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Sex Differences in monocytes and TLR4 associated immune responses; implications for systemic lupus erythematosus (SLE)

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Abstract

It has been shown that TLR7 and TLR9 signaling play a role in SLE pathogenesis. Our recent study revealed that estrogen receptor α knockout mice have impaired inflammatory responses to TLR3, TLR4, TLR7 and TLR9 ligand stimulation in DCs, B cells and whole spleen cells. These findings indicate that estrogen receptor mediated signaling may impact universal TLR responsiveness. Whether estrogen has a direct or indirect effect on TLR responsiveness by immune cells is not clear. There is evidence of a role of TLR4 in SLE disease pathogenesis, such as the kidney damage, the induction of CD40 and autoantibodies, the suppression of regulatory T cells, and the role of pro-inflammatory cytokines (e.g., IL-6, IL-1β, TNF-α) in SLE pathogenesis that can be induced by TLR4-mediated monocyte activation, suggesting that TLR4 and TLR4 responsiveness are also important for SLE disease. This review will focus on TLR4 responses and monocytes, which are understudied in systemic autoimmune diseases such as SLE.

Keywords

Toll-like receptor; monocytes; sex; autoimmunity; SLE

Women exhibit stronger cellular-mediated and humoral-mediated immune responses compared to men, and a higher risk of autoimmune disease [1]. The ratio of female to male disease prevalence of systemic lupus erythematosus (SLE), for example, is 9:1 [2]. Although several mechanisms, such as Toll-like receptor (TLR) 7 expression, activity of T regulatory cells, or genetic and environmental factors [1–10], could account for heightened immune responses and increased incidences of autoimmune disease in women, the exact mechanisms are not fully understood. Though sex chromosomes partially account for the sex differences in autoimmune diseases; sex hormones and their receptors are also a likely major determinant as the onset of SLE most often occurs in women at the age of child-bearing potential [11].

In the periphery, human B cells express estrogen receptor β, while plasmacytoid dendritic cells (pDCs) and CD4 T cells express estrogen receptor α. CD8 T cells and monocytes

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express low to undetectable levels of estrogen receptors [12]. Studies from Guery's group [13] showed that pDCs from premenopausal women have heightened responses to TLRs compared to men, while pDCs from postmenopausal women do not. Adding estrogen *in vitro* to pDC cultures had no effect on TLR7 responses. When postmenopausal women were given estrogen replacement, their pDCs had responses similar to premenopausal women. Again, *in vitro* addition of estrogen had no effect. These effects were mediated via ERα and were pDC centric, and indicate that the effect of estrogen on TLR responses of pDCs from women is via an indirect mechanism [13]. Our previous study showed that TLR3, TLR4, TLR7 and TLR9 responsiveness was decreased in immune cells from estrogen receptor α knockout mice [14], suggesting that not only TLR7 responsiveness, but other TLR responsiveness is modified by estrogen receptor signaling. But whether estrogen has a direct effect on TLR responsiveness in peripheral lymphocytes is not clear. Dendritic cells (DCs), especially pDCs produce a large amount of IFN-α in response to TLR7 and TLR9 ligands, which play an important role in the pathogenesis of SLE disease [15,16]. pDCs produce more IFN-α in women than men in response to TLR7 ligands, perhaps due to TLR7 being located on the X chromosome with variable expression of TLR7 between men and women leading to variable responsiveness [8,17]. The universal heightened TLR7 responsiveness in women versus men would argue against variable TLR7 expression in individual women being the proximate mechanism. To expand the scope of sex differences in TLR responsiveness beyond TLR7 and dendritic cells, this review will focus on sex differences in TLR4 responsiveness and monocyte populations in healthy individuals and patients with SLE.

Monocytes

Human monocytes represent 5–10% of peripheral blood mononuclear cells (PBMCs) and are progenitors of macrophages and DCs [18–20]. They express high levels of TLR1, TLR2 and TLR4 compared to lymphocytes [21], and produce pro-inflammatory cytokines (e.g., IL-6, TNF-α, IL-1β) triggered through TLR activation [16]. Little is known about the effect of sex hormones on the modulation of monocyte activation, maturation, subset differentiation, and antigen-presentation function. Previous studies showed increased total monocyte numbers in the periphery in the luteal phase compared to the follicular phase in women [22]. The data on estrogen receptor expression on monocytes is controversial [12,23–26]. Progesterone and testosterone receptors are not expressed in monocytes.

Monocyte subsets

Monocytes can be defined into two subsets (CD14+CD16+, CD14+CD16−) or three subsets (CD14++CD16−, CD14++CD16+, CD14+CD16++) as identified recently [27–31]. CD14++CD16− classic monocytes produce IL-10; and CD16-expressing non-classic monocytes (either intermediate or non-classical subset) produce TNF-α, IL-6 and IL-1β in response to a variety of TLR ligands [32,33]. The non-classic monocyte subset (CD14+CD16++) expresses a unique pattern of chemokine receptors and produces pro-inflammatory cytokines, and plays a role in cardiovascular risk in chronic kidney disease [31]. Moreover, these cells have distinct effector responses to virus and immune complexes containing nucleic acids, via a TLR7 or TLR8 pathway [29]. Virus and certain pro-inflammatory

cytokines (e.g., type I IFN) have the function of regulating the expression of CD16 on monocytes [29,34,35]. Elevated levels of CD16-expressing monocytes are seen in blood during inflammatory conditions, such as HIV disease, atherosclerosis [27,30,36], sepsis [37], rheumatoid arthritis, SLE [38–40], and cancer [41], suggesting that inflammation (including microbial TLR ligands) promotes monocyte differentiation into a CD16-expressing subset *in vivo*. CD16 expression on monocytes can be regulated by estradiol *in vitro*, but the results are controversial [42,43].

Monocyte activation and maturation

LPS activates and promotes maturation of monocytes [44,45]. After activation and maturation, monocytes increase expression of CD80, CD40, CD86 and HLA-DR, secrete pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β and sCD14), and change their ability for phagocytosis and antigen presenting and processing function [44,45]. These cells can differentiate to macrophages and DCs under certain conditions [46–48]. DCs are professional antigen presenting cells due to their ability to prime naïve T cells and cross present to CD8 T cells [49,50]. On the other hand, monocytes, as another type of antigen-presenting cells, account for 5–10% of cells in the peripheral blood, compared to 1% of DCs. Although less ability to present antigens to T cells compared to DCs, monocytes are important in antigen presentation overall due to their large number in the periphery and their roles as DC progenitors.

Monocytes in SLE

An increased number of monocytes and increased activation of monocytes are present in the periphery in SLE patients compared to controls [51]. Monocytes spontaneously release pro-inflammatory cytokines such as IL-6 and are a predominant source of IL-6 in SLE [52]. CD16+DR++ monocytes are also the major source of TNFα in response to TLR stimulation [33]. Treatments targeting such pro-inflammatory cytokines (e.g., TNFα, IL-6 and IL-1β) are effective in animal models of SLE and patients with SLE [53–56]. These results suggest that monocytes are activated *in vivo*, produce pro-inflammatory cytokines (e.g., IL-6), and play a key role in chronic inflammation and disease pathogenesis in SLE [57]. Moreover, LPS also may account for kidney damage in SLE disease [58,59]. Therefore, there may be a link between TLR4 signaling, LPS-mediated monocyte activation, subset differentiation, and SLE pathogenesis. An elevated plasma level of soluble CD14, which is released by monocytes in response to LPS, is present in SLE patients [60]. Our previous work indicated that TLR9 ligands, bacterial CpG ODNs, induce monocytes to express CD80, CD86, CD40 and HLA-DR, and drive monocytes to be better antigen-presenting cells; this effect is through type I IFN [61]. Moreover, *in vitro* IFN-α induces monocyte activation as measured by expression of CD80, CD86, CD40 and HLA-DR [61]. Levels of IFN-α are elevated and involved in the pathogenesis of SLE [62]. *In vitro*, these monocytes have impaired ability to up-regulate CD80 and CD86 expression following stimuli such as IFN-γ, [51,63], suggesting that *in vivo* monocytes in SLE are pre-activated. Therefore they may be desensitized to be activated again *in vitro*. Moreover, Fc gamma receptor genes, associated with monocyte activation, partially account for the underlying immune mechanisms resulting in SLE [64–69]. Patients with SLE have increased levels of pro-inflammatory

cytokines in plasma, implying that heightened levels of innate immune responses, including TLR signaling, may contribute to the etiology and pathogenesis in SLE.

TLRs

TLRs play an important role in innate immunity and recognize pathogens through pathogen associated molecular patterns (PAMPs). In the periphery, antigen-presenting cells (monocytes/macrophages, DCs and B cells) are the predominant cell populations to express TLRs, and directly respond to TLR ligands [16,70]. TLR signals are essensal for maintaining normal immunity, and certain TLR ligands such as CpG ODNs and imiqimod are used as vaccine adjuvants to increase vaccine-specific responses [71,72]. Cytoplasmic Toll-IL-1 receptor (TIR) domains are activated by TLR signaling pathways initially. The TLR-activated TIR domain is associated with MyD88, which recruits IL-1 receptor associated kinase (IRAK) to TLRs upon activation. MyD88 knockout mice have no response to stimulation by TLR5, TLR7 and TLR9 ligands [73–76]. These evidences indicate that the TIR domain-associated adaptor MyD88 is nessessary for these TLR mediated responses [77]. Consistently, responses to TLR2, TLR3, TLR4, and TLR9 agonists are almost abolished in IRAK-4 knockout mice [78]. There are, however, also MyD88-independent TLR signaling pathways [79]. These findings in animal models suggest that TLR signaling knockout results in immune-deficiencies, while, robust TLR-mediated hyperactivity could drive autoimmune diseases.

It is well recognized that females have heightened responses to TLR7 ligands [8,17]. Human B cells, pDCs and myeloid dendritic cells (mDCs) express TLR7, and respond to its ligands, imiquimod, HIV viral sequences, gardiquimod or loxoribine et al [21]. TLR7 signaling is involved in SLE disease largely due to its downstream cytokine IFN-α production by pDCs, resulting in higher levels of IFN-α in cells from females compared to males, and in SLE patients compared to controls [17,80–82]. TLR7, TLR8 and TLR9 signaling pathways in pDCs in SLE are extensively studied, and treatment with inhibitors against TLR7/8 and TLR9 are in Phase I trials in patients with SLE [83–86].

TLR4 expression and responsiveness

In the periphery, human monocytes express the highest TLR4 levels of PBMCs. MDCs are the other cell type to express TLR4; both cells produce pro-inflammatory cytokines such as IL-1β, TNF-α or IL-6 in response to the TLR4 ligand LPS [21,87,88]. Human pDCs, B cells, T cells, and NK cells do not express TLR4, and do not directly respond to its ligand LPS [21]. TLR4 knockout or mutations in mice exhibit defects in responses to LPS, including pro-inflammatory cytokine production, susceptibility to bacterial infections, tissue injury induced ischemia, myocardial infarction, neuro-degeneration, and cancer related immunities [77,89–95].

Sex differences in TLR4 responsiveness in monocytes are listed as follows: TNF-α

Monocytes from males produce higher levels of TNF-α in response to LPS compared to females [96–99]. However, the results from *in vitro* experiments are conflicting [96,97,99–102]. IL-1β. There are increased plasma levels of IL-1β and LPS-induced IL-1β-producing monocytes in the luteal phase compared to the follicular phase [25,103,104]. IL-12. LPS induced IL-12 production by monocytes was higher in men compared to women, but similar in women in luteal phase versus follicular phase [25,96], suggesting that androgens may affect IL-12 production by monocytes through TLR4. IL-6. Results related to sex differences in IL-6 production in response to LPS in controls and patients with SLE are conflicting [102,105–109]. Aulock's group reported that TNFα, IL-1β, IL-6 and IL-8 production by monocytes in response to LPS was similar or less in women compared to men [99]. Conflicting data were also reported whether estrogen/progesterone affect cytokine production by LPS-stimulated monocytes in humans [96]. The sex differences in monocyte activation and maturation may include both differences in quantity and quality (e.g., genetic factors). It is difficult to draw a conclusion on sex differences in TLR4 responsiveness in monocytes; nevertheless, women seemingly have a reduced TLR4 responsiveness to LPS in monocytes *in vitro*. This could be due to pre-activation and desensitization in monocytes in women, or due to sex differences in TLR expression and signaling responses in monocytes.

The responses to the TLR4 ligand LPS involve the LPS binding protein (LBP), HDL particles, MD2, TLR4 and soluble CD14 [110–113]. Peripheral LPS is mainly cleared in the liver [114]; LBP transfers LPS to HDL particles, which leads to sequestration of LPS-induced responses [112,115]. A previous study showed that plasma sCD14 also plays a role in the inactivation of LPS-induced host responses [110]. There is no clear evidence of a sex difference in TLR4 expression on monocytes. Although these results were not always consistent, as we stated in the last paragraph, *in vivo* the levels of several cytokines and *in vitro* monocyte responses to LPS are different based on female menstrual cycles, suggesting that there is an effect of sex hormones on TLR4 responses and monocytes *in vivo*. However, it is not clear *in vitro* whether monocytes have a direct response to estrogen.

Several mechanisms could be accounting for the effect of estrogen on TLR4 effects, including direct effects through levels of estrogen and estrogen receptors, and indirect effects through sex mediated differences in cytokine patterns. TLR4-responding cells may express estrogen receptors and directly respond to estrogen. As a result, estrogen activation may change TLR expression or signaling transduction at the single cell level. In contrast, TLR-responding cells may not express estrogen receptors. Their response to estrogen is through indirect activation by estrogen-responsive cells. For example, pDCs express ERα and TLR7/TLR9. Estrogen increased TLR7 or TLR9-mediated IFNα production in pDCs, but there is no evidence that this is a direct response of pDCs to estrogen [116].

TLR4 responsiveness in SLE

TLR4 responses play a role in SLE pathogenesis in murine models [117–120]; the potential mechanisms include TLR4-mediated suppression of regulatory T cells [121], induction of

CD40 expression on antigen-presenting cells [122], and induction of autoantibodies [123]. There is no reported difference in the TLR4 expression in PBMCs from controls and SLE patients [124]. Monocytes spontaneously secrete TNF-α or IL-6 in SLE disease [57]. *In vivo*, plasma levels of IL-6, IL-10 and TNF-α are elevated in SLE patients compared to controls. Moreover, SLE is associated with increased numbers of monocytes in the periphery, increased expression of Fc receptors, increased levels of IgG production, decreased function of phagocytes in response to LPS, and increased levels of soluble CD14 and LBP [60,125–128]. LPS has a reported pathogenic role in SLE pathogenesis [58,117,129]. *In vitro*, IL-1β and IL-6 production by monocytes from SLE patients in response to LPS is reduced regardless of disease activity, but TNF-α production remains the same in monocytes compared to controls [57,130]. In murine macrophages, TLR4 expression and pro-inflammatory cytokine production are decreased after removal of endogenous estrogens, and exogenous replacement of 17β-estradiol reverses this effect [131]. Moreover, treatment with low dose steroids or chloroquine did not have a significant effect on TLR4 expression and signaling activation. High dose corticosteroids decrease cytokine production (TNF-α and IL-6) in response to LPS [57,124]. These results suggest that monocytes from SLE are activated, release pro-inflammatory cytokines, and contribute to disease pathogenesis, especially at target tissue sites (e.g., kidney) [58,117,129].

TLR4 responsiveness and monocyte activation in other autoimmune diseases

TLR4 responsiveness is reported to play a role in the pathogenesis of other autoimmune diseases besides SLE including coxsackievirus-induced autoimmune myocarditis [132] collagen-induced arthritis [133], primary biliary cirrhosis [134], experimental autoimmune uveitis (EAU) [135], antibody-mediated glomerulonephritis [136] and autoimmune destructive arthritis [137]. However, most data were in mice; data in humans are largely lacking. Furthermore, the subset of CD14+/CD16+ blood monocytes is expanded in autoimmune diseases such as rheumatoid arthritis, [38], and plays a role in the pathogenesis of experimental autoimmune encephalomyelitis (EAE) [138]. Importantly, TLR4 downstream pro-inflammatory cytokines such as IL-1β, TNF-α and IL-6 are key mediators in several autoimmune diseases [139–142] besides SLE. Therefore, TLR4 signaling is involved in the pathogenesis of several autoimmune diseases, and needs to be studied further.

Genetic predisposition in SLE

There are variant genes associated with the etiology and pathogenesis of SLE, including antigen presentation molecules (HLA-DQ, HLA-DR alleles) [143,144], complement related genes (C1q, C2 and C4) [145–148], Fc gamma receptors (CD64, CD32 and CD16), [64–69], the programmed cell death 1 gene (PDD1) [149–151], IFN and TNF related genes [152–154], and the C-reactive protein (CRP) gene [155,156].

Female cells carry both maternal and paternal X chromosomes, whereas male cells carry only the maternal X chromosome. The inactivation of X chromosomes is not random. However, roughly 16% of healthy females aged 50 or older are shown to have a skewed X-

chromosome inactivation [157,158]. Furthermore, certain frequencies of X-linked genes are known to escape inactivation, and express both alleles on the X chromosomes [159–161]. It is possible that perturbation in X-chromosome inactivation results in the breakdown of tolerance and the induction of autoimmunity.

Anti-estrogen treatment in SLE

In female (NZB × NZW) F1 and MRLlpr/lpr mice, anti-estrogen had beneficial effects on experimental SLE, including reduction of anti-DNA production and immune complex–mediated glomerulonephritis, and prolonged survival [162–164]. Clearly, estrogen treatment in mice not only enhances disease progression but also drives increased serum anti-dsDNA antibody titers [162,163,165]. However, in SLE patients, treatment with anti-estrogens, has led to mixed responses [165–168]. Treatment of female lupus patients with estrogen containing birth control pills premenopausal or use of hormone replacement therapy post menopausal had minimal to no effect on disease. There is no evidence that use of estrogens increases the risk for developing lupus.

Summary

The subset of CD14+/CD16+ blood monocytes is expanded in sepsis patients, and also elevated in SLE. This subset of monocytes is a major source of pro-inflammatory cytokines such as TNF-α. Data in mice indicate that LPS and TLR4 play a role in mediating autoimmunity, pro-inflammatory cytokine production, and other immune activation. Sex hormones impact TLR4-associated innate immune responses in monocytes in healthy individuals and in patients with SLE (Figure 1). In our model, sex hormones (e.g., estrogen) could directly activate or indirectly activate monocytes, and change TLR4 responsiveness in monocytes through several mechanisms, such as sex hormone associated changes in the levels of TLR4 ligands, TLR4 expression, TLR4 signaling pathway, and LPS-TLR4 interaction cofactors (Figure 1). Monocytes in SLE patients are activated and produce pro-inflammatory cytokines. Importantly, TLR4-mediated pro-inflammatory cytokines (e.g., IL-6, IL-1β and TNF-α) are increased and play an important role in the etiology and pathogenesis of SLE [169]. Treatments targeting these cytokines or specific TLRs are at least partially effective in animal models of SLE and are in clinical trials in patients with SLE [15,170]. Therefore, further therapeutic strategies should not only focus on TLR7/8 and TLR9 signaling, but also should investigate the contribution of TLR4 signaling in lupus pathogenesis and sex differences in the prevalence of autoimmune diseases.

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Abbreviations

TLR	Toll-like receptor
TIR	Toll/IL-1 receptor

ERα	Estrogen receptor alpha
SLE	systemic lupus erythematosis
pDCs	plasmacytoid dendritic cells
IFN-α	Interferon alpha
PAMPs	pathogen associated molecular patterns
PBMCs	peripheral blood mononuclear cells

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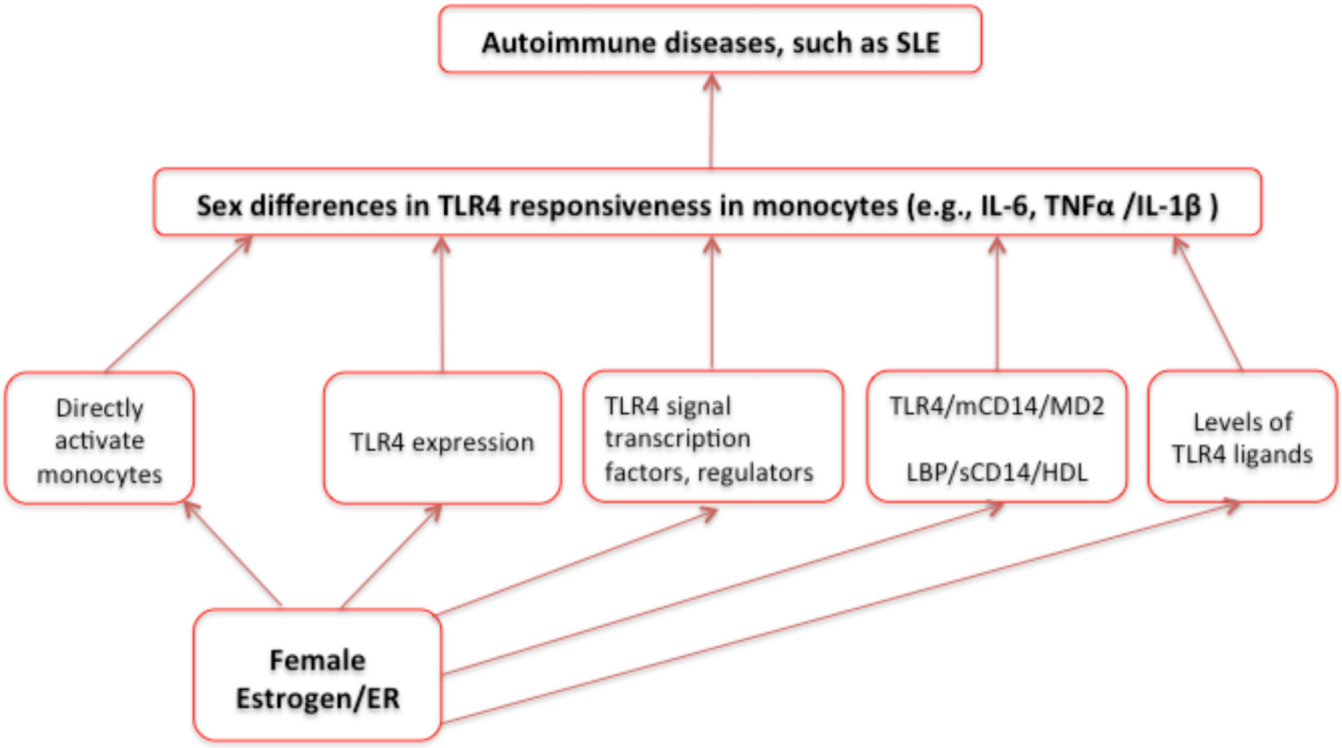

Figure 1. A model of sex differences in monocytes and TLR4 responsiveness

The effect of sex hormones (e.g., estrogen) on TLR4 responsiveness and monocyte activation could be through direct activation of monocytes, or through indirect activation of monocytes. These actions include estrogen effects on TLR4 expression, TLR4 signaling pathways, LPS interaction cofactors (e.g., TLR4, CD14, MD2 and LBP), and levels of TLR4 ligands. As a consequence of monocyte activation and altered TLR4 responsiveness, there are increased levels of downstream pro-inflammatory cytokines (e.g, TNFα, IL-1β and IL-6), which play a role in autoimmune diseases such as SLE.