Immunometabolism

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Sex bias in systemic lupus erythematosus: a molecular insight

Moumita Bose[1,2], Caroline Jefferies[1,2,*]

Abstract

Acknowledging sex differences in immune response is particularly important when we consider the differences between men and women in the incidence of disease. For example, over 80% of autoimmune disease occurs in women, whereas men have a higher incidence of solid tumors compared to women. In general women have stronger innate and adaptive immune responses than men, explaining their ability to clear viral and bacterial infections faster, but also contributing to their increased susceptibility to autoimmune disease. The autoimmune disease systemic lupus erythematosus (SLE) is the archetypical sexually dimorphic disease, with 90% of patients being women. Various mechanisms have been suggested to account for the female prevalence of SLE, including sex hormones, X-linked genes, and epigenetic regulation of gene expression. Here, we will discuss how these mechanisms contribute to pathobiology of SLE and how type I interferons work with them to augment sex specific disease pathogenesis in SLE.

Keywords: SLE, sex disparities, inflammation, estrogen, IFNα, X chromosome dosage, epigenetics, mitochondria

Abbreviations: ER: estrogen receptor, IFN: interferon, ISG: IFN-stimulated gene, PBMC: peripheral blood mononuclear cell, SLE: systemic lupus erythematosus, XCI: X chromosome inactivation

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic, autoimmune, and multisystem disorder characterized by autoantibody production and dysregulated immune cell function. SLE is strongly sex-biased disease, affecting women nine times more frequently than men [1]. Factors such as intrinsic differences in the immune system [2], sex hormones [3], sex differences in gene regulation, sex-dependent environmental factors [4] have been put forward to explain this sex bias. Sex hormones are an important contributor to sex bias in the immune response and in the incidence of disease as noted above [5–7]. For example, estrogens in general are considered immunostimulatory for both innate and adaptive arms of the immune responses [8–10]. On the other hand, androgens drive immunosuppressive or protective immune responses, leading to a lower prevalence of autoimmune diseases but a higher susceptibility to viral infection, one of the many mechanisms contributing to increased prevalence of COVID-19 in men [11]. The changes in the hormonal milieu throughout the lifespan also impacts sex differences in disease. For example, prevalence in asthma and allergic diseases is higher in boys but, following puberty, the prevalence changes and adult females have a higher prevalence of asthma and allergic disease [12,13]. Women also elicit a stronger innate immune response to viral infection, as evidenced by the recent COVID-19 outbreak. Differences in detection of and responses to viral nucleic acids may account for this. For example, the nucleic acid sensing Toll like receptors, *TLR7* and *TLR8* are encoded on the X chromosome and may escape X inactivation, leading to stronger expression in females than males. This in turn drives higher expression of the antiviral cytokines interferon (IFN)α and β, collectively called type I IFNs, in part explaining the stronger immune response in females compared to males in response to viral infection [14]. In addition, plasmacytoid dendritic cells (pDCs) derived from women produce markedly more IFNα in response to TLR7 ligands than do pDCs from men [15]. Estrogen receptor signaling, X chromosome dosage and enhanced levels of the transcription factor IRF5 (itself and estrogen regulated gene) have been shown to contribute to these enhanced IFN responses in female pDCs [16–18].

Although SLE is a complex, heterogeneous disease, there is a consensus that increased expression of type I IFN is an important driver of pathology. Approximately 50% of patients have increased expression of IFN-stimulated genes (ISG), which correlate positively with disease activity and severity [19,20]. In SLE, uncontrolled nucleic acid sensing through TLRs or cytosolic nucleic acid sensors leads to aberrant production of IFNs and hyperactivation of the immune system and SLE flares [21–23]. Indeed, IFNα levels in SLE patients correlate with increased expression of *TLR7*, promoting IFNα-driven gene expression [24]. Moreover, immune cells from SLE female patients showed enhanced, monocyte antigen presentation and serum IgG level compared to male patients, driving a stronger humoral response and contributing to SLE vulnerability in female patients [25].

Given the inherently sexually dimorphic nature of immune responses and particularly with respect to type I IFN, the female bias in SLE and other autoimmune diseases is it not surprising. This review will address likely mechanisms contributing to the sex bias in SLE, including mechanisms that contribute to altered immune reactivity and type I IFNs in SLE. The role of sex hormones, epigenetics and mitochondrial signaling in IFN production and SLE pathogenesis will be addressed (outlined in Figure 1), with emphasis on how these mechanisms contribute to disease pathology in SLE.

2. Influence of sex hormones and receptors in SLE

One of the strongest lines of evidence for a role for sex hormones in SLE comes from the observation that women with SLE

[1]Division of Rheumatology, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [2]Research Division of Immunology, Department of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA, USA

*Correspondence: Caroline Jefferies, E-mail: caroline.jefferies@cshs.org.

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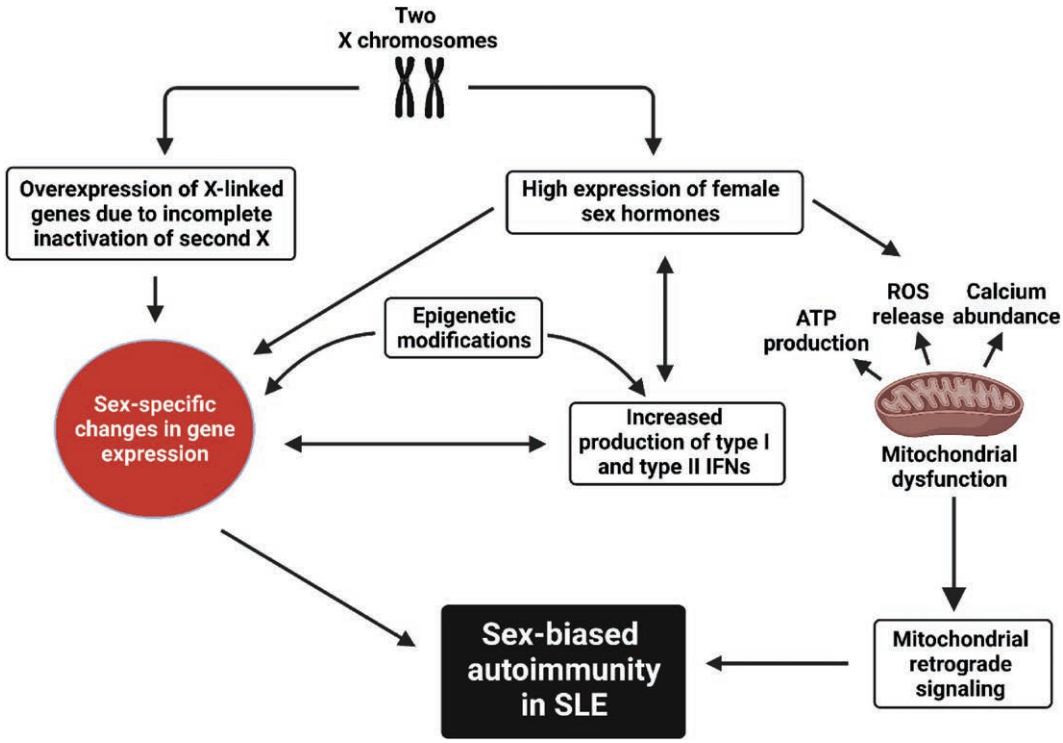

Figure 1. Overview of mechanisms that contribute to sex-bias in SLE. SLE: systemic lupus erythematosus.

experience disease exacerbations during pre-menstrual periods and pregnancy. In addition, clinical manifestations of the disease predominantly occur in women ages 20 to 50, the period of their lives when estrogen and progesterone levels are highest [26]. In women, treatment with estrogen-containing medications increases susceptibility to developing SLE and, in SLE patients, increases risk of flares [27,28]. Interestingly, supplementation of a transgender female with cross-gender hormones resulted in lupus nephritis, supporting a role for estrogen in driving SLE pathology [29]. Animal studies also support a role for estrogen and female sex hormones in SLE. Ovariectomized lupus prone NZB/NZW F1 mice ameliorates disease, while estrogen supplementation in castrated male NZB/NZW F1 mice worsens the disease. In contrast, administration of androgen to female NZB/NZW F1 mice improves the SLE disease phenotype [30–33]. Meanwhile, antagonizing estrogen using tamoxifen in this model reduces disease severity and lowers autoantibody levels [34]. In addition, targeted B-cell deletion of *Esr1* reduces the production of autoantibodies and development of nephritis in NZB/NZW F1 mice [35].

However, studies in SLE patients have provided no real consensus regarding whether hormone imbalances exist in SLE [8]. Similarly, use of oral contraceptives or hormonal replacement therapy have also been shown to be safe in SLE [36]. So how might the link between changes in hormone levels during the lifetime of SLE patients and disease activity be explained? Estrogen mediates its effects by binding to estrogen receptors alpha and beta (ERα and ERβ), members of the steroid hormone nuclear receptor family that function as transcription factors that regulate gene expression. In their inactive form, they are in the cytosol but translocate to the nucleus and drive gene expression following estrogen binding. Receptors for progesterone (progesterone receptor) and testosterone (androgen receptor, AR) are also members of the steroid hormone nuclear receptor family of transcription factors. Interestingly, steady-state levels of ERα mRNA and protein have been reported to be significantly higher in immune cells from SLE patients compared with control [37,38]. In addition, variation in a CAG repeat region in exon 1 of the AR, which reduces its signaling capacity (and hence immunomodulatory capacity) is associated with autoantibody production in SLE in both men and women [39,40]. Murine models have also demonstrated ERα-deficiency in NZM2410 and MRL/lpr female (and not male mice) protects against kidney disease and prolongs survival [38,41,42].

Regarding how sex hormones affect the immune system, both AR and ER are expressed in a variety of immune cells, including lymphocytes and myeloid cells. Responses to estrogen can be both pro- or anti-inflammatory, depending on the cell type, organ microenvironment, or the relative expression of ERα and ERβ. Androgens and progesterone on the other hand are broadly immunosuppressive. Estrogen has broadly inflammatory effects on immune responses, triggering both direct and indirect expression of cytokines including IFNα and IFNγ, in addition to driving the upregulation of TLRs on macrophages in mice. In both mice and humans, estrogen and ER signaling is found to modulate the expression of immunostimulatory cytokines and exacerbates disease activity in lupus mouse model and in human patients [43]. Previous studies indicated the influence of male and female sex hormones on immune cell functions in SLE [44]. Particularly estrogen plays a pivotal role in functional modulation of T and B cells and their immune functions. It also regulates the expression of the transcription factor IRF5, which regulates the expression of inflammatory genes and IFNα and which has been identified as a risk factor for SLE in multiple GWAS studies [45]. Sexually dimorphic expression of *IRF5* has been linked to higher IFNα in women [16]. Another target of estrogen in SLE monocytes is the E3 ubiquitin ligase TRIM21 (also known as Ro52/SSA1), which regulates expression of the IRF family of transcription factors [37].

Studies have also indicated that genetic variations in ER genes might influence SLE susceptibility through the expression of

cytokines, such as type I IFNs or IFNγ [38]. Moreover, higher IFNα level corresponds to increased expression of ERα, indicating potential presence of a feedback loop between IFN and ERα signaling in SLE. Indeed, both IFN and ER signaling act together to further activate expression of IFN and estrogen responsive genes in SLE [38]. Therefore, it is likely that the female sex hormone levels in women play a crucial role in the pathogenesis of SLE (and possibly in other autoimmune diseases) and sex-biased disease outcome. Of note, sex hormones play a crucial role in B-cell development and survival, with estrogen upregulating the expression of genes important for B-cell development and activation (CD22, SHP-1) and survival (Bcl-2) [46,47]. Also, ERα and ERβ differentially regulate the maturation and selection of B cells and ERα but not ERβ can induce the development of autoimmunity through increased production of autoantibodies [8,48]. For example, administration of the ERα agonist PPT to ovariectomized NZB/W mice increased autoantibody production and resulted in earlier disease onset compared with controls. However, treatment with the ERβ agonist DPN resulted in lower autoantibody production and reduced disease. Therefore, imbalance in signaling through the sex hormone receptors, either through increased expression of ERα or decreased signaling though AR, is sufficient to prime the immune system for autoreactivity through enhanced IFNα signaling or production.

3. X chromosome dosage and SLE

A number of lines of evidence support altered X chromosome inactivation (XCI) and gene-dose-effect as a driving factor for sex bias in SLE [49]. For example, men with Klinefelter syndrome (47, XXY) have a 14-fold higher risk of SLE than do men with a single copy of the X chromosome (XY) [50]. Furthermore, females with Turners' syndrome [46, X, del(X)(q13)], where there is only one X chromosome, are less susceptible to get SLE, further supporting X-linked genes and gene-dosage in contributing to the female bias in SLE [51]. DNA methylation of the X chromosome acts as an important epigenetic mechanism for maintaining gene-dose effect between sexes [52]. In normal healthy females, one X chromosome is transcriptionally silenced by DNA methylation to prevent overexpression of X-linked genes [53]. Failure to suppress X-linked genes on the inactive X chromosome contributes to sex bias in various autoimmune diseases including SLE [54]. The long noncoding RNA (lncRNA) *XIST* is encoded by the X chromosome and is expressed in a female-specific manner in adult somatic cells [55,56]. *XIST* is the major effector of XCI and deletions/mutation of *XIS*T reduces XCI [57]. Recently, perturbations in *XIST* function have been associated with altered X inactivation and overexpression of X-linked genes in T cells from SLE patients [54]. The X chromosome comprises several immune-related genes compared to the Y chromosome, such as *TLR7*, *TLR8*, *IL2RG*, and the transcription factor *FOXP3* [58]. *IRAK1* is another X-linked gene, which is a key signaling component activated downstream of multiple TLRs [45]. These and other immune-related X-linked genes are upregulated in SLE patients and demonstrate a female dominant expression pattern. For example, *CXCR3* (Xq13), *OGT* (Xq13), and *CD40LG* (Xq26) are overexpressed in CD4$^+$ T cells of female SLE patients due to reduced methylation of their DNA [59]. Similarly, *FOXP3* (Xp11) is also found to be significantly higher in female SLE CD8$^+$ T cells although whether this is as a result of altered methylation is unknown [60]. Specifically with respect to X chromatin inactivation, *TLR7* has been found to bypass X chromosome inactivation in pDCs, B cells and monocytes in SLE patients or men with Klinefelter syndrome, resulting in increased *TLR7* expression and TLR7 ligand responsiveness in B cells, driving them to differentiate into antibody secreting cells [61]. Another TLR, *Tlr8* has been reported to increase IFNα production in 564Igi mice which have been crossed with *Tlr7/9*$^{-/-}$ mice in females but not in males. Increased *Tlr8* expression is thought to be due to its location on the X chromosome, although whether it escapes XCI remains to be determined [62]. Another functionally important gene that escapes X inactivation is the histone demethylase KDM6A [63]. It regulates histone 3 lysine 27 trimethylation (H3K27me3) and in doing so regulates gene expression [64]. Indeed, *KDM6A* was shown to be the most sexually dimorphic gene in CD4$^+$ T cells from patients with multiple sclerosis and deletion of *Kdm6a* in mice was protective in experimental autoimmune encephalitis [65].

4. Epigenetic modifications and sexual dimorphism in SLE

4.1 DNA methylation

Among all epigenetic mechanisms, DNA methylation is most widely studied in SLE [66]. Indeed, significantly lower expression of the DNA methylating enzymes, DNA methyl transferases (DNMTs), were evident in SLE patients compared to healthy control. Additional evidence for the role of methylation in SLE progression comes from studies using drugs that demethylate DNA. For example, 5-azacytidine, procainamide (DNMT inhibitor) and hydralazine (an ERK pathway signaling inhibitor) all induce SLE in rodents [67]. Changes to DNA methylation also contribute to B cell–specific abnormalities in SLE. A recent study demonstrated that resting naïve B cells are epigenetically distinct in SLE in an African American SLE cohort with high disease activity [68]. Another study demonstrated differences in B-cell DNA methylation (CpG) between African American and European American SLE patients in various development stages [69]. Specifically, epigenetic abnormalities were evident in immature B cells from African American women with SLE, whereas abnormalities developed later during B-cell development in European American women with SLE. Enrichment of CpG sites was also reported in the IFN regulated genes (IRGs) in African American patients, suggesting ethnicity as an important factor regulating DNA methylation and potentially severity in SLE [70]. Studies in SLE-prone mice also support a role for DNA methylation as being important for B-cell abnormalities in SLE. Specifically, the DNA methylases, Tet2, and Tet3, were shown to be important regulators of CD86 expression on self-reactive B cells, a mechanism that may contribute to female biased disease exacerbations. Deletion of *Tet2* and *Tet3* in B cells led to hyperactivation of B cells, autoantibody production, and lupus-like disease progression in mice [71]. All these studies indicated a prominent role of immune cell–specific epigenetic mechanisms in SLE disease development.

4.2 Histone modifications

Various type of histone acetylation and methylation regulate chromatin accessibility to transcription factors and hence control gene expression. For example, acetylation of histones on lysine promotes more open chromatin and hence enhanced promoter accessibility [72]. Methylation marks are more complex, with H3K4 trimethylation (me3) promoting recruitment of open chromatin remodeling complexes, such as the NURF complex. In contrast, H3K27me3 and H3K9me3 mediate transcriptional silencing [73]. Sex differences in histone modifications have been associated with differences in learning and memory between males and females [74]. Sexual dimorphism in the immune transcriptome has been suggested to be at the level of chromatin accessibility and regulated by type I IFN, suggesting potential sex differences in epigenetic remodeling may also underpin immune responses and potentially female-driven diseases such as SLE [75]. Indeed, KDM6A, a histone demethylase specific for H3K27me3, is an X-linked gene, with interesting implications

for female-driven disease [76]. Indeed, both acetylation and methylation have been implicated in T-cell dysregulation and SLE pathogenesis by modulating immune-related gene expression. Hypomethylation of H3K27 positively corelated disease development whereas hypoacetylation of H3 was negatively associated with disease development [77]. $CD4^+$ T cells from SLE patients have been reported to have decreased histone acetylation and histone H3K9 methylation. The *IL17* gene cluster in SLE patient T cells was shown to have increased H3K18ac and reduced levels of H3K27me3 leading to uncontrolled expression of IL-17A [78]. On the contrary, the *IL2* gene, which promotes immature T-cell differentiation into its effector phenotype, was found to be silent due to reduced histone acetylation and increased histone H3K9 methylation [79]. Another study demonstrated that in T cells from SLE patients, increased expression of *IL10* (which correlates with the high disease activity) occurs as a result of modified histone acetylation and DNA methylation [80]. All these observations suggest that altered gene expression due to inaccessibility of promoters by epigenetic modifications play a role in SLE development.

4.3 MicroRNAs and long noncoding RNA

Noncoding RNA (including miRNA and lncRNA) is found throughout the genome. However, startling differences between the X and Y chromosome exist with respect to miRNA content. Approximately 10% of all miRNAs (~120) are encoded by the X chromosome, whereas only 2 miRNAs are contained within the Y chromosome. A number of these X-linked miRNAs also regulate immune responses, suggesting a link between X-linked miRNAs and sexually dimorphic immune responses [81]. Although a link with SLE has not been described to date, X-linked miRNAs have been found to be increased in patients with rheumatoid arthritis and increased between women and men with RA [82].

Dysregulated expression of miRNAs in SLE have been described by numerous groups [83–86]. Many have multiple targets in multiple cell types, making their contribution to disease highly significant if their expression is dysregulated [86,87]. Interestingly, expression of miRNA regulates epigenetic changes in gene expression. For example, miR148a plays a role in DNA hypomethylation of SLE $CD4^+$ T cells by targeting DNMT1 and has higher expression in SLE patients than healthy individuals [88]. In contrast, miR146a negatively regulates the IFNα pathway has lower expression in SLE patients [89]. Estrogen regulation of microRNA expression has also been demonstrated with implications for SLE. For example, miR-125a is estrogen regulated, decreased in SLE and targets the inflammatory cytokine IL-16 and protects against pristane-induced lupus lung inflammation [90]. Similarly, another estrogen regulated microRNA, miR-302d, targets the transcription factor IRF9 and regulates IFN-induced gene expression in SLE [91]. Thus, the effects of sex hormones and X-linked expression on microRNA and lncRNA expression have a profound effect on gene expression with important implications for the sex bias of SLE.

5. Mitochondrial dysfunctions in SLE

Abnormal mitochondrial bioenergetics has been implicated in both animal models of SLE and human patients. For example, PBMCs from SLE patients were found to have significantly reduced mitochondrial complex-I activity compared to control [92], whereas chronic T-cell activation in SLE resulted into increased mitochondrial ATP production [93]. T cells from SLE-prone mice displayed markedly increased energy production via activation of both OXPHOS and glycolysis compared to healthy control mice and that inhibition of metabolism using metformin or 2-deoxyglucose could reverse disease activity [94]. These results suggest that alteration in mitochondrial function play a pivotal role in SLE development. Since SLE is a sex-biased disease, alteration of mitochondrial function may occur in a sex-biased manner, which ultimately affects disease phenotype [95,96]. Recent studies indicated that mitochondrial functions such as calcium uptake, ROS generation, and quality control are influenced by sex [97]. For example, ATP levels and mitochondrial content are higher in PBMCs from female blood compared to males [98]. Recent evidence also indicates that estrogen may exert substantial effects on mitochondrial function which in turn may influence female-specific immune cell function and disease phenotype [99]. For example, estrogen regulates (i) mitochondrial ATP and ROS production, (ii) mitochondrial calcium abundance, and (iii) activation of mitochondrial retrograde signaling [100,101], suggesting abnormal estrogen responses in SLE may have profound effect on mitochondrial function. Also, given the important role mitochondrial metabolites such as acetyl Co-A and α-ketoglutarate play in regulating histone modification, it will be interesting to study how these mitochondrial changes relate to epigenetic modifications and potentially contribute to sex bias in SLE.

6. Outlook

Understanding the molecular mechanisms regulating sexual dimorphism in immune responses is essential for the understanding of the female bias in SLE and how we might utilize this information to develop new therapies. Epigenetic studies in T and B cells from SLE patients have greatly enhanced our understanding of the role of these processes in regulating these cells in this disease. Identification of sex and cell type–specific epigenetic modifications, their downstream cellular pathways and how they impact IFN-driven immune responses in the context of SLE will be important in helping us understand the triggers contributing to disease susceptibility. IFN signaling may also be an important contributing factor for female-specific disease exacerbations by modulating cellular and mitochondrial pathways through a sex hormone dependent manner. Given the role that mitochondrial metabolites play in regulating epigenetic regulation of gene expression, it is intriguing to speculate that chronic IFN signaling may alter these pathways in specific cell types and contribute to disease pathology. Indeed, given the growing interest in immunometabolism in disease, understanding sex differences in how these pathways are regulated in specific immune cells will be important, particularly as drugs targeting metabolic pathways are currently being evaluated for various disease, including SLE. Similarly, environmental factors such as diet, drugs, or nutrition and the microbiome may also influence epigenetics and the expression of silenced genes in the inactive X chromosome [102]. Further experimental evidence is required to understand the role of environmental factors in driving autoimmune pathology in SLE and whether these responses are sexually dimorphic.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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