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Estrogen Impact on Autoimmunity Onset and Progression: the Paradigm of Systemic Lupus Erythematosus

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Abstract— **Autoimmune diseases (ADs) are thought to result from a combination of genetics, environmental triggers, and stochastic events. Female prevalence in ADs and the effects of sex hormones on the immune system support a role for these hormones in the pathogenesis of ADs. Systemic Lupus Erythematosus (SLE) is a prototypical AD with a significant predominance in women, and estrogen is likely to play a pathogenic role in this disease. Estrogen's primary effects are mediated by transcription activity of the intracellular estrogen receptors (ERs), ERα and ERβ, to produce genomic effects. Rapid estrogen-mediated effects (referred to as non-genomic) are triggered through the membrane-associated ER (mER) activation and are independent of transcription pathways and protein synthesis. Depending on cell type, hormone concentration, and receptor subtype, estrogens may exert both pro-inflammatory and anti-inflammatory responses. In addition to endogenous estrogens, the immune system can be targeted by natural or synthetic chemicals with estrogenic activity, i.e., the estrogenic endocrine disruptors (EEDs), which are widely found in the environment. EEDs could trigger or alter the onset and/or progression of ADs by modifying the function of immune cells. Estrogens can be also administered through medications (oral contraceptives and hormone replacement therapy). Here, we provide a review of the *in vivo* and *in vitro* effects of endogenous and exogenous estrogens on the immune system, focusing on the evidence of association between estrogen exposure and SLE.**

Index Terms—**autoimmune diseases, estrogens, estrogenic endocrine disruptors, Systemic Lupus Erythematosus, immune system, lymphocytes.**

I. INTRODUCTION

Autoimmune diseases (ADs) affect over 5% of the population of the Western countries. Of this 5%, the majority are women and ADs are considered the fourth leading cause of disability for them [1]. The multitude of susceptibility genes, immunological defects and symptoms suggests the involvement of different pathogenic pathways. Among the most prominent of these is the contribution of sex hormones [2-5]. 17β-estradiol (E2) is the most potent form of mammalian estrogenic steroids. The primary mechanism of E2 activity is mediated by the intracellular ERα and ERβ which are encoded by separate genes (ESR1 and ESR2, respectively) present on distinct chromosomes (locus 6q25.1 and locus 14q23-24.1, respectively) [6-8]. Numerous mRNA splice variants exist for both ERα and ERβ although their exact function in physiology and human diseases remains to be elucidated. At least three ERα and five ERβ isoforms have been identified [9]. The ERβ isoform receptor subtypes can trans-activate transcription only when a heterodimer with the functional ERβ1 receptor of 59 kDa is formed [10]. The ERα isoforms are 66, 46 and 36 kDa [9]. ERα and ERβ function as ligand-dependent transcription factors which directly bind to specific estrogen responsive element (ERE) present into DNA and, in turn, regulate the transcription of E2-sensitive genes. In addition, ERα and ERβ, without direct binding to DNA, regulate transcription indirectly by binding to other transcription factors, activating or inactivating the transcription of E2-dependent-ERE-devoid genes [6-8]. A variety of cellular responses to estrogens occurs rapidly, within seconds to few minutes. These rapid estrogen-mediated effects (referred to as non-genomic) are triggered through the activation of membrane-associated ER (mER) which are the same proteins as the intracellular ER, transported to the plasma membrane by unclear mechanisms [11, 12]. Previous studies in cultured cell lines point at mERα as capable of inducing cell cycle progression and preventing the apoptotic cascade via activation of the ERK/MAPK and PI3K pathways. By contrast, mERβ has been demonstrated to contribute to the occurrence of the apoptotic cascade via p38/MAPK pathway [13].

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II. ESTROGEN RECEPTORS IN IMMUNE CELLS

Intracellular ERs are expressed in all immune cell types [14, 15]. Particularly, our group has recently demonstrated the intracellular expression of both ERα and ERβ in T, B lymphocyte subsets, and peripheral NK cells [16]. The ERα46 isoform appeared to be the most represented ER in lymphocytes without significant differences among lymphocyte subsets. Although ERβ was expressed in all lymphocyte subsets, our data suggest a lower expression level of this receptor with respect to ERα46.

The typical physiological level of E2 is extremely low, in the range of 10–900 pg/ml, and it varies based on the age and physiological status of the individual (i.e., E2 levels are typically less than 100 pg/ml, but just before ovulation they spike to 800 pg/ml, and during the third trimester of pregnancy vary from 0.5 to 140 ng/ml) [17]. 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. Table I summarizes the most important effects of high and low concentrations of E2 on different types of immune cells. In brief, at pregnancy levels, E2 inhibits pro-inflammatory pathways such as TNFα, IL-1β, IL-6, and activity of natural killer (NK) cells, whereas E2 at the same concentration stimulates anti-inflammatory pathways such as IL-4, IL-10, and TGFβ [2]. Additionally, it enhances the number and function of CD4+CD25+ regulatory T cells [18, 19]. Surprisingly, no direct effect of E2 on Th17 cells or IL-17 production has been described in humans until now, whereas conflicting results have been reported in animal models where E2, at high concentrations, either enhances [20] or decreases [21] IL-17 production. At lower concentrations, E2 stimulates TNFα, IFN-γ, IL-1β, and activity of NK cells [2]. Differently, E2 stimulates antibody production by B cells throughout the concentration range [2].

Regarding cell surface expression of ERs on human lymphocytes, previously reported data, obtained using E2 covalently bound to bovine serum albumin (BSA)-FITC, indicated that an estrogen binding protein exists on the plasma membrane of human lymphoblastoid B cells [22]. More recently, by using epitope-binding technologies, we demonstrated the cell surface expression of a functionally active ERα46 isoform, but not of ERβ, on lymphocytes, supporting the idea that E2 level fluctuations may be associated with a prompt lymphocyte response [16]. In particular, E2-BSA significantly increased CD4+ and CD8+ T lymphocyte proliferation in response to anti-CD3 monoclonal antibody and IFN-γ production by NK cells. Further studies are needed to a better definition of mER expression and its signal transduction pathway in different lymphocyte subpopulations. In this regard, the development of a novel transgenic mouse in which mER-signaling is blocked [23] may be helpful to elucidate how mER signaling contributes to the transcriptional functions of intracellular ERs and could lead to identify the rapid ER signaling pathway as a potential target for novel therapeutic agents.

TABLE I
ESTROGEN EFFECTS ON IMMUNE CELLS

17β estradiol (E2) levels		
	PREGNANCY	POSTMENOPAUSAL
B lymphocytes	↑ antibodies	↑ antibodies
T lymphocytes	↑IL-4, IFN-γ, TGFβ, IL-10 ↓ TNFα	↑ TNFα, IFN-γ
Macrophages/ dendritic cells	↑ IL-10 ↓TNFα, IL-6, IL-1β	↑ IL-1β
NK cells	↓ activity	↑ activity

↑, indicates stimulation by E2, ↓ indicates inhibition by E2

III. SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Sex hormones, including estrogens, have been proposed to play an important role in autoimmunity, [14, 24-26], although the precise mechanisms by which estrogens modulate the cellular and molecular processes that govern immune homeostasis are far to be fully elucidated. A prototypic autoimmune disease is SLE which is a multifactorial and highly polymorphic systemic AD with a higher incidence in women than man [27]. Pre-menopausal women have SLE incidence rates of 9:1 when compared to age-matched males [28]. These rates decline to 5:1 after menopause. In the pre-adolescent population, where estrogen levels are more similar between genders, females have SLE with a frequency of 3:1 when compared to males.

SLE affects multiple organs, including skin, muscle, joints, and vital internal organs, such as kidneys and heart. Despite the number of studies reported so far, the etiology of SLE remains unknown. However, it is likely that the complex interaction between genetic, environmental (e.g., infectious agents, UV light, drugs), and hormonal factors promotes the immune dysfunction underlying the pathogenesis of the disease [29, 30]. SLE is characterized by autoantibody production by dysregulated B cells, target organ infiltration by inflammatory T cells, and aberrant immune cell activation due to abnormal antigen presenting cell function. The autoantigen-autoantibody interaction triggers the formation of immune complexes that, once deposited, cause tissue injury. In particular, immune complexes, containing autoantibodies against DNA and ribonucleoproteins, activate Toll like receptors (TLR)7 and TLR9 on dendritic cells and B cells, and this event leads to enhanced autoantibody production and IFN-α secretion, which is suggested to be key modulator in the pathogenesis of SLE [31].

As stated above, the incidence of SLE increases after puberty and flares are more common during the pre-menstrual period and pregnancy, time frames with increased estrogen levels. Additionally, the disease is more prevalent in some ethnic groups, such as Afro-Americans and Asians. Interestingly, estrogen levels were shown to be higher in Asian (Japanese) and African (Bantu) women than in Caucasian women [32]. This evidence implies an important role of estrogens in SLE pathogenesis but the mechanisms involved have not been fully elucidated [33, 34].

IV. ESTROGENS AND ERs IN SLE

In vitro studies revealed that lymphocytes from SLE patients exhibit an increased sensitivity to E2 [33]. A summary of *in vitro* effects of E2 on lymphocytes from SLE patients is reported in Table II. It is important to underline that all the studies described below were performed with physiological E2 concentrations. E2 *in vitro* enhanced total IgG production as well as anti-dsDNA autoantibody production in SLE patients by promoting B cell activity and by increasing IL-10 production in monocytes [35]. Autoantibodies were not secreted by B lymphocytes from healthy donors treated in the same way [35]. Additionally, mRNA expression of the T cell activation markers calcineurin and CD154 were up-regulated by E2 in SLE but not in normal T cells through both ERα and ERβ [36-39]. Calcineurin and CD154 mRNA expression was also down-regulated in SLE patients treated with the ER antagonist Fulvestrant (Faslodex) in association which a reduction of disease activity [40]. Interestingly, although E2 induced ERK phosphorylation in a wide variety of cell types, it suppressed ERK activation in activated T cells from patients with inactive or mild disease but not from patients with active disease [41]. Whether E2-dependent dampening of ERK signalling is important for maintaining inactive disease remains to be elucidated. E2 was also found to inhibits apoptosis in activated T cells, this favouring the persistence of autoreactive clones [42]. On the other hand, Rastin et al. [43] showed that E2 increased the mRNA expression level of FasL and caspase-8 in resting T lymphocytes.

More recently, E2 has been found to alter different signaling pathways in SLE T cells, that are associated with disease onset and progression, including IFN-α signaling [44]. A further potential mechanism of action of E2 in SLE pathogenesis has been suggested by Young et al. [45] who found that the signaling and transcription molecule ZAS3, which is involved in regulating inflammatory responses, was overexpressed in peripheral blood mononuclear cells (PBMC) from SLE patients and it was up-regulated by E2. E2 induction of ZAS3 requires ERα. Intriguingly, ZAS3 and E2 both target NFκB and lead to its functional repression, just as observed in SLE [46]. The expression of ER has been investigated in T cells from SLE patients to determine whether the hyper responsiveness of SLE lymphocytes to E2 could be ascribed to differences in ER levels. No alterations in the expression of ERα or ERβ (both at mRNA and protein levels) were detected in SLE [39, 47, 48], although ERα protein was found to exhibit a greater degree of variation than that in control T cells [39].

The contributions of microRNA (miRNA) to pathogenesis of SLE are beginning to be uncovered [49]. miRNAs are short (19–24 nucleotides in length) non-coding RNAs that regulate messenger RNA (mRNA) or protein levels either by promoting mRNA degradation or by attenuating protein translation. Evidence suggests that estrogens may

contribute to the gender bias in SLE modulating selected miRNA expression [50]. miR-146a, which is a negative regulator of the IFN-α pathway, and miR125a, which negatively regulates the inflammatory chemokine RANTES, were profoundly decreased in PBMC from patients with SLE as compared to healthy donors [51, 52]. Conversely, miR21 and miR148a, which contribute to DNA hypomethylation in lupus CD4+ T cells [53], were found up-regulated [54]. Notably, Dai et al. [55] observed that miR148a was up-regulated whereas miR146a and miR125a were down-regulated by E2, at least in splenocytes from estrogen-treated mice. Together, the aforementioned studies show that miR-146a, miR-125a, and miR-148A are dysregulated in SLE contributing to disease pathogenesis and estrogens regulate these miRNA expression [50].

As stated above, ERα and ERβ are encoded by the ESR1 and ESR2 genes which are both polymorphic. rs2234693 and rs4986938 are two single nucleotide polymorphisms (SNPs) whose C and A variants increase transcription of ESR1 and ESR2, respectively. Although no associations between rs2234693 genotype and SLE were found, this polymorphism has been suggested to influence the risk for particular forms of disease [56-58]. Notably, two studies performed in Asian [57] and Caucasian [58] populations reported that the T allele of rs2234693 (ESR1) was associated with early onset of SLE. Conversely, in another study, Kisiel et al. [59] reported the association of the allele C of rs2234693 (ESR1) with juvenile SLE, and they also found an association of allele A of rs4986938 (ESR2) with adult SLE. In contrast, two genome-wide association studies in SLE were published but neither reported association with the ESR1 or ESR2 variants [60, 61]. In summary, genetic variation in estrogen-related pathways might be important for SLE development, but this field needs further investigations taking into account clinical characteristics of patients.

Studies of mice models revealed that lupus also predominates in females. Moreover, ovariectomized female (NZBxNZW)F1 mice live longer and castrated males develop an accelerated autoimmune disease [62]. The role of ERα in lupus-like disease has been suggested by different studies. A study in (NZBxNZW)F1 mice that utilized ERα-selective and ERβ-selective agonists indicated that the ERα activation plays an immunostimulatory role in murine lupus, whereas the ERβ activation has mild immunosuppressive effects [63]. The key role of ERα, but not ERβ, in the pathogenesis of lupus was further confirmed in experiments with ERα −/− NZM2410 and ERα −/− 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 [64]. Since anti-dsDNA antibody levels and number and percentage of B/T cells were not significantly impacted by ERα genotype, the authors hypothesized that the primary benefit of ERα deficiency in lupus nephritis was via modulation of the innate immune response. In a subsequent study, they found that ERαKO-derived cells have a significantly reduced inflammatory response after stimulation with TLR agonists [65]. In fact, in the absence of ERα, the inflammatory response to TLR9 stimulation was significantly blunted. Additionally, ERα was required for TLR-induced stimulation of IL-23R expression, which may have paracrine and autocrine effects on T cells and dendritic cells involved in the IL-23/IL-17 inflammatory pathway [65] . In contrast, ERβ deficiency had no effect on lupus activity [64]. Overall, these data implicate the role of estrogen and ERα in the progression of lupus-like disease.

V. ESTROGEN RECEPTOR MODULATORS

A. Environmental estrogens

In addition to the endogenous estrogens, the immune system can be targeted by natural (phytoestrogens and mycoestrogens) or synthetic (xenoestrogens) compounds with estrogenic activity, i.e., the estrogenic endocrine disruptors (EEDs) [66, 67]. Xenoestrogens are widely found in plastics (e.g., bisphenol-A, BPA), detergents and surfactants (e.g., octylphenol, nonylphenol), pesticides (e.g., methoxychlor, chlordecone, and o,p'-dichlorodiphenyltrichloroethane, DDT), and industrial chemicals (e.g., 2,3,7,8-tetrachlorodibenzo-p-dioxin, TCDD). The three major classes of phytoestrogens are isoflavones, coumestans, and lignans. Genistein and daidzein are the major bioactive isoflavones, principally available in soybean and soy products. It is worthy to underline

that soy is found in up to 60% of processed food, being a food additive and a meat substitute. Food sources of coumestans (e.g., coumestrol) include clover sprouts, alfalfa sprouts, dry split peas, and other legumes [68]. Food sources of lignans include sesame seed, Brassica vegetables and olive oil. Zearalenone, produced by *Fusarium* moulds growing on damp [69], is the best characterized mycoestrogen, and it is a fungal contaminant of corn and grains.

EEDs are able to exert their effects through multiple methods of action. They have the ability to bind a variety of nuclear receptors including ERs [70]. Through these interactions, EEDs are able to alter the activity of response elements of genes, block natural hormones from binding to their receptors, or in some cases increase the activity of endogenous hormone by acting as a hormone agonist. Although they are less potent than estrogen, long-term exposure to these compounds could result in accumulation in the body fat and lead to key alterations in the immune system [67, 71]. Epidemiological evidence and studies in animal models suggest a link between EEDs exposure and increasing prevalence of ADs. In fact, by interacting and modifying the function and/or response of immune cells, EEDs could trigger, aggravate, or alter the development and/or progression of ADs. Because of the predominance of females in ADs, the role of estrogens of therapeutic sources, i.e., oral contraceptives and hormone replacement therapy, should also be taken into consideration. Here, we summarize those studies investigating the potential effects of EEDs on autoimmunity focusing on SLE (Table III). To note that these studies do not have a direct counterpart in humans, an aspect which warrants intense investigation.

Xenoestrogens

BPA is a classic example of an estrogen mimic [72, 73]. It binds as an agonist to ERβ, albeit with a much lower affinity (> 1000-fold) than E2 [74], and has been observed to have both agonist and antagonist activity at the ERα *in vitro* [75]. *In vitro* and *in vivo* data suggest that BPA displays significant effects on the immune system. For instance, BPA has been shown to increase T cell proliferation and Th1/Th2 polarization skewing T cells toward a Th2 phenotype, to increase the production of IgA and IgG2a in B cells, and to decrease number of CD4+ CD25+ regulatory T cells [72]. Studies of BPA-treated lupus mice are not definitive in their results. Short term exposure of (NZBxNZW)F1 mice to BPA suppressed autoimmunity development through a reduction of IFN-γ production, a delay in proteinuria development, and an increase in the disease-free period [76]. In a subsequent study, subcutaneous administration of BPA for 3 to 4 months promoted IgM autoantibody production by B1 cells in ovariectomized (NZBxNZW)F1 mice [77]. In contrast to BPA, organochlorine pesticides with estrogenic activity such as chlordecone, methoxychlor, and DDT were found to speed the progression of lupus in ovariectomized female (NZB × NZW)F1 mice [78]. In particular, a dose-response study conducted with chlordecone showed a dose-related early appearance of elevated anti-dsDNA IgG titres and immune complex deposition in the kidneys [78]. It is worthwhile noting that the lowest doses of methoxychlor and chlordecone used in the above mentioned study were below the oral reference dose (i.e., the maximum acceptable oral dose of a toxic substance) established by the United States Environmental Protection Agency for these compounds (for information concerning human exposure relevant doses, consult http://www.epa.gov/iris). This suggests that an effect on autoimmunity might be a sensitive toxic end point (an effect that occurs at doses lower than other adverse effects) for these compounds, and therefore of particular interest for risk assessment. Surprisingly, in a subsequent study examining the effects of exposure to high doses of DDT and TCDD in female (NZB × NZW)F1 mice, DDT did not show any effect on disease development and TCDD had marked immunosuppressive effects on murine SLE [79]. Overall, xenoestrogens, while sharing estrogen agonistic and antagonistic activities, appear to have compound- and tissue-specific effects. It is likely that variations in compound dose, administration route and exposure duration would produce different results, which require further evaluation in future works.

Phytoestrogens

Soybeans and foods containing soy have significant levels of isoflavones such as genistein and daidzein [80]. In contrast to E2, which binds ERα and ERβ with similar affinities, genistein and daidzein have greater affinity for ERβ than ERα [81]. Despite the limited estrogenic potency of these compounds,

their high levels in humans under certain nutritional conditions could induce significant biological effects. Although an extensive literature showed that genistein exerts a dose dependent suppression of both humoral and cell-mediated immune responses, other studies reported that genistein or other phytoestrogens stimulate various aspects of immune function [81, 82]. In autoimmune prone MRL/Mp-lpr/lpr (MRL/lpr) mice, a soy diet (20% soybean protein and 5% soybean oil) was found to exacerbate renal damage, leading to accelerated proteinuria, elevated serum creatinine, reduced creatinine clearance, and increased glomerular disease severity [83]. In contrast, a study by Hong et al. [84] showed that dietary supplementation of soy isoflavones decreased serum anti-dsDNA IgG and anticardiolipin IgG levels, decreased IFN-γ secretion from stimulated T cells, and prolonged life span in MRL/lpr mice. Similarly, alfalfa sprout ethyl acetate extract prolonged the life span of MRL/lpr mice [85]. A mild beneficial effect on lupus disease was also exerted by a low dose of coumestrol (a phytoestrogen in alfalfa) in (NZB × NZW)F1 mice [86]. Overall, a generalized conclusion concerning whether phytoestrogens have beneficial or detrimental immune effects is not possible. Future studies should take into account that a particular exposure could have different immune effects depending on the species, sex, level of exposure, dosing regimen, and age at exposure.

B. Oral contraceptives and hormone replacement therapy

Diethylstilbestrol (DES), a synthetic estrogen with strong estrogenic activity, was prescribed in the past to pregnant women to ameliorate problems during pregnancy. It caused adverse effects on the female offspring known as ‘‘DES daughter syndrome’’ [87]. Limited studies in humans have suggested that DES-exposed women developed a variety of ADs [88]. Animal studies have confirmed that DES has profound immunomodulatory effects, including the induction of autoantibodies to cardiolipin [89]. These results are consistent with findings by Yurino et al. [77] who showed that DES implant resulted in increased IgG anti-DNA antibody production and immune complex deposition in ovariectomized (NZB × NZW)F1 mice. Even if it is no longer used during pregnancy, exposure to DES may occur through consumption of milk and meat products from animals that received DES as a food additive.

17α-ethinyl estradiol (EE), a synthetic analog of E2, is a primary component in hormonal contraceptives and it is also used in hormone replacement therapy. Clinical trials have now proven that the use of hormonal contraceptive in SLE patients with stable diseases does not increase the risk of flare [90]. Differently, mild to moderate flares, but not severe flares, are increased in women under hormone replacement therapy [91]. EE as well as E2 have been also identified in the environment, most prominently in the aquatic environment where the main sources of contamination are sewage treatment plants and agricultural runoff or discharge [92]. EE tends to be present in the environment at much lower levels than E2 but it is more persistent and less volatile [93]. Surprisingly, there are no published reports on the effect of EE in animal prone to develop ADs and many key questions in relation to potential immunologic effects of EE are unanswered. Studies in animal models are needed to assess whether sub-acute or chronic exposure to EE at low concentrations affect the immune system, whether EE effects occur equally with regard to age (pre- versus post-menopausal women), sex, and route of exposure (subcutaneous and oral).

C. Anti ERα antibodies

Alterations of T lymphocyte homeostasis and the production of multiple pathogenic autoantibodies, including antibodies specific to ER (anti-ER antibodies), have been repeatedly demonstrated in the peripheral blood of patients with SLE [29, 94]. In a recent study, our research group found that autoantibodies specific to ERα (anti-ERα Abs) were present in 45% of SLE patients, and they were significantly associated to clinical parameters, i.e., the SLE Disease Activity Index and arthritis [95]. Anti-ERα Abs are able to induce cell activation and consequent apoptotic cell death in resting T lymphocytes. Conversely, they increase proliferation of anti-CD3-stimulated T cells. The pro-apoptotic effect of anti-ERα Abs on T lymphocytes may contribute to the release of nuclear material in the circulation that can represent an important source of autoantigens if not timely removed. In this regard, an impaired clearance of dying cells is a typical feature of SLE where accumulation of nuclear autoantigens

may stimulate the immune system to produce autoantibodies [96, 97]. On the other hand, the increased proliferation of activated T lymphocytes treated with anti-ERα Abs, might contribute to the autoreactive T lymphocyte expansion. Our data suggest that anti-ERα Abs play a pathogenetic role in SLE interfering with T cell homeostasis. The impact of endogenous and EEDs in combination with anti-ERα Abs remains under scrutiny.

TABLE II
SUMMARY OF THE *IN VITRO* EFFECTS OF 17β ESTRADIOL (E2) ON LYMPHOCYTES FROM PATIENTS WITH SLE

Study	E2 concentration	Effects
[35]	10^{-10}M - 10^{-6}M	↑ total IgG and anti-dsDNA autoantibody serum levels
[36, 38, 39]	10^{-9}M - 10^{-8}M	↑ calcineurin and CD154 mRNA expression in T cells
[41]	10^{-7}M	↓ ERK suppression in activated T cells from patients with inactive/mild SLE
[42]	10^{-8}M - 10^{-6}M	↓ apoptosis and FasL mRNA expression in activated T cells
[43]	10^{-8}M	↑ FasL and caspase-8 mRNA expression in T cells
[44]	10^{-7}M	↑ IFN-α pathway in activated T cells
[45]	10^{-8}M	↑ ZAS3 protein expression in PBMC

↑, indicates up-regulation; ↓, indicates down-regulation. PBMC, peripheral blood mononuclear cells.

VI. FUTURE PROSPECTS

Deciphering the multi-faceted influences of estrogens on the regulation of immune responses could be critical in elucidating key pathogenic mechanisms in ADs and could lead to novel therapeutic interventions for disease management. Epidemiological evidence suggests a link between EED exposure and increasing prevalence of ADs. However, up to date, there is scant experimental data to link EEDs with autoimmunity. Additionally, there is no information about the effects on human health of the interactions between endogenous and exogenous estrogens.

TABLE III
SUMMARY OF THE IN VIVO EFFECTS OF ESTROGENIC ENDOCRINE DISRUPTORS (EEDS) ON DEVELOPMENT OF LUPUS MICE

Compound	Mice model	Effects	Study
BPA (plastics)	(NZBxNZW)F1	↓ IFN-γ production, ↓ proteinuria, ↑ symptom-free period	[76]
	ovariectomized (NZBxNZW)F1	↑ IgM autoantibody production by B1 cells	[77]
Chlordecone, methoxychlor, DDT (insecticides)	ovariectomized (NZBxNZW)F1	↑ Anti-dsDNA antibody production and ↑ immune complex deposition in the kidney	[78]
DDT (insecticide) TCDD (industrial chemical)	(NZBxNZW)F1	for DDT, no effects on immunity and mortality; for TCDD, ↓ proteinuria, ↓ serum anti-DNA antibody and total IgG levels, ↓ mortality	[79]
Soy diet (isoflavones)	MRL/lpr	↑ renal damage, ↑ proteinuria, ↑ serum creatinine, ↓ creatinine clearance	[83]
Soy diet (isoflavones)	MRL/lpr	↓ anti-dsDNA and anti-cardiolipin antibody production; ↓ IFN-γ; ↑ life span	[84]
Alfalfa sprout (coumestrol, coumestans)	MRL/lpr	↑symptom-free period, ↓ proteinuria, ↓ IFN-γ, IL-4, TNFα, IL-1β	[85]
Coumestrol (coumestans)	(NZB×NZW)F1	↓ proteinuria	[86]
DES	ovariectomized (NZB ×NZW)F1	↑ anti-dsDNA antibody production and immune complex deposition in the kidney	[77]

↑, indicates increase; ↓, indicates decrease.
BPA, bisphenol-A, DDT, *o,p'*-dichlorodiphenyltrichloroethane, TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin, DES, diethylstilbestrol.

Future studies in animal models should address the effects of endogenous and exogenous estrogens on the immune system at mechanistic levels by studying their influence on the lymphocyte function (e.g., signaling, proliferation, apoptosis). Whether EEDs can act on mER need to be explored. To note that in the experiments reported in this review lupus models with a high genetic predisposition for disease were used. With these models, it is possible to demonstrate an effect of estrogens to modify the progression of lupus but not to test whether they can influence the onset of the disease. Answering this question will require testing estrogens in mouse strains with

differing genetic background with respect to SLE susceptibility genes [98] and will be important in better characterizing the autoimmune hazard associated with their exposure. Future *in vitro* studies in human cells should address i) cellular and molecular mechanisms by which EEDs lead to a dysregulation of T and B cell functions both in healthy donors and patients with ADs; ii) the ability of EEDs to act in combination with an endogenous estrogen via additive, synergistic, or antagonistic mechanisms. In conclusion, the future challenge will be to establish whether estrogens may contribute, at least on a susceptible background, to development of autoimmunity, in an individual that might not otherwise develop it, or to the worsening of the disease in affected individuals. Minor changes in consumer habits could have drastic effects on the exposure of the general population; lifestyle changes and dietary adjustments could be suggested as an adjuvant therapy for SLE.

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