IC-mediated pathology during autoimmune or CVDs. However, the critical role that IC deposition plays in driving inflammation and fibrosis suggests that estrogen may promote ADs in women. Additionally, a Th2-skewed immune response in females may allow infections to persist, resulting in increased production of RF in women which, together with high levels of other autoAbs, could increase thromboembolism and CVD in women. A better understanding of the influence of sex hormones on autoAbs and ICs should provide important information on why CVD is increased in patients with rheumatic ADs. Future studies need to address the pathogenesis of sex-specific responses of the immune system to CVD and AD.

Five-year view

A greater understanding of the importance of sex differences in the pathogenesis of CVD and rheumatic ADs is beginning to be realized. In the next 5 years, investigators who previously analyzed their data by controlling for sex will now also study sex differences. Findings from the study of sex differences will provide critical information concerning the pathogenesis of rheumatic disease, AD and CVD. More research is required to establish whether RF is increased in men with CVD and whether sex hormones such as testosterone regulate its levels. New techniques to study gene–environment interactions will rapidly increase our understanding of the role of infections and sex hormones in the pathogenesis of inflammatory heart disease. Understanding epigenetic mechanisms and the influence of X and Y chromosomes on disease pathogenesis will complement the study of the effect of sex hormones on the immune response. Breakthroughs in these areas will provide a better understanding of CVD risk factors between sexes and how to prevent and treat CVD and AD.

Box 1. Infectious causes of myocarditis**Viral**

- Adenovirus[†]
- Coxsackievirus B[†]
- CMV[†]
- Epstein–Barr virus
- Hepatitis C virus
- Herpes simplex virus
- HIV[†]
- Influenza virus
- Mumps
- Parvovirus B19
- Poliovirus
- Rubella
- Varicella zoster virus

Bacterial

- Chlamydia
- Cholera
- Mycoplasma
- Neisseria
- Salmonella
- Staphylococcus
- Streptococcus
- Tetanus
- TB

Spirochetes

- Leptospirosis
- Lyme disease
- Relapsing fever
- Syphilis

Protozoa

- Chagas disease
- Leishmaniasis
- Malaria

[†]Frequent cause of myocarditis.

Adapted from [84].

Box 2. Risk factors common to atherosclerosis, systemic lupus erythematosus and rheumatoid arthritis

- Family history
- Autoantibodies
- Inflammation, e.g., CRP, complement activation
- Infections, e.g., CMV
- Toxins, e.g., tobacco smoke
- Oxidative stress, e.g., oxLDL
- Innate TLR activation e.g., IFN- α/β
- Proinflammatory/profibrotic cytokines, e.g., TNF- α , IL-1 β , IL-6 and osteopontin
- Hyperlipidemia, e.g., LDL
- Lp(a)
- Hypertension
- Stress

CRP: C-reactive protein; LDL: Low-density lipoprotein; Lp(a): Lipoprotein(a); oxLDL: Oxidized low-density lipoprotein; TLR: Toll-like receptor.

Data taken from [11].

Box 3. Sex differences in systemic lupus erythematosus

- The prevalence of SLE is higher in women under 40 and the female to male ratio is 9:1.
- SLE is often more severe in men than women.
- Cardiovascular diseases such as atherosclerosis are more common in men than women with SLE.
- Women with SLE are more likely to have malar rash, photosensitivity, oral ulcers, alopecia, Raynaud's syndrome or arthralgia.
- Men with SLE are more likely to have cardiovascular disease, peripheral vascular disease, myocardial infarction, thrombosis, neuropsychiatric symptoms or renal damage.
- Men with SLE have poorer survival rates than women.

SLE: Systemic lupus erythematosus.

Box 4. Cardiac involvement in rheumatic autoimmune diseases

Systemic lupus erythematosus

- Atherosclerosis
- Pericarditis

- Myocarditis
- Valve disease
- Vascular thrombosis
- Hypertension

Rheumatoid arthritis

- Atherosclerosis
- Pericarditis
- Myocarditis
- Valve disease
- Vascular thrombosis

Scleroderma

- Atherosclerosis
- Vasculitis
- Myocarditis

Myositis

- Atherosclerosis
- Pericarditis
- Myocarditis
- Valve disease
- Congestive heart failure
- Hypertension

Antiphospholipid syndrome

- Thrombosis
- Valve disease
- Mural thrombi

Myositis: also called dermatomyositis; Scleroderma: also called systemic sclerosis.

Data taken from [199].

Box 5. Examples of infections known to induce rheumatoid factor

Bacterial

- *Mycobacterium tuberculosis*†
- *Borrelia burgdorferi*†
- *Chlamydia pneumoniae*†
- *Klebsiella pneumoniae*
- Syphilis

Viral

- Epstein–Barr virus[†]
- Parvovirus[†]
- Hepatitis virus A, B and C[†]
- CMV[†]
- Coxsackievirus B[†]
- HIV[†]
- Herpes simplex virus[†]
- Rubella virus[†]
- Measles virus
- Dengue virus

Parasitic

- *Trypanosoma cruzi*[†]
- Toxoplasmosis
- Onchocerciasis
- Malaria

[†]Infections that induce myocarditis in humans and/or animal models.

Adapted from [186].

Box 6. Infections associated with rheumatic autoimmune diseases**Systemic lupus erythematosus**

- Epstein–Barr virus
- Parvovirus B19
- CMV
- Salmonella
- HIV
- Escherichia coli

Rheumatoid arthritis

- Epstein–Barr virus
- Parvovirus B19
- CMV
- Human T-lymphotrophic virus
- Mycobacteria
- E. coli

Scleroderma

- Epstein–Barr virus
- Parvovirus B19
- CMV
- Human T-lymphotrophic virus
- HIV
- Helicobacter pylori

Myositis

- Coxsackievirus
- Parvovirus B19
- Toxoplasma
- Human T-lymphotrophic virus
- HIV

Sjögren's syndrome

- Epstein–Barr virus
- Coxsackievirus
- CMV
- Human T-lymphotrophic virus
- HIV
- Hepatitis C virus

Myositis: also called dermatomyositis; Scleroderma: also called systemic sclerosis.

Data taken from [200].

Key issues

- Cardiovascular diseases are more prevalent in men, and autoimmune diseases more prevalent in women.
- Autoantibodies are important in the pathogenesis of cardiovascular and autoimmune diseases but information on sex differences in autoantibodies is lacking.
- Estrogen activates B cells and increases autoantibodies, Tregs and Th2 responses that protect against heart disease but may lead to increased immune complex deposition during autoimmune disease.
- Testosterone elevates components of the innate immune response following infection or injury that increase cardiac inflammation and fibrosis, leading to atherosclerosis, dilated cardiomyopathy and heart failure.
- Cardiovascular disease is the leading cause of death in rheumatic autoimmune diseases.
- Infections known to induce rheumatoid factor are implicated in the pathogenesis of rheumatic autoimmune diseases and inflammatory heart disease.

- A small number of studies suggest that rheumatoid factor is elevated in men in the general population and in men with rheumatic or cardiovascular diseases.

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Figure 1. Proposed role of sex hormones in regulating immune function during autoimmune and cardiovascular disease

Toll-like receptors (TLRs) are activated by infections and damaged self. In men, Te promotes a proinflammatory Th1 and/or Th17-type immune response that leads to cardiac remodeling and fibrosis. In men, AutoAbs such as RF and ICs contribute to atherosclerosis and thrombosis and promote progression to DCM and HF following myocarditis. By contrast, E2 promotes a regulatory Th2 response in women that leads to increased autoAbs following infection and/or tissue damage. IC deposition in females promotes inflammation and fibrosis that leads to rheumatic AD. Additionally, a Th2-skewed response in females may allow infections to persist, resulting in increased RF, ICs and inflammation that predisposes women to premature cardiovascular disease.

AutoAb: Autoantibody; AD: Autoimmune disease; DCM: Dilated cardiomyopathy; E2: Estrogen; HF: Heart failure; IC: Immune complex; RF: Rheumatoid factor; Te: Testosterone; TLR: Toll-like receptor.