

Estrogen, A Double-Edged Sword: Modulation of TH1- and TH2-Mediated Inflammations by Differential Regulation of TH1/TH2 Cytokine Production

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Abstract: Estrogen appears to play a central role in the immune response and immune-mediated diseases. Estrogen receptors are expressed in a variety of immunocompetent cells, including CD4⁺ and CD8⁺ T cells and macrophages. Clinical observations indicate that some autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis, frequently remit during pregnancy but exacerbate, or have their onset during the postpartum period. Pharmacological levels of estrogen also appear to ameliorate certain autoimmune diseases. In addition, estrogen is known to suppress certain infectious diseases, as well as T cell-mediated responses toward oxazolone, keyhole limpet hemocyanin, *Listeria* soluble protein and purified protein derivatives. The immune basis for these phenomena is poorly understood. Based on a distinctive profile of cytokine production, data accumulated thus far have revealed modulatory effects for estrogen on the TH1-type and TH2-type cells, which represent two polarized forms of the effector specific immune response. Recent evidence indicates that estrogens inhibit the production of TH1 proinflammatory cytokines, such as IL-12, TNF- α and IFN- γ , whereas they stimulate the production of TH2 anti-inflammatory cytokines, such as IL-10, IL-4, and TGF- β . This can explain why estrogen suppresses and potentiates TH1- and TH2-mediated diseases, respectively. We hypothesize that exacerbation or suppression of inflammatory diseases by estrogen is mediated by skewing TH1-type to TH2-type response. This view represents a novel mechanism for the modulatory effect of estrogen on certain inflammatory diseases that can lead to beneficial or detrimental impacts depending on the type of immune involved. Such a concept is valuable when considering the application of combination therapies that include estrogen.

Keywords: Estrogen, Cytokines, TH1, TH2, Inflammation, T cells, Autoimmune diseases, *Listeria monocytogenes*

INTRODUCTION

T CD4⁺ (helper) cells are responsible for orchestrating and directing an immune response [1]. After activation, T helper cells can be differentiated either into TH1 or TH2 cells that secrete specific subsets of cytokines. In general, TH1 cells secrete the cytokines IL-2, IL-12, IFN- γ and TNF- α , whereas TH2 cells secrete the cytokines IL-4, IL-5, IL-10 and IL-13. The TH1 immune response is associated with a strong cell-mediated response whereas a TH2 response is characterized by a humoral or antibody-mediated immune response [1]. TH1 and TH2 type cytokines are mutually inhibitory. Thus, IL-12 and IFN- γ inhibit TH2, and IL-4 and IL-10 inhibit TH1 responses. Importantly, TH2 cytokines inhibit M ϕ activation, T-cell proliferation and the production of pro-inflammatory cytokines [2]. The balance between TH1 and TH2 cytokines is crucial for the orientation of the inflammatory response toward cell-mediated or humoral-mediated responses. Any factors that can interfere with TH1/TH2 axis might affect the outcome of the response.

1. ENDOGENOUS LEVEL OF ESTROGEN UP-REGULATES TH1/TH2 RATIO

Both clinical and experimental data have demonstrated the presence of a naturally occurring sexual dimorphism in the immune response [3-8]. There is now a large body of evidence suggesting that sex hormones in males and females are significant factors responsible for the gender dimorphism. During their reproductive years, females have more vigorous cellular and humoral immune responses than males as evidenced by a more developed thymus, higher immunoglobulin concentrations and a greater ability to reject tumors and homografts [9,10]. Furthermore, evidence suggests that physiological levels of estrogen stimulate humoral and cell-mediated immune responses, while the male hormone, testosterone, does the opposite [11]. Antigen presentation of professional macrophages (M ϕ) and dendritic cells (DCs) and non-professional (uterine epithelial) antigen presenting cells (APCs) from female mice are more efficient than that from male mice [12].

A link between the gender and TH1/TH2 cytokine has also been observed both in human and animal. Higher levels of IFN- γ and IL-2 and lower levels of IL-4 and IL-10 were detected in the phytohemagglutinin-stimulated lymphocyte culture supernatants of men compared with women [13]. The production of TH1 cytokines such as IL-12 and IFN- γ was significantly less in lymph node cells from male as compared with female mice after Ag-specific stimulation [14]. Interestingly in women, there is now a large body of

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evidence suggesting that the decline in ovarian function with menopause is associated with spontaneous increases in proinflammatory TH1-type cytokines. Furthermore, it has been shown that while male BALB/c mice infected with coxsackievirus group B type 3 developed typical TH1-type cytokines, female mice under the same conditions developed a typical TH2-type response [2]. Given these results, it is conceivable that endogenous levels of sex hormones contribute to the gender difference in the development of inflammatory diseases by influencing the balance of TH1/TH2 cytokines. In certain autoimmune disease, such as rheumatoid arthritis (RA), experimental allergic encephalomyelitis (EAE) and type-1 diabetes, TH1-type cytokines play a pathogenic role, whilst the TH2-type cytokines play a preventive role in the development of the disease [15]. In this context, it has been known that females are generally more susceptible to TH1-mediated diseases such as multiple sclerosis (MS), RA, systemic lupus erythematosus (SLE), Sjögren's syndrome, myasthenia gravis, and EAE [16-18].

Type I diabetes in NOD mice is an animal model of type 1 diabetes [19]. The incidence of type 1 diabetes both in human and in NOD mouse shows female prevalence of the disease [20]. Castration of male NOD mice increases, whereas castration of female NOD mice decreases the frequency of autoimmune diabetes, and treatment of female NOD mice with testosterone prevented the development of diabetes [20,21]. The expression of IFN- γ was significantly higher in T cells from young female NOD mice, coincided with a decrease in the expression of IL-4 [19]. This differential expression of TH1/TH2 cytokine profile was correlated with upregulation of IL-12-induced STAT-4 activation by endogenous estrogen. Altogether, these findings implicate that physiological levels of estrogen in females direct the cytokine profile for TH1 type. Although this profile could favor protection from some infectious diseases, it can also exacerbate certain autoimmune diseases, which are mediated by TH1 cytokines.

2. INCREASED TH2/TH1 RATIO BY PREGNANCY LEVEL OF ESTROGEN SUPPRESSES INFLAMMATION

A large body of data shows that pregnancy levels of estrogen are immunosuppressive. For instance, estrogen has been shown to suppress T cell-specific responses toward oxazolone, keyhole limpet hemocyanin [22,23], *Listeria* soluble protein [24], purified protein derivatives (PPD) [24,25] and non-specific responses to Talc and lipopolysaccharide [26]. It also ameliorates remote organ inflammation induced by burn injury [27-29], atherosclerosis [30], neurodegenerative disorders [31] and certain autoimmune diseases [32-36]. In addition, pregnancy levels of estrogen suppress the protection against pathogens such as *Listeria*, *Chlamydia*, *Neisseria gonorrhoeae* and *Salmonella* [37-40]. Although, the mechanism mediating such differential effect of pharmacological levels of estrogen on the immune responses is not well understood, accumulated body of data implicates that modulation of cytokine production by TH1- and TH2-type cells might play a significant role.

3. UPREGULATED TH2/TH1 RATIO BY PREGNANCY LEVEL OF ESTROGEN AVOIDS REJECTION OF FETUS

There is a large body of data implicating the impact of pregnancy levels of estrogen on the TH1/TH2 cytokines. For instance, during the luteal phase of the ovarian cycle, when estrogen level is high, the immune response is shifted toward a TH2-type response, as reflected by increased IL-4 production in this phase of cycle [41]. In addition, the level of TH1 (IL-2 and IFN- γ) cytokines is augmented in women after menopause, and hormone replacement therapy prevents this increase, thereby improving the aberration of TH1/TH2 balance [42,43]. Pregnancy is also associated with alteration in TH1/TH2 balance, where pregnancy appears to be a "TH2-type phenomenon" [44-47]. The switch from TH1- to TH2-type cytokine during pregnancy has been demonstrated at the maternal-fetal interface [46]. The predominance of TH2-type cytokines in pregnancy could be important in avoiding rejection of the semiallogenic fetoplacental unit. In line with this concept, levels of IL-4 and IL-10 increase in the peripheral blood during the first weeks of gestation, but later in gestation decrease to levels below normal [48]. The ratios of TH1:TH2 (IFN- γ :IL-4) cytokines are predominant in the second and third trimesters of normal pregnancy, but TH1 cells predominated in preeclamptic [49]. Both cycling and pregnant endometrium express the genes for IL-10 and its receptor, which was significantly increased in decidual cultures compared with that by endometrial cells both in proliferative and secretory phases of the cycle [50]. In contrast to the beneficial role of TH2 cytokine in pregnancy, a significantly increased TH1 cytokine expression may mediate immune etiology for reproductive failures [50] including fetal resorption [51]. In addition, TH1 cytokines impair implantation and trophoblast proliferation, as well as trophoblast outgrowth from attached blastocysts [44,52]. This correlation has been recently addressed; where it was found that expression of IFN- γ and TNF- α decrease with the progress of gestation (third trimester) during normal pregnancies, and increases in women with implantation failures [14] to avoid rejection of the semiallogenic embryo [53]. Thus, successful pregnancy may depend on a TH2-type cytokine response, whilst, conversely, a poor pregnancy outcome may be associated with an increase in TH1 cytokines and a concomitant decrease in TH2 cytokines.

Exogenous estrogen equivalent to its pregnancy level has also been shown to modulate the TH1/TH2 cytokine axis. For instance, estradiol was found to suppress IL-2 production from activated peripheral blood T cells and CD4⁺ T cell lines [54,55]. Diethylstilbestrol (DES), a synthetic estrogen, treatment also inhibited IL-2 production by splenic lymphocytes from naïve and *Listeria*-infected mice in response to phytohemagglutinin, and IL-2 administration ameliorated the suppressive effect of DES [3,4,37,56], in lupus autoimmune mice [56]. In recent studies we analyzed the modulatory effect of estrogen on TH1/TH2 axis using TH1-mediated models, including DTH reaction toward purified protein derivatives (PPD) and *L. monocytogenes* infection. In the PPD-mediated DTH response, we found that contraceptive level of β -estradiol suppressed the DTH reaction, as measured by the decrease in footpad swelling, toward sensitization with PPD [25,57] coincided with

downregulation of the gene expression and production of IL-2 and IFN- γ (TH1-type) cytokines, and enhancement of the gene expression and production of IL-4 and IL-10 (TH2-type) [58]. The effector cells of *Listeria*-infected mice treated with β -estradiol showed similar TH1/TH2 cytokine profile, where remarkable decreases in the gene expression of IFN- γ , IL-2 and IL-12, and increases in IL-4, IL-10 and TGF- β by T cells were observed [25]. Taken together, it appears that pregnancy levels of estrogen drive the TH1/TH2 cytokine axis to TH2 profile leading to aggravation or amelioration of certain diseases. Consistent with this hypothesis, TH1-dependent autoimmune diseases, such as rheumatoid arthritis [5], improved after estrogen treatment [59-62], while TH2-dependent diseases, such as lupus erythematosus [45], tended to become exacerbated [23,32,40,63,64].

4. MECHANISMS MEDIATING MODULATION OF TH1/TH2 BY ESTROGEN

4.1. Expression of Estrogen Receptors

Estrogen acts on target cells by binding to two distinct estrogen receptors (ER), ER- α and ER- β [65,66]. The activation of gene transcription by estrogen requires ER dimerization and binding to an estrogen response element (ERE), followed by activation of transcription factors and co-factors [67]. ER is expressed by immunocompetent cells, including T- and B-lymphocytes and M ϕ [68-73]. ERE has been identified in a number of TH1 genes. For example, an ERE has been mapped to the 5'-flanking sequence of the IFN- γ gene (TH1 cytokine), and endogenous level of estrogen has been shown to induce transcription of IFN- γ [74]. Short-term exposure to estradiol also increases IFN- γ mRNA expression in Con A-treated murine spleen cells. In a transient expression assay, 17 β -estradiol markedly increases activity of the IFN- γ promoter in lymphoid cells that express the appropriate hormone receptor [21]. This effect is mediated by sequences in the 5'-flanking region of the gene, and can augment the effect of T cell-activating agents. Hormonal regulation of this pleiotropic cytokine may account in part for the ability of endogenous levels of estrogen to potentiate many types of immune responses and for the disproportionate susceptibility of females to autoimmune disease. In addition, an estrogen inhibitory element was mapped to the TNF- α (TH1 cytokine) promoter [75], which might explain the inhibitory effect of estrogens on the expression of TNF- α in target cells [76]. Estrogen also suppressed the transcription of IL-2 production from activated peripheral blood T cells and CD4⁺ T cell lines at the transcriptional level [54]. Although these data implicate that the modulation of TH1 cytokine production by estrogen is tightly controlled at the transcription levels, where the dose of estrogen is a crucial factor, further studies are required to clarify this hypothesis.

4.2. Modulation of Expression of Chemokines

The recruitment of inflammatory TH1 and anti-inflammatory TH2 cells is tightly governed by the expression of certain chemokines. Some of the chemokines are expressed constitutively and are involved primarily in the organization of lymphoid tissue ("homeostatic chemokines"). "Inflammatory chemokines", such as monocyte chemoattractant

protein-1 (MCP-1 or CCL2), M ϕ inflammatory protein (MIP)-1 α (CCL3), MIP-1 β (CCL4), and regulated on activation normal T cell expressed and secreted (RANTES, CCL5), recruit effector cells to the site of inflammation [77]. MIP-1 α , MIP-1 β and RANTES are secreted by a variety of cells, among them M ϕ activated NK cells, and T cells [78], and their receptor CCR5 is expressed on M ϕ , DCs, and activated TH1 cells. MCP-1 expression has been associated with TH1 development [79]. Studies using mice that lack CCR2, the only known functional receptor for MCP-1, have generally demonstrated that this receptor promotes TH1 development in infection models [79]. Using a model of pulmonary *Cryptococcus neoformans* infection, both MCP-1 neutralization and CCR2 deficiency resulted in significantly diminished IFN- γ production, and increased IL-4 and IL-5 production by lung leukocytes (TH1 to TH2 switch) [80].

Given the central role of chemokines in orchestrating the immune response, interference with chemokine expression by estrogen can substantially alter the quality of the immune response. In this regard, the decrease in EAE in mice by estrogen was coincided with inhibition of mRNA expression of the chemokines RANTES, MIP-1 α , MIP-2, IP-10, and MCP-1, and of the chemokine receptors CCER1, CCR2 and CCR5 [81]. MCP-1 has been demonstrated to stimulate the migration of monocytes through an arterial endothelial monolayer [82]. Estradiol has been shown to inhibit MCP-1 mRNA expression induced by lipopolysaccharide [83] and talc, [84] as well as in platelet-derived growth factor-induced murine fibroblasts [85]. Estradiol in addition inhibited the migration of MCP-1-stimulated human monocytes *in vitro* [86]. It was observed that both in ovary-intact and ovariectomized animals, MCP-1 protein and mRNA expression were significantly increased, whilst attenuated after supplementation with estradiol [87]. Given together, these reports implicate that the downregulation of TH1-type cytokines by estrogen may be mediated, at least in part, by inhibition of certain chemokines, such as MCP-1 and MIP-1 α .

4.3. Modulation of the Expression of Adhesion Molecules

Recruitment of inflammatory cells into inflammatory lesions is a crucial step in the initiation and progression of the immune response. This process is mediated by the expression of adhesion molecules, such as LFA-1, CD62L and CD44, by the inflammatory cells, and ICAM-1 and VCAM-1 by the endothelial cells [88]. Adhesion molecules are known to tether the circulating inflammatory cells to the endothelial cell surface to facilitate their entry into vessel wall [89,90]. One potential mechanism that might mediate the inhibitory effect of estrogen on the inflammatory response is the alteration of trafficking of the inflammatory cells. *In vitro* studies showed that physiological and high doses of estrogen induced a decrease in the adhesion of monocytes to TNF- α -stimulated endothelial cells, and their secretion of TNF- α -induced IL-8 and MCP-1 [91]. Estrogen was also found to decrease the recruitment of granulocytes, M ϕ , and T cells into the inflammatory site [57,59]. CD44 and LFA-1 are adhesion and costimulatory molecules for T cell activation, their expression levels increase on the inflammatory cells after priming with antigen, and facilitate

their homing to the inflammatory locus to mount inflammation [92]. Estrogen has been reported to decrease the expression levels of ICAM-1, VCAM-1 in endothelial cells and LFA-1 [57,89] and CD44 and LFA-1 in the inflammatory cells [57,58,93]. These data support the notion that inhibition of TH1 inflammatory responses by estrogen is mediated through modulation both of quantity (decreasing recruitment of the inflammatory cells) and quality (establishment of TH2 type) of the response.

4.4. Modulation of Antigen Presentation

Activated M ϕ and DCs, professional APCs, regulate and orchestrate the immune response, leading to generation of TH1 or TH2 CD4 T cells [2]. Naive CD4⁺ TH0 (antigen-inexperienced) cells are clearly bipotential and serve as precursors of TH1 and TH2 cells. Among the factors currently known to influence the differentiation of these cells towards the TH1 or TH2 subsets, cytokines produced by cells of APCs are the most important. IL-12, produced by activated APCs, is a major inducer of TH1 differentiation and hence cellular immunity; this cytokine acts in concert with NK-cell-derived IFN- α to promote TH1 responses [94]. APC-derived IL-12 and TNF- α , in concert with NK- and TH1-cell-derived IFN- γ stimulate the functional activity of T cytotoxic cells, NK cells and activated M ϕ . All three cytokines – IL-12, TNF- α and IFN- γ – also stimulate the synthesis of nitric oxide and other inflammatory mediators that drive chronic delayed-type inflammatory responses. Because of these crucial and synergistic roles in inflammation, IL-12, TNF- α and IFN- γ are considered the major pro-inflammatory cytokines [2].

One potential mechanism for the orientation of TH response from TH1 to TH2 by estrogen could be mediated through the modulation of APC function. Several data from literature provide evidence for this hypothesis. Treatment with pregnancy level of estrogen was found to inhibit subsequent maturation of M ϕ to full competence in response to activating stimuli [95]. In addition, estrogen inhibits cardiac allograft-induced MHC class II expression both by professional and non-professional APC in animal models [96]. *In vitro* exposure to estrogen of human breast carcinoma cells suppressed IL-1-induced MHC II expression [97,98]. Moreover, cytokines such as IL-10 and TGF- β , which prevent upregulation of MHC-II were upregulated by estrogen [99]. A deficit in the APC function during the induction or the effector phases of the DTH reaction has been reported to downregulate the effector function of T cell giving rise to inhibition of the DTH response [100]. Recently, we tested the involvement of APCs in mediation of the immune response by estrogen. We found that the APCs of β -estradiol-treated mice could not induce optimal proliferation of PPD-sensitized T cells *in vitro* [58], demonstrating a direct effect of estrogen on APC function. In support for this notion, it has been reported that T cells are not the targets for estrogen-mediated suppression of DTH in female SCID mice reconstituted by T cells from estrogen-treated mice [101]. In addition, a marked decrease in the number of the cells expressing CD40 was observed in estradiol-treated mice [58], which is expressed on the APC [102] and interact with its ligand, CD154 (CD40L), leading to priming and expanding CD4 TH cells in response to antigen [103]. All the observations suggest that the

mechanism of estrogen-mediated impairment of T cell priming may be mediated by downregulation of MHC class II and CD40 expression by APCs leading to a deficit in antigen presentation.

DCs are extremely efficient at processing and presenting antigen [104] and play a potentially critical role in the activation and/or regulation of pathogenic T cell populations [105]. Mature DCs induce the development of effector T cells [106], while immature DCs induce the development of regulatory T cells that suppress the activation of effector T cells. In addition, it has been found that CD8⁺ DCs and CD8⁻ DCs drive TH1- and TH2-type responses, respectively [105]. Estrogen treatment has been found to induce a significant decrease in the frequency of DCs migrating into the CNS at EAE onset, and their production of TNF- α and IFN- γ [107]. Pretreatment of DCs with estrogen *in vitro* blocked their ability to present antigen to specific T cells [156], and induced myelin basic protein-specific T cells to show higher TH2:TH1 cytokine profile [156].

Non-professional APCs are also regulated by estrogen. In response to estradiol, antigen presentation by uterine epithelial cells is stimulated at a time when antigen presentation by APC in the uterine stroma and vagina is inhibited [12]. Moreover, with repeated injections of estradiol, APC numbers increase in the vagina at a time when inhibition of antigen presentation persists [108,109], which is mediated through the local production of TGF- β by vaginal cells [110]. Altogether, these data support the notion that the modulation of TH1/TH2 cytokine axis is a feedback of the effect of estrogen on the APC function.

4.5. Modulation of T Cell Phenotype and Function

Although the finding in the previous section implicates a direct effect of estrogen on APC, one cannot exclude any direct effects on T cells. For instance, CD4⁺ T cell clones, from multiple sclerosis patients, produced high level of IL-10 and low level of TNF- α when treated *in vitro* with estrogen [111]. In addition, it was reported that *in vitro* treatment with estrogen induces a rapid and dose-dependent increase in Ca²⁺ influx in T cells isolated from spleen of female mice [72]. Moreover, responses of murine T cells to anti-CD3 [72], and human lymphocytes to PPD or ConA [112] were suppressed when exposed *in vitro* to estrogen. Expression of activation markers, such as CD25 (IL-2R α), CD44 and CD69, by activated T cells reflects the magnitude of activation of T cells [92,101]. Recently, we reported a decrease in the expression of these activation markers by effector enriched T cells from PPD-sensitized mice treated with β -estradiol [57]. Although these observations implicate a modulatory effect of estrogen on the TH1-type cells per se, it is still not clear if the deficit in T cell function by estrogen is due to direct and/or indirect effects. Further investigations are required to address this hypothesis.

5. EXAMPLES FOR DISEASES LINKED TO THE MODULATION OF TH1/TH2 AXIS BY ESTROGEN

5.1. *Listeria monocytogenes* Infection

Infection of mice with *Listeria monocytogenes* induces a strong TH1-type cell response that is essential for bacterial

clearance from the host [113,114]. The TH1-type cytokines IL-12 and TNF- α play a protective role during *Listeria* infection [107,115,113]. On the other hand, the TH2-type cytokines IL-4, IL-10 and TGF- β , which decrease the intracellular killing, have been reported to show suppressive role in the course of *Listeria* infection [116-118]. Estrogens have been reported to suppress the protection toward *Listeria* infection [25,37] coincided with a decrease in the ability of splenocytes to proliferate and produce IL-2, and that injection of IL-2 into estrogen-treated mice restored the suppressive effect of estrogen [37], implicating depression of the TH1-type cytokines. By analyzing the gene expression of TH1 and TH2 cytokines by T cells and APCs from *Listeria*-infected mice treated with or without estrogen, we found a significant decrease in the expression of the TH1 representative cytokines IFN- γ , TNF- α , IL-2 and IL-12 by the inflammatory cells from β -estradiol-treated mice. In sharp contrast, the expression of the TH2-representative cytokines (IL-4, IL-10 and TGF- β) increased in β -estradiol-treated mice [25]. These finding clearly show that estrogen suppresses cell-mediated immunity not only by downregulating the expression of TH1 cytokines but also by upregulating the TH2 cytokines. These data are of great interest in order to design better strategies of hormone replacement therapy.

5.2. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disorder, where cytokines are the main mediators of inflammation. TH2 cytokines (IL-4 and IL-10) have protective properties to this disease, while the TH1 cytokines IL-2 and IFN- γ are supporting proinflammatory microenvironment in joints from patients with RA [119-122]. It has been reported that although about three times more women are affected than men, the symptoms and signs of RA are ameliorated during pregnancy [122], and that treatment with the estrogen metabolite 2-methoxyestradiol has been reported to suppress type II collagen-induced arthritis [59]. In addition, general TH2 response reflected by high IL-10 levels was found in RA patients, however, a significant change in IFN- γ was observed in RA patients but only during the first trimester of pregnancy compared with a major TH1 response in healthy pregnant women [123]. Decreased production of IFN- γ and IL-2, and enhancement of IL-4 and IL-10 production [124] has been found in whole blood from pregnant patients with RA compared to healthy controls and nonpregnant RA patients [124,125]. Thus, the shift of TH1/TH2 cytokine axis toward TH2 profile can explain amelioration of RA symptoms in pregnant women.

5.3. Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease that is characterized by multifocal damage to central nervous system (CNS) myelin. Myelin protein-specific CD4⁺ T cells secreting proinflammatory TH1 cytokines are thought to coordinate an autoimmune response within the CNS, resulting in the destruction of the myelin sheath and episodes of neurological dysfunction [126]. A distinct female predominance exists for MS, with women developing the disease two times more often than men [127,128].

EAE is an inflammatory demyelinating disease of the CNS that is commonly induced by immunizing susceptible strains of laboratory rodents with myelin proteins or peptides [130]. EAE is a useful model that has provided considerable insights into the pathogenesis of MS. The inflammatory CD4⁺ T cells that mediate EAE secrete proinflammatory TH1 cytokines, and TH2 cells are thought to play a role in disease recovery [76]. Gender differences in the susceptibility and severity of EAE can parallel gender differences in MS. For example, female SJL mice develop more severe EAE after immunization with proteolipid protein peptide or after the adoptive transfer of Ag-specific T cells [131-133]. In contrast, pregnancy has been shown to protect animals from EAE [133], and estrogen administered at levels equal or greater than those found during pregnancy also suppress the clinical and histopathological symptoms of EAE in mice and rats [61,134]. Recent studies have found that estradiol, a hormone produced by the placenta during pregnancy, had profound effects on EAE [14], and, based on these results, human trials using estradiol to treat MS patients have begun. In recent studies, ovariectomy and loss of endogenous estrogen enhanced the severity of EAE, whereas treatment of mice with estrous and diestrous levels of exogenous estrogen effectively suppressed EAE [50,81,131]. This is coincided with drastic reduction in CNS cellularity and chemokine synthesis [81] in the absence of a significant shift toward TH1-type cytokine [131]. Estradiol-mediated protection toward EAE development might involve both systemic inhibition of TNF- α expression [130]. Recipients of encephalitogenic T cells from low-dose, estrogen-treated mice developed less severe paralysis than mice received T cells from placebo-treated mice. In addition, treatment with exogenous 17 β -estradiol effectively suppresses EAE in several mouse strains, including IL-4 and IL-10 knockout mice, susceptible to different encephalitogenic peptides coincided with a dramatic decrease in TNF- α and IFN- γ [76]. Ethinyl estradiol, like 17 β -estradiol, drastically suppressed EAE, and significantly decreased the secretion of proinflammatory cytokines (IFN- γ , TNF- α , and IL-6) by activated T cells, but increased the expression of TGF- β 3 in the CNS [126]. It was also found that estrogen treatment leads to a significant decrease in the frequency of TH1 DCs migrating into the CNS at EAE onset and their secretion of TNF- α and IFN- γ in the spleen [135]. These results suggest that estrogen such as ethinyl estradiol, through induction of the anti-inflammatory TH2-type cytokines, might be a successful candidate as therapy for multiple sclerosis.

5.4. Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of Abs specific for numerous self-Ags, expansion of autoreactive B cells, and glomerular deposition of Ig complexes that contribute to kidney damage [122]. SLE is characterized by immune complex-mediated pathology linked to excess TH2 cytokine production. The disease has its peak onset in women of childbearing age with a 9:1 female predominance after puberty [122,136]. Women who develop SLE during reproductive years were found to have a 4.2 times higher relative mortality risk compared to the healthy population and to women with disease onset in nonreproductive years [137]. Estrogens increase and enhance the development and

severity of lupus in mice, whereas suppression of estrogens slows down the disease process [122,138]. Elevation of serum estradiol is often found in female patients with SLE, and sometimes is linked to active disease [139]. Interestingly, it has been observed that estrogen treatment suppressed arthritis, but aggravated glomerulonephritis in the MRL-lpr mouse strain [140,141]. Similar findings were made in a prospective study of SLE patients where pregnancy suppressed arthritis, but increased the frequency of renal flare [142,143]. It has become apparent that pregnancies resulted in favorable outcomes in the majority of cases, although SLE flares still remain common during pregnancy and postpartum [144,145]. Treatment of BALB/c mice transgenic for the heavy chain of a pathogenic anti-DNA Ab with 17 β -estradiol induces a lupus-like phenotype with expansion of anti-DNA B cells, elevation of anti-DNA Ab titers and glomerular Ig deposition [146]. 17 β -estradiol is able to polyclonally increase the production of IgG, including IgG anti-double-stranded DNA, in SLE patients' peripheral blood mononuclear cells by enhancing B cell activity and by promoting IL-10 production by monocytes [147]. Peripheral blood cells from patients with SLE respond to estrogen treatment with a reduction of TNF- α [148,149]. These and results of other works show that the pregnancy-induced shift to a TH2 response is a contributing factor to the flare observed in a proportion of pregnant SLE patients [148].

5.5. Inflammatory Bowel Disease

The impact of female sex hormones on the inflammatory bowel disease (IBD) is conflicting. On one hand, IBD is believed to flare during a first pregnancy and postpartum and, on the other hand, to be better controlled during subsequent pregnancies [150]. Others have proposed that the course of IBD during pregnancy depends on disease activity at conception [151]. Oral contraceptives have been suggested as a risk factor for relapse in Crohn's disease [150], but this is not supported by other studies [152]. A recent report cited female gender, but not oral contraceptive use, as a risk factor for relapse in ulcerative colitis [153].

Experimental colitis, lymphocyte-dependent model for IBD, can be induced by intracolonic administration of dinitrobenzene sulfonic acid (DNB). Immune response in DNB colitis results from a DTH response reaction against haptenized colonic proteins and is characterized by a TH1 cytokine response [154]. Estrogen has been reported to suppress T cell-dependent DTH and activation of inflammatory cells producing TNF- α and IFN- γ [25,57,58,155]. It has been reported that three days after induction of DNB colitis, the severity of colitis, the infiltration of colonic tissue with granulocytes and a decrease in ICAM-1 expression in β -estradiol-treated mice than in placebo-treated mice with DNB colitis, both 3 and 14 days post-colitis, was observed [155]. Most importantly, 17 β -estradiol also reduced the severity of tissue damage, the infiltration of tissue with mononuclear cells, and the mRNA expression of IFN- γ . Although these data implicate a potential role for estrogen in the progression of IBD, further studies are needed to characterize the underlying mechanisms.

6. CONCLUSION

Studies extending over a decade have provided much evidence to suggest that exposure of immune cells to estrogen markedly altered the expression of pro-inflammatory cytokines results in unique immunoregulation of the cognate immune response so as to benefit or harm the host. The findings indicate that both the physiological and pharmacological (pregnancy) levels of estrogen act as double-edged swords toward immune responses. Physiological levels of estrogen shift the TH1/TH2 axis toward the TH1 profile, leading to enhancement and downregulation of TH1- and TH2-type cytokine, respectively. By contrast, pharmacological levels of estrogen appear to shift the immune response toward the TH2 profile, leading to suppression and augmentation of the TH1- and TH2-type cytokine respectively. In addition, these data suggest that such modulation of TH1- and TH2-type cytokine by estrogen might play a role in the regulation of physiological responses to foreign antigens as well as to autoantigens. This is evidenced from the observation that pregnancy or pharmacological levels of estrogen lead to: 1) increase in the rate of the TH1-mediated infectious diseases, 2) aggravation of the TH2-mediated autoimmune diseases, and 3) amelioration of the TH1-mediated autoimmune diseases. Much evidence is accumulating that a significant portion of the immunomodulatory effect of estrogen on TH1/TH2 balances is mediated by modulation of professional APC and T cells. Consequently, the regulation that TH1/TH2 cytokines superimpose on autoimmunity is a finely tuned balance between activation and downmodulation of an individual autoreactive T cell repertoire by the physiological and pharmacological levels of estrogen, respectively. Although neutralization of inflammatory cytokines is beneficial in specific human autoimmune diseases, it is possible that the studies reviewed in the present article may lead to the therapeutic exploitation of certain levels of estrogen derivatives as a means of controlling the inductive or effector phases of different autoimmune processes. Further studies are encouraged to analyze the therapeutic effect of different levels of estrogenic compounds, which lack feminine proprieties, on different settings of autoimmune diseases.

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