Abstract

The etiology of SLE is not clearly understood but strong genetic predisposition has been recognized. Environmental and hormonal factors are known to contribute towards the expression of the disease. Among the above risk factors, female gender is considered to be of greatest significance. Thus estrogens and their receptors have been proposed as obvious candidates to explain this sexual dimorphism.

The present review summarizes our experience, as well as previously reported data in literature about the involvement of estrogen, estrogen receptor-α and ESR1 genetic variants in the pathogenesis of SLE, its clinical manifestations and outcome.

Keywords: Estrogen; Estrogen Receptor-α; ESR1 polymorphisms; Systemic lupus erythematosus

1. Introduction

The etiology of SLE is not clearly understood but strong genetic predisposition has been recognized. Environmental and hormonal factors are known to contribute towards the expression of the disease. Among the above risk factors, female gender is considered to be of greatest significance (Cervera et al., 1993). The observed female prevalence is highest after puberty. The pre-puberty female to male ratio is 3:1. It increases to 10:1 during the childbearing years and decreases again to 8:1 after menopause. Thus estrogens and their receptors have been proposed as obvious candidates to explain this sexual dimorphism (Lahita, 1999).
2. Role of Estrogen in Autoimmunity

The typical physiological level of estrogen (E2) is extremely low, in the range of 10–900 pg/ml, and it varies during the age and the physiological status of the individual (Neill, 2005). E2 can produce different effects depending on its concentration but also on the type of target cell, the receptor subtype present on a given cell type, and the timing of administration. During pregnancy E2 inhibits pro-inflammatory pathways such as TNF-α, IL-1β, IL-6, and the activity of natural killer (NK) cells, whereas E2 at the same concentration stimulates anti-inflammatory pathways such as IL-4, IL-10, and TGF-β (Straub, 2007). Thus E2 can influence the Th1, Th2 and Th17 responses which regulation is thought to play a key role in the induction of autoimmune diseases. E2 is also a potential physiological regulatory factor for the peripheral development of CD4+CD25+ Treg cells. E2, at physiological doses, stimulates the conversion of CD4+CD25− T cells into CD4+CD25+ T cells which exhibits enhanced Foxp3 and IL-10 expression in vitro. Such converted CD4+CD25+ T cells have similar regulatory function as naturally occurring Treg cells, as demonstrated by their ability to suppress naïve T cell proliferation in a mixed lymphocyte reaction. The estrogen receptor (ER) was found expressed in the CD4+CD25− T cells and the conversion of CD4+CD25+ T cells into CD4+CD25+ T cells, which is stimulated by E2, could be inhibited by ICI182,780, a specific inhibitor of the estrogen receptors. This supports that E2 may directly act on CD4+CD25− T cells via ER(s) (Tai et al., 2008). At lower concentrations, E2 stimulates TNF-α, IFN-γ, IL-1β, and the activity of the NK cells (Straub, 2007).

3. Animal Models of SLE – Role of Estrogen and Estrogen Receptor-α

Recent studies of anti-DNA antibody transgenic mice clearly demonstrated that an elevation in either estrogen or prolactin breaks tolerance of high affinity DNA-reactive B cells and induces a lupus phenotype (Grimaldi, 2006). It was proved that the induction of the lupus phenotype by estrogen is performed via an estrogen receptor-α-dependent pathway (Feng et al., 2010). The role of ER-α in lupus-like disease has been suggested by different studies carried out on animal models. A study in (NZBxNZW)F1 mice that utilized ER-α-selective and ER-β-selective agonists indicated that the ER-α activation plays an immunostimulatory role in murine lupus, whereas the ER-β activation has mild immunosuppressive effects (Li et al., 2007). The key role of ER-α, but not ER-β, in the pathogenesis of lupus was further confirmed in experiments with ER-α−/− NZM2410 and ER-α−/− MRL/lpr lupus prone mice. ERα-deficient mice manifested significantly less pathologic renal disease and proteinuria and had significantly prolonged survival compared to wild-type mice (Svenson et al., 2008). It was shown that the inflammatory response to toll like receptor (TLR) ligands was significantly impacted by the presence of ER-α despite the absence of estradiol, and may partially explain the protective effect of ER-α deficiency in lupus-prone animals (Cunningham et al., 2012).
4. Role of Estrogen in SLE Patients

There is evidence that E2 plays a role in SLE by altering the thresholds for B cell apoptosis and activation. Earlier it was shown that E2 may polyclonally increase the production of IgG, including IgG anti-dsDNA, in SLE patients' peripheral blood mononuclear cells by enhancing B cell activity and by promoting IL-10 production in monocytes (Kanda et al., 1999). Increased levels of estrogen were reported in men with autoimmune disease including SLE (Doukas et al., 2013). There are data to support the role of sex hormones as a trigger for the disease and a modulator of the disease severity (Cohen-Solal et al., 2008). Hyper estrogenic levels in premenopausal SLE women are associated with increased risk of cardiovascular manifestations (Kaliterna et al., 2014). The role of the hormones in the pathogenesis of the disease has been further clarified by Bernier et al. (2009) who demonstrated that the use of combined oral contraceptives was associated with an increased risk of SLE. The risk was particularly elevated in women who have recently started the contraceptive use. It was also reported that the use of oral contraceptives and the use of hormonal replacement therapy increase the chance of venous thromboembolism in SLE patients, especially in those with antiphospholipid antibodies (Mok et al., 2001). Physicians generally do not prescribe hormone replacement therapy to women with SLE because of the widely held view that such treatment can activate SLE. Safety of Estrogens in Lupus Erythematosus - National Assessment (SELENA) is a body which aims to clarify that issue and set adequate treatment criteria (Furie et al., 2014; Thanou et al., 2014).

5. Role of Estrogen Receptor-α in SLE Patients

Estrogen acts through two nuclear receptors—estrogen receptor-α (ER-α) and estrogen receptor-β (ER-β). ER-α is mainly expressed in uterus, prostate (stroma), ovary (theca cells), epididymis, bone, breast, and various regions of the brain, liver and white adipose tissue. ER-β is expressed in colon, prostate (epithelium), ovary (granulosa cells), bone marrow, salivary gland, vascular endothelium and certain regions of the brain. Furthermore, in some tissues, both ERs are expressed albeit in different cell types. The expression of the ERα gene (ESR1) and its protein (ERα) in lupus patients was significantly higher than in healthy controls. The enhanced expression of ERα mRNA and protein in SLE was associated with DNA demethylation within the proximal promoter region located between -232 and +81 base pair relative to transcription start site of human ERα gene (Liu et al., 2014).

6. ESR1 Polymorphisms and SLE

Estrogen receptor-α (ER-α) is coded by ESR1 gene, located on chromosomes 6q25.1. Numerous mRNA splice variants exist for ER-α although their exact function in physiology and human diseases remains to be elucidated. The most extensively studied polymorphisms on terms of SLE are the PvuII P/p and XbaI X/x in intron 1. PvuII P and XbaI X variants were found to enhance the ER-α activity (Alonso et al., 2011; Wang et al., 2010) although these results were challenged by Maruyama et al. (2000). A recent study has proved relationship between the estrogen receptor ESR1 PvuII and XbaI polymorphisms and the Th1 and Th2 cytokine expression in patients with SLE.
According to the results, the polymorphisms are associated with an alteration in the Th-1/Th-2 balance in favor of Th-2, increasing the susceptibility to SLE. The findings also indicated that ER-α gene polymorphisms could influence the expression of IL-10, IL-4, IL-2 and IFN-γ in SLE, with the Th-2 cell being predominant in patients with PpXx and Ppxx genotypes (Lu et al., 2009).

An association between the PvuII P/p and XbaI X/x polymorphisms and SLE has been reported in several studies concerning Asian population (Liu et al., 2010; Li et al., 2008; Thorburn et al., 2006; Lee et al., 2004; Liu et al., 2002, Liu et al., 2000) but most of the studies concerning Europeans have not found any (Kamenarska et al., 2012; Tanev et al., 2011; Thorburn et al., 2006; Johansson et al., 2005). The incompatibility in the results especially those, concerning the allele and genotype distribution among patients and controls might be due to racial, ethnical or gender variation as well as illness classification. It was proved that ethnic variation plays a major role in genetic regulation of estrogen or estrogen receptor activity and related polymorphism to individual diseases (Hsieh et al, 2007).

Some authors support the idea that ESR1 polymorphisms are not associated with the disease susceptibility but they rather have a disease modifying role associated with the clinical features and laboratory manifestations.

The ESR1 polymorphisms have been related to disease onset (Liu et al., 2010, Johansson et al., 2005, Kassi et al., 2005, Lee et al., 2004). Skin rashes were found more common in patients with the dominant X (Kamenarska et al., 2012) and P alleles (Johansson et al., 2005) and in patients with PpXx genotype (Liu et al., 2002). The P allele and the PPXX genotype appeared associated with photosensitivity (Tanev et al., 2011; Johansson et al., 2005) which is tightly linked to skin rashes. The frequency of hematological abnormalities, hypertension, capillary thrombi and glomerular sclerosis was higher in patients with ppfx genotype (Liu et al., 2002). The neurological disease was higher in patients with ppfx (Tanev et al., 2011), pp and xx genotype (Johansson et al., 2005) and p allele (Kisiel et al., 2011).

More detailed information concerning the association of ESR1 polymorphisms with the susceptibility and the clinical manifestations of SLE could be found in Table 1.

**Table 1 Summary of association studies of ESR1 polymorphisms with SLE**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>SLE/Controls</th>
<th>Polymorphisms</th>
<th>Clinical feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kamenarska et al., 2012</td>
<td>Bulgarian</td>
<td>45/69</td>
<td>PvuII, XbaI (intron 1)</td>
<td>No association with lupus nephritis. Association of X with malar rash and of X, P, XX+Xx and PP+Pp with hematological disease.</td>
</tr>
<tr>
<td>Tanev et al., 2011</td>
<td>Bulgarian, female</td>
<td>112/50</td>
<td>PvuII, XbaI</td>
<td>No association with SLE. No association with disease on-set and duration. Association of</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Sample Size</td>
<td>Genotypes</td>
<td>Case/Control</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>------------------</td>
<td>-------------</td>
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<td>--------------</td>
</tr>
<tr>
<td>Kisiel et al., 2011</td>
<td>Polish</td>
<td>84 j/ 112a/1001</td>
<td>Pvull</td>
<td>PPXX</td>
</tr>
<tr>
<td>Liu et al., 2010</td>
<td>Chinese Han, female</td>
<td>95/100</td>
<td>Pvull, Xbal</td>
<td>P</td>
</tr>
<tr>
<td>Wang et al., 2010</td>
<td>American, female</td>
<td>46/102</td>
<td>Pvull, Xbal, GT repeat</td>
<td>P</td>
</tr>
<tr>
<td>Lu et al., 2009</td>
<td>Chinese, female</td>
<td>221/157</td>
<td>Pvull, Xbal</td>
<td>P</td>
</tr>
<tr>
<td>Li et al., 2008</td>
<td>Chinese, female</td>
<td>70/200</td>
<td>Pvull, Xbal</td>
<td>P</td>
</tr>
<tr>
<td>Thorburn et al., 2006</td>
<td>Asian Caucasian Hispanic African American</td>
<td>633/656</td>
<td>Pvull, Xbal, rs2228480 (594G/A exon 8), rs3841686 (T deletion in intron 5), rs313874 (T deletion in intron 3), rs313874 (TA repeat, S-short, x-y – long, promoter)</td>
<td>P, PP, Pp, X, SPX and SP with lupus nephritis in Asians.</td>
</tr>
<tr>
<td>Kassi et al., 2005</td>
<td>Greek, female</td>
<td>36/38</td>
<td>rs2228480 (594G/A exon 8)</td>
<td>P</td>
</tr>
</tbody>
</table>
The fundamental studies aiming to clarify the role of ER-α and E2 in SLE were carried out mostly in animal models. There are data which support a role of ER-α in E2-induced autoimmunity in lupus-prone mice, but the results and conclusions may not necessarily be applicable to the development of lupus in humans. Evidently more studies concerning SLE in humans are needed till the data finds application into clinical practice.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Ethnicity</th>
<th>Sample Size</th>
<th>Genotype</th>
<th>Phenotypic Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al., 2004</td>
<td>Korean, female</td>
<td>137/268</td>
<td>PvuII, XbaI</td>
<td>Association of PP with late onset. Association of Xx and ppXx with early onset.</td>
</tr>
<tr>
<td>Kassi et al., 2001</td>
<td>Greek, female</td>
<td>19/11</td>
<td>Sequencing of exon 1 and 2</td>
<td>No association with SLE.</td>
</tr>
</tbody>
</table>

The fundamental studies aiming to clarify the role of ER-α and E2 in SLE were carried out mostly in animal models. There are data which support a role of ER-α in E2-induced autoimmunity in lupus-prone mice, but the results and conclusions may not necessarily be applicable to the development of lupus in humans. Evidently more studies concerning SLE in humans are needed till the data finds application into clinical practice.

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