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REVIEW

Hormonal Modulation of Dendritic Cells Differentiation, Maturation and Function: Implications for the Initiation and Progress of Systemic Autoimmunity

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Abstract Hormonal homeostasis is crucial for keeping a competent and healthy immune function. Several hormones can modulate the function of various immune cells such as dendritic cells (DCs) by influencing the initiation of the immune response and the maintenance of peripheral tolerance to self-antigens. Hormones, such as estrogens, prolactin, progesterone and glucocorticoids may profoundly affect DCs differentiation, maturation and function leading to either a pro-inflammatory or an anti-inflammatory (or tolerogenic) phenotype. If not properly regulated, these processes can contribute to the pathogenesis of autoimmune disease. An unbalanced hormonal status may affect the production of pro-inflammatory cytokines, the expression of activating/inhibitory receptors and co-stimulatory molecules on conventional and plasmacytoid DCs (pDCs), conferring susceptibility to develop autoimmunity. Estrogen receptor (ER)-α signaling in conventional DCs can promote IFN-α and IL-6 production and induce the expression of CD40, CD86 and MHCII molecules. Furthermore, estrogen modulates the pDCs response to Toll-like receptor ligands enhancing T cell priming. During lupus pathogenesis, ER-α deficiency decreased the expression of MHC II on pDCs from the spleen. In contrast, estradiol administration to lupus-prone female mice increased the expression of co-stimulatory molecules, enhanced the immunogenicity and produced large amounts of IL-6, IL-12 and TNF-α by bone marrow-derived DCs. These data suggest that estradiol/ER signaling may play an active role during lupus pathology. Similarly, understanding hormonal modulation of DCs may favor the design of new therapeutic strategies based on autologous tolerogenic DCs transfer, especially in sex-biased systemic autoimmune diseases. In this review, we discuss recent data relative to the role of different hormones (estrogen, prolactin, progesterone and glucocorticoids) in DC function during systemic autoimmune pathogenesis.

Keywords Estrogen · Prolactin · Progesterone · Glucocorticoids · Autoimmunity · Dendritic cells · Systemic lupus erythematosus

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Abbreviations

cDCs	Conventional dendritic cells
DCs	Dendritic cells
Dex	Dexamethasone
E2	17-β-Estradiol
E3	Estriol
EAE	Experimental autoimmune encephalomyelitis

GC   Glucocorticoids
DMPA   Medroxyprogesterone acetate
pDCs   Plasmacytoid dendritic cells
Pg   Progesterone
PR   Progesterone receptor
PRL   Prolactin
PRR   Pattern recognition receptors
RA   Rheumatoid arthritis
SLE   Systemic lupus erythematosus
TLRs   Toll-like receptors
Tregs   Regulatory T cells

Introduction

In susceptible individuals, immune tolerance shaped by self-antigens recognition may fail, leading to a harmful autoimmune response (Shum et al. 2009). Unfortunately, up to date the etiology for many autoimmune diseases remains unknown, but a number of studies have suggested that these ailments are strongly associated with factors such as genetics, hormonal status, infections and/or environment factors (Albornoz et al. 2013; Bentham et al. 2015; Luo et al. 2011). The fact that systemic lupus erythematosus (SLE), as well as other autoimmune diseases, preferentially affects women over male would suggest that the female hormonal status could play a pivotal role during autoimmunity onset and progression (Whitacre et al. 1999). In relation to hormonal status, it has been reported that 25 % of SLE patients showed high prolactin (PRL) levels, which have also been associated to disease activity in a group of patients (Lahita 1999; Peeva et al. 2004). Similarly, female SLE patients showed an increased expression of mRNA for estrogen receptor (ER)-α in peripheral blood mononuclear cells, while mRNA for ER-β was decreased as compared to healthy controls. These observations suggest that immune cells may be more sensible to 17β-estradiol levels or estrogen (Inui et al. 2007). Unfortunately, the heterogeneity of autoimmune diseases such as SLE and rheumatoid arthritis (RA) has limited the development of antigen-specific therapeutical approaches (Ginzler et al. 2005).

DCs could initiate immune responses by priming antigen-specific T cells, but also promote T cell tolerance by presenting self-antigens in the context of a balanced expression of activating or inhibitory receptors (Perez et al. 1997; Yogev et al. 2012). The contribution of hormonal status to DC homeostasis has been underscored by the observation that estrogen, progesterone, PRL, triiodothyronine and glucocorticoids (GC) can modulate immune cells and DC differentiation, maturation and function (Griesbeck et al. 2015; Nieto et al. 2016; Yang et al. 2006b, c). However, the precise contribution of endogenous estrogen and other hormones to DC homeostasis during autoimmune development remains to be established. It also remains undetermined whether E2/ER-α signaling modulates the immune system through direct or indirect mechanisms. Although, lot of studies have reported E2/ER-α effects on the immune system, their data showed no clear evidence on an hormonal direct effect over specific immune mediator derived from DCs (Khan and Ansar Ahmed 2016). Furthermore, although several studies have shown that DCs derived from lupus patients display altered maturation and functional features, whether hormone levels could contribute to these alterations remains unknown (Carreño et al. 2009; Mozaffarian et al. 2008). It is likely that hormone levels could contribute to phenomenon aberrant expression of several modulatory molecules (activating or inhibitory receptors) such as CD40, CD86, Fcγ receptors (FcγRs) for IgG and programmed cell death-ligand 1 (PD-L1) shown by DCs derived from SLE patients.

During the past decade, significant progress has been made in the understanding of autoimmune pathogenesis leading to the development of new immunotherapeutic approaches, including new biological agent- and cell-based transfer strategies (Benham et al. 2015; Bluestone et al. 2015; Hahn 2013; Schwarz and Ritchlin 2007). However, specific therapies for systemic autoimmune diseases such as SLE have not yet been proven to be successful. A great number of autoimmune disease patients fail to respond to the new biological agents highlighting the need of focusing in new molecular networks such as hormonal modulation of pro-inflammatory mediators and immunological resistance mechanisms in immune cells, including DCs and T cells (Albornoz et al. 2013; Emery et al. 2015; Nieto et al. 2016).

The design of DC-based immunotherapies to promote antigen-specific tolerance for autoimmune diseases is being extensively evaluated (Lee et al. 2014). A phase I clinical trial based on DCs transfer to RA patients was conducted, in which tolerogenic DCs (tolDCs) derived from blood monocytes treated with dexamethasone (Dex) and vitamin D3 are administered locally into an affected knee (Autologous Tolerogenic Dendritic Cells for Rheumatoid Arthritis (AutoDECRA) 2011). On the other hand, Giannoukakis et al. conducted a Phase I clinical trial in Type 1 diabetes patients based on the administration of tolDCs induced ex vivo with antisense phosphorothioate-modified oligonucleotides targeting the primary transcripts of the CD40, CD80 and CD86 co-stimulatory molecules (Giannoukakis 2013; Giannoukakis et al. 2011). Although much work is based in the generation of autologous tolDCs by pharmacological and genetic approaches, the DC sensibility to hormonal milieu has not been fully addressed (Kovats 2012, 2015). Thus, hormonal milieu may control the phenotype of DCs and contribute to the onset of an autoimmune disorder, as well as block the potential effect of antigen-specific tolDCs-based therapies. In this review,

we discuss recent data relative to hormonal modulation of DC differentiation, maturation and function, during autoimmune diseases, with special emphasis in SLE pathogenesis.

Hormonal Milieu Modulates DCs Function

ER-α and ER-β belong to the steroid hormone superfamily of nuclear receptors, which work as transcription factors after binding to estrogen (Hewitt et al. 2016). These receptors are extremely complex because they are modulated by others molecules in addition to estrogen, which can even show opposite effect that could be crucial in the immunopathogenic mechanism of autoimmune diseases (Pierdominici et al. 2015). By means of two main domains AF-1 and AF-2, ERs can regulate transcription of several genes including progesterone receptor, cathepsin D, transforming growth factor-α, as well as ER expression in different cell lines such as MCF-7 and HeLa cells (Brooks and Skafar 2004; Castles et al. 1997). After ligand binding in the nucleus, ER can directly bind to estrogen response elements and interact with other transcription factors like NF-κB, SP1 and AP-1 that are crucial for DC differentiation, activation and function (Goriely et al. 2003; Kalaitzidis and Gilmore 2005; Kovats 2012; Leitman et al. 2010; O'Lone et al. 2004).

The differential expression of ER-α in a cell type- or tissue-specific manner will lead to different biological responses (Seillet et al. 2013; Zhou and Slingerland 2014). Recent studies suggest that signaling from E2/ER-α through AF-1 domain could modulate various types of immune cells including DCs, although data for ER (α and β) expression in DCs are scarce (Kovats 2015; Seillet et al. 2013).

ERs Expression on Murine and Human Conventional DCs

While murine conventional DCs (cDCs) express large amounts of ER-α (Kovats 2012; Lambert et al. 2004; Mao et al. 2005; Paharkova-Vatchkova et al. 2004), expression of ER-β in these cells remains controversial. In vivo assays have shown that splenic cDCs from mice express ER-α but fail to express ER-β (Lambert et al. 2004). Similarly, in vitro-differentiated DCs from murine bone marrow precursors also express ER-α (Paharkova-Vatchkova et al. 2004). Likewise, human cDCs derived from peripheral blood monocytes also express ER-α (Escribese et al. 2008). It has been reported that human primary monocytes and monocytes-derived DCs from male and female also express the G protein-coupled receptor 30/G protein estrogen receptor 1, which could bind to E2 (Fig. 1) (Pelekanou et al. 2016).

ERs Expression on Plasmacytoid DCs

Although the ERs expression on murine plasmacytoid DCs (pDCs) has been little studied, there are some reports that indicate that the pDCs also express high levels of ER-α (Kovats 2012; Seillet et al. 2012). Similarly, human pDCs express both ER-α and ER-β (Laffont et al. 2014).

E2/ER-α Modulates Murine and Human cDC Differentiation, Maturation and Activation

E2/ER-α modulates DC homeostasis including the induction of an enhanced Granulocyte macrophage colony-stimulating factor (GM-CSF)-mediated differentiation from murine bone marrow (BMDDCs) precursors, as shown by the observation that ER-α knockout (KO) mice displayed reduced numbers of differentiated DCs than do wild-type mice (Douin-Echinard et al. 2008). In contrast, ER-β KO mice showed normal DCs differentiation suggesting that ER-β was not essential for this biological process (Douin-Echinard et al. 2008). Furthermore, E2/ER-α induced cDCs maturation displaying an immunogenic phenotype with increased expression of CD40 and CD86 molecules in murine BMDDCs (most cDCs) (Douin-Echinard et al. 2008; Siracusa et al. 2008) (Fig. 1). The binding of E2 to ER-α in murine DCs differentiated with GM-CSF promotes the activation of interferon regulatory factor 4 (IRF4), suggesting that the AF-1 domain is required at an early phase of this process (Kovats 2012; Seillet et al. 2012, 2013). Similarly, it has been reported that nonsteroidal anti-estrogens toremifene and tamoxifen inhibit the differentiation of DCs from human primary peripheral blood monocytes keeping their precursors in a low functional level and that fail to activate T cells, due to reduced expression of the co-stimulatory molecules CD80 and CD86 (Komi and Lassila 2000). Multiple studies indicate that E2/ER-α promotes the production of pro-inflammatory cytokines such as interleukin (IL)-6 and IL-12 by BMDDCs after stimulation with Toll-like receptor (TLR) ligands (Cunningham et al. 2012; Douin-Echinard et al. 2008; Seillet et al. 2013; Yang et al. 2006a) (Fig. 1). However, other studies have shown that the ER-α stimulation reduces the IL-6 production after lipopolysaccharide (LPS) stimulation by a direct modulation of NF-κB pathway, which is mediated by the interaction of an ER-α 36-kDa splice variant with the G protein-coupled receptor 30/G protein estrogen receptor 1 (Feldman et al. 2007; Pelekanou et al. 2016).

Conversely, it has been reported that E2 can suppress the immune response of human DCs against RNA viruses, impairing the pro-inflammatory cytokines and chemokines production, such as interferon (IFN)-α/-β and IP-10 in in vitro assays (Escribese et al. 2008).

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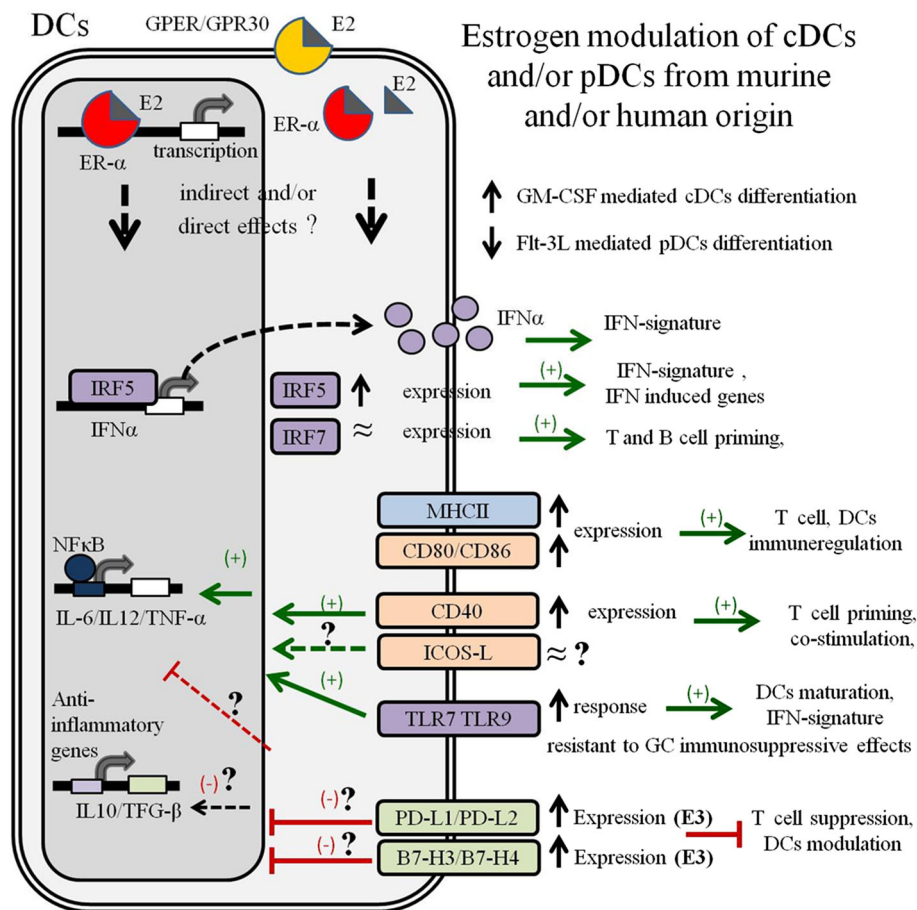Arch. Immunol. Ther. Exp. (2017) 65:123–136

Fig. 1 Modulation of DCs by estrogen. E2/ER-α (and GPER/GPR30) signaling promotes an enhanced immunogenicity status in DCs displaying a mature phenotype. Of note, E2/ER-α promotes GM-CSF-mediated DCs differentiation. Similarly, E2/ER-α signaling promotes the expression of IFN-α, TNF-α, IL6 and IL12 by DCs after TLR stimulation with Poly I:C and CpG leading to an enhanced T and B cell priming. MHCII and co-stimulatory molecules also induced their expression in the presence of E2. Similarly, E2/ER-α signaling promotes cellular activation upon TLR7 and TLR9 ligation which is resistant to GC therapy. Although it has been reported that E2 promotes the increase expression of several inhibitory co-stimulatory molecules such as PD-L1, PD-L2, B7-H3 and B7-H4, their role in DCs immunogenicity has not been assessed. DCs stimulation with E2 may modulate B cell response, plasma cell differentiation and would play a role in breaking tolerance to self-Ags and in the generation of autoantibodies

E2/ER-α Downmodulates the Differentiation of Murine pDC

It has been reported that the E2/ER-α signaling, during murine pDC differentiation induced by Flt3 (Fms-like tyrosine kinase 3) reduces the proliferation and differentiation of these cells, maintaining the ability to present antigen and to activate T cells, for which the AF-1 domain is crucial (Carreras et al. 2008; Kovats 2012) (Fig. 1).

PRL Modulates Differentiation and Maturation of Murine and Human cDC

In addition to the modulatory effects of E2/ERs on cDCs, it was shown that PRL promotes a mature-like phenotype in murine splenic DCs (cDCs and pDCs), increasing the expression of MHC II and CD40 molecules (Yang et al.

2006b). Furthermore, in these cells, PRL increased the production of several pro-inflammatory cytokines such as IL-6 and IL-12 (Yang et al. 2006b). Similarly, PRL collaborated with GM-CSF to promote the differentiation of human primary monocytes into cDCs (Matera et al. 2000).

Progesterone and GC Modulate the Differentiation, Maturation and Activation of Murine and Human cDC and pDCs

Progesterone (Pg) receptor has a fundamental role during pregnancy and is actively expressed by murine BMDDCs, mostly cDCs (Butts et al. 2008). It has been demonstrated that Pg decreases the expression of co-stimulatory molecules and reduces the tumor necrosis factor (TNF)-α and IL-1β production by BMDDCs (Butts et al. 2007, 2008). Similarly, it has been reported that Pg prevents the IFN-α

production by human and murine pDCs after TLR9-ligand CpG stimulation (Hughes et al. 2008). Furthermore, human DCs (no subset specified—cDCs and pDCs) stimulated with Pg decreases the allogeneic naïve T cell proliferation and prevents the upregulation of CD40 and CD80 molecules after stimulation with TLR3 agonist (Quispe Calla et al. 2015). However, other studies suggest that Pg modulates the BMDDCs (cDCs) activity increasing the expression of MHC II and CD40, and the IL-6 and IL-10 production, without affecting the regulatory T cell (Treg) differentiation (Xu et al. 2011). On the contrary, Pg decreases the IL-12 production in murine splenic DCs (no subset specified—cDCs and pDCs), thus underscoring that hormonal milieu can interfere with different functional pathways in DCs (Yang et al. 2006c).

Tolerogenic DCs Induction by GC

Glucocorticoids, such as Dex have been widely used to promote tolDCs development (Unger et al. 2009a; Xing et al. 2002). It has been reported that the glucocorticoid receptor (GR)-D isoform is the variant mostly expressed in murine immature cDCs, while GR-A isoform is the most abundant in mature cDCs from murine BMDDCs and human monocyte-derived DCs (Cao et al. 2013). The GR-A and D expression might be regulated at the translational level, because GR mRNA does not modify its expression after LPS stimulation in murine cDCs. Moreover, in this work it is thought that the apoptotic effect of Dex on murine mature cDCs was mainly mediated by the GR-A isoform (Cao et al. 2013). GR mainly acts by repressing the inflammatory gene expression, inhibiting the AP-1 and NF-κB activation and translocation (Adcock and Caramori 2001) in in vitro assays, Dex-treated human monocyte-derived DCs displayed a semi-mature phenotype with low expression of MHC II and co-stimulatory molecule CD86 (Unger et al. 2009b; Xing et al. 2002). Similarly, murine and human cDCs treated with Dex prevents the maturation induced with TLR ligands, reducing the inflammatory cytokine production and endotoxic-shock response, without affecting IL-10 secretion (Li et al. 2015; Roca et al. 2007). In addition, human monocyte-derived DCs treated with Dex promote the differentiation of naïve CD4$^+$ T cells to Tregs and suppress the effector T cell proliferation (Unger et al. 2009b). Interestingly, GR-polymorphisms seem to be associated with more susceptibility to suffer SLE and with the resistance to GC therapy (Lee et al. 2004; Zou et al. 2013, 2015). Glucocorticoid-induced leucine zipper (GILZ) is one of the regulated genes by GCs in immune cells including T cells and DCs (Cohen et al. 2006; D'Adamio et al. 1997). GILZ is involved in different functions of human monocyte-derived cDC such as activation and differentiation (Cohen et al. 2006). Meanwhile

in human macrophages, GILZ modulates the expression of co-stimulatory molecules CD80 and CD86 (Berrebi et al. 2003). Furthermore, GC/GR/GILZ signaling promotes the IL-10 production in human immature cDCs stimulated with anti-CD40L (Cohen et al. 2006). Patients with alcoholic hepatitis, symptomatic sinusitis and acute cervico-brachial neuralgia under GC treatment showed an increased expression of GILZ suggesting that this protein can be part of the required anti-inflammatory mechanism for this condition (Cohen et al. 2006). In patients with SLE, B cells may express lower levels of GILZ (Jones et al. 2016). Interestingly, GILZ-deficient mice develop a lupus-like syndrome with B cell expansion (Jones et al. 2016). Although cDCs and pDCs have been associated to lupus pathogenesis, a primary defect in hormonal modulation of DCs function has not yet been reported in the literature (Mackern-Oberti et al. 2015).

Modulation of DC Function by Steroids and PRL During SLE

E2/ER-α Modulates Murine cDC, pDCs and SLE Disease Activity in Experimental Mouse Models

Since last decade, researchers have demonstrated the important role of cDCs and pDCs during autoimmune pathogenesis; however, their association with female hormones is still unknown (Grimaldi 2006). Interestingly, murine cDCs loaded with necrotic cells and transferred to lupus-prone mice initiates systemic autoimmunity with high titers of anti-dsDNA antibodies, developing glomerulonephritis, making clear the importance of DCs in lupus pathogenesis and autoimmune modulation (Bondanza et al. 2003; Ginzler et al. 2005). Equally, the depletion of all DCs subsets (cDCs and pDCs) in lupus MRL^{lpr} mice ameliorates the disease, decreases inflammation and prevents the progression of kidney infiltration (Teichmann et al. 2010). Although extensive work has been done using lupus murine models deficient in hormones receptors or pharmacologic approaches, still it has not been defined if hormones/hormone receptors expressed on cDCs and/or pDCs contribute to lupus pathogenesis and progression. Interestingly, it was demonstrated that E2 promotes the development of systemic autoimmunity in different lupus murine models (MRL/lpr, B6.Sle1, NZB/W F1 and NZM2410), and that the loss of ER-α in these mice models decreases immune cell activation and disease activity (Bynote et al. 2008; Scott et al. 2015; Yoachim et al. 2015). However, in the NZB/W F1 female experimental model, ER deficiency did not prevent lymphoproliferation and splenomegaly suggesting that proliferation of lymphoid cells could be separated from

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Fig. 2 ER-α deficiency on DCs reduced immunogenicity. ER-α deficiency reduced GM-CSF-mediated DCs differentiation murine bone marrow (BMDDCs) precursors. ER-α KO mice displayed splenic DCs with a reduced expression of MHCII. Furthermore, ER-α deficiency prevents IFN-α production by pDCs after TLR7-ligand stimulation displaying decreased IFN signature
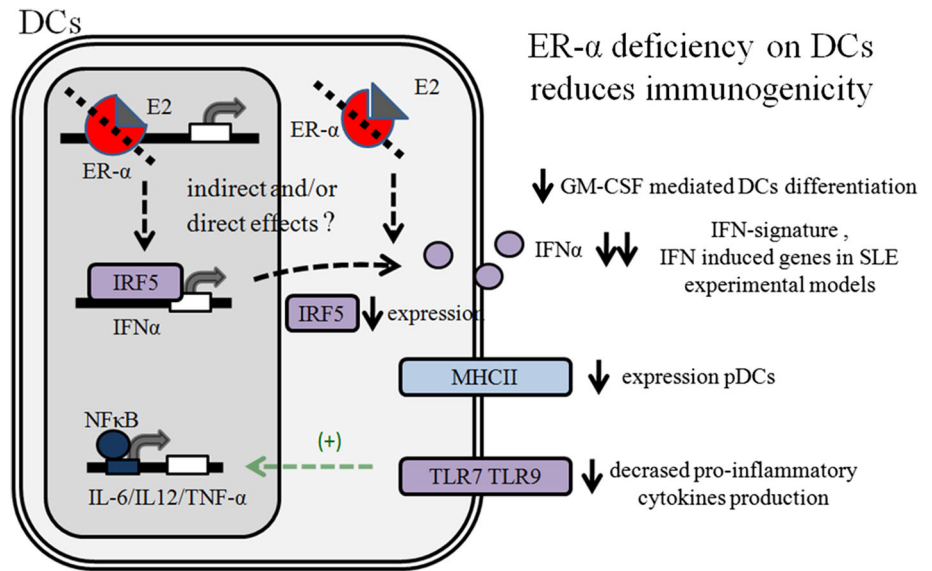
loss of tolerance and in which E2 may promote autoreactive responses (Bynote et al. 2008). Interestingly, in the NZM2410 lupus murine model, the ER-α deficiency decreased the expression of MHC II and PDC-TREM receptor by pDCs from spleen showing that E2/ER-α signaling plays a crucial role in T cell priming (Scott et al. 2015) (Fig. 2). Of note, it has been demonstrated that the stimulation of immature BMDDCs (cDCs) from lupic NZB/W F1 female mice with E2 increases the expression of co-stimulatory molecules and enhances immunogenicity (Jiang et al. 2008). Furthermore, E2 increases the pro-inflammatory cytokines production such as IL-6, IL-12 and TNF-α in BMDDCs (cDCs) from lupus mice suggesting that E2/ER signaling may play an active role during lupus pathology (Jiang et al. 2008) (Fig. 2). In contrast, in the experimental autoimmune encephalomyelitis (EAE) model, a T cell-mediated disease, ER-α and ER-β activation may ameliorate disease severity preserving the axons and myelin in spinal cords by decreasing infiltration of cDCs to the central nervous system and reducing TNF-α production (Du et al. 2011; Papenfuss et al. 2011). These data highlight the notion that E2/ER-α and E2/ER-β signaling may play different, even opposite, roles during autoimmune diseases (Du et al. 2011; Morales et al. 2006).

Pg Modulates SLE Disease Activity in Experimental Mouse Models

In contrast to ER-α, studies focusing on Pg/progesterone receptor's (PR) role on cDCs and pDCs function during SLE pathogenesis are scarce (Wong et al. 2015). However, in lupus murine models it has been demonstrated that PR signaling ameliorates disease severity, decreasing antinuclear antibodies levels (Wong et al. 2015). Moreover, the

administration of medroxyprogesterone acetate (DMPA) to NZB/W F1 female experimental model decreased the levels of antinuclear antibodies IgG2a and IgG3 (Hughes et al. 2009). This reduction induced by DMPA treatment reduces mortality, decreased glomerular lesions accompanied by lower IgG deposits, complement and lower proteinuria incidence (Hughes et al. 2009). Furthermore, NZB/W F1 female lupus mice treated with DMPA reduced the expression of CD86 on splenic DCs (cDCs and pDCs) suggesting that T cell priming is affected (Hughes et al. 2009).

PRL Modulates SLE Disease Activity in Experimental Mouse Models

Similar to E2, PRL has also been associated to lupus pathogenesis in human and murine models but their role on DCs has been poorly studied (Gonzalez et al. 2013; Legorreta-Haquet et al. 2013). In the B6.Sel3/5 mice, PRL induces a lupus-like disease (Peeva et al. 2006) in which PRL increases CD80 expression on cDCs (Gonzalez et al. 2013). Additionally, adoptive transfer of DCs (cDCs and pDCs) from PRL-treated B6.Sel3/5 mice promotes the development of lupus-like disease increasing DNA-reactive B cells suggesting that PRL may promote immune tolerance rupture to DNA (Gonzalez et al. 2013).

GC Modulates SLE Disease Activity in Experimental Mouse Models

Studies based in the generation of tolDCs have used Dex and 1,25 dihydroxyvitamin D(3) (vitD3) to develop new immunotherapies to SLE and RA patients (Wu et al. 2015). These tolDCs from lupus patients keep their immature

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phenotype after inflammatory stimulation, with a low IL-12 production and high levels of IL-10 (Wu et al. 2015). Interestingly, it has been demonstrated that pDCs from NZB/W F1 and TLR7.Tg.6 lupus mice show an altered resistance to GC treatment mainly due to an enhanced TLR7 and TLR9 activation, which could be extremely important in choosing specific therapies for SLE patients (Guiducci et al. 2010).

Estrogen and TLRs

Since decades, it is well known that pro-inflammatory stimuli induce phenotypic changes in immature cDCs and pDCs leading to the maturation and enhancing their immunogenicity (Blasius and Beutler 2010; Bueno et al. 2010; Ioannou and Voulgarelis 2010). It is widely known and reviewed that the TLR and FcγRs play a crucial role in the activation of DCs leading to maturation and T cell priming (Kalergis and Ravetch 2002; Mackern-Oberti et al. 2015). Polymorphisms of pattern recognition receptors (PRR) have been associated to pathogenesis of immune-mediated diseases in humans but their role in DCs immune response has not been assessed (Brain et al. 2013; Cooney et al. 2010; Ferwerda et al. 2008; Mackern-Oberti et al. 2015).

As mentioned earlier, it has been extensively demonstrated that ER-α-deficiency in lupus murine models prevents disease (Bynote et al. 2008). However, the precise contribution of pro-inflammatory factors and E2/ER in different pathogenic processes observed during lupus progression has not been elucidated.

First, it has been demonstrated that the stimulation of murine mesangial cells with TLR3, 4 and 7 ligands enhances ER-α expression and activation, suggesting that pro-inflammatory stimuli increases the sensitivity of glomerulus to E2 (Svenson et al. 2014). In contrast, ER-α deficiency in murine mesangial cells reduces IL-6 and monocyte chemoattractant protein-1, secondary to TLR-ligand stimulation (Svenson et al. 2014). Similarly, the treatment of differentiated THP-1 cells (human monocytic cell line) with E2 promotes the expression of TLR2, suggesting that hormonal modulation increases the sensitivity to TLR2 ligands being an estrogen-regulated innate receptor (Li et al. 2014).

Potential Role of Immune Complexes Recognition by TLR on pDCs in Lupus Pathogenesis

Several TLRs may also recognize self-molecules such as immune complexes (ICs) containing RNA or DNA molecules leading to tissue destruction and inflammation (Leadbetter et al. 2002; Wen et al. 2013). Extracellular self-DNA of murine and human pDCs needs to be transported into PRRs containing endosomes to trigger inflammation and autoimmunity (Doring et al. 2012; Lande et al. 2007; Sandgren et al. 2004). During lupus pathogenesis, the TLR2 expression induced by E2 may have a pathogenic role when this hormone interacts with TLR2-ligands containing immune complexes such as HMGB1–DNA–IgG and then promoting tissue destruction (Wen et al. 2013). It has been reported in in vitro assays that pDCs from female produce higher amounts of pro-inflammatory cytokines than male and the treatment of murine pDCs with E2 enhances the production of IFN-α after TLR7 ligand stimulation (Seillet et al. 2012) (Fig. 1). Interestingly, clinical studies show that the administration of E2 to postmenopausal women increases the production of pro-inflammatory cytokines after stimulation with immune complexes containing RNA and DNA, suggesting a synergistic effect of E2/ER, TLRs and FcγRs (Seillet et al. 2012). For the other hand, AF-1 domain deficiency prevents activation of murine female pDCs through ER-β after TLR7-mediated IFN-α production (Seillet et al. 2013). Of note, cDCs (BMDDCs) deficient in ER-α fail to produce IL-6 via IgG-DNA (or RNA) immune complexes which could explain the phenotype observed in lupus experimental models (Cunningham et al. 2012) (Figs. 2, 3). Furthermore, TLR8 expression is increased in peripheral blood mononuclear cells (PBMCs) from SLE patients (Young et al. 2014). Moreover, TLR8-ligand stimulation of female PBMCs showed a sex-biased response which may help in understanding female restricted SLE pathogenesis (Young et al. 2014).

In contrast to these findings, a study performed in cDCs from rats treated with E2 in vitro showed a decrease in T cell priming induced by LPS or R848-TLR7/8 agonist and a decrease in Th1 cell differentiation (Stojic-Vukanic et al. 2015).

Estrogen and Fcγ Receptors

ICs play an active role in the inflammatory response and they are involved in lupus pathogenesis and progression (Brown et al. 2007; Clynes et al. 1998). IC deposition contributes to kidney damage mainly glomerulonephritis in SLE caused by autoantibodies (Clynes et al. 1998). The balance of activating/inhibitory signals from FcγRs on murine cDCs and B cells may modulate the immune response and where failure of this mechanism may lead to autoimmunity (Iruretagoyena et al. 2008). Thus, ICs binding to activating receptors FcγRI/III on murine cDCs lead to maturation and pro-inflammatory cytokines production, while binding to inhibitory FcγRIIb keeps DCs in a tolerogenic and immature phenotype (Herrada et al.

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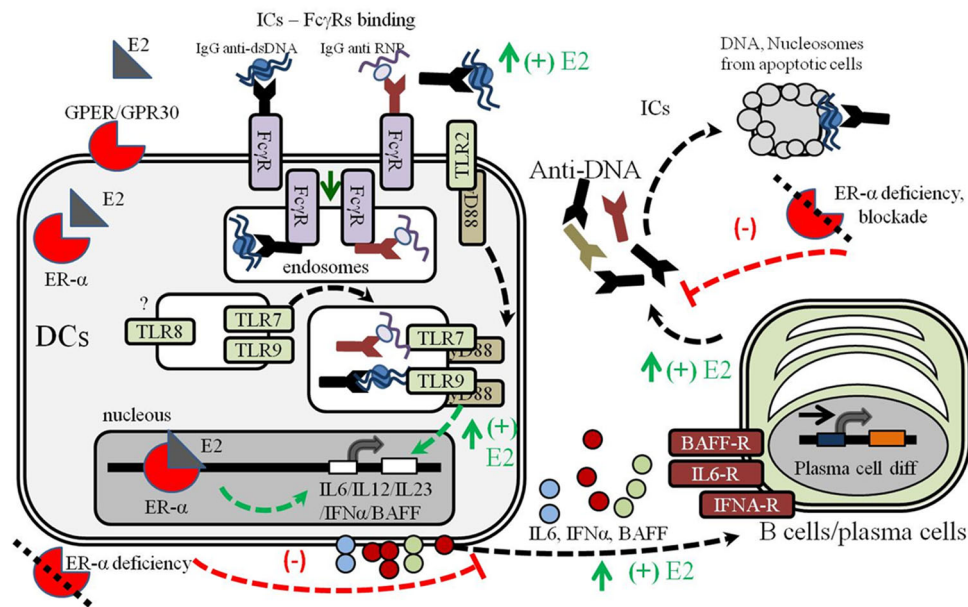Arch. Immunol. Ther. Exp. (2017) 65:123–136

Fig. 3 Hypothetical mechanism of E2/ER signaling in modulating DCs and B cells in SLE. In lupus-susceptible hosts E2/ER signaling may modulate TLR7/9 response to ICs containing self-DNA/RNA, promoting the production of several pro-inflammatory cytokines including IFN-α, BAFF and IL-6. These cytokines are involved in B cell homeostasis supporting plasma cell differentiation and antibody production, which in susceptible host with tolerance failure, may lead to auto-antibody development and autoimmunity. Higher amounts of autoantibodies containing self-DNA/RNA in the presence of E2/ERs signaling may continue fueling this TLR/ICs-mediated fully DCs activation. In contrast, ER-α deficiency decrease autoimmune susceptibility decreasing autoreactive B cells. These E2/ERs signaling modulation may partially explain the sex-biased autoimmune pathogenesis observed in female SLE patients

2007; Kalergis 2003; Llanos et al. 2011; Nimmerjahn et al. 2005; Nimmerjahn and Ravetch 2007; Ravetch and Bolland 2001). Of note, cDCs from SLE patients displayed an increased expression of activating FcγRs while inhibitory FcγRIIb expression is decreased leading to an unbalanced ratio of activating/inhibitory FcγRs and correlates with disease activity (Carreño et al. 2009). This strongly suggests that ICs may differentially modulate DCs from lupus patients and healthy controls (Carreño et al. 2009). Although the role of hormonal milieu in modulating FcγRs on DCs has not been assessed, since 1980s it is known that in vivo estrogen administration to mice or guinea pig increased the expression of FcγRs by macrophages in the spleen, enhancing the clearance of immune complexes (Friedman et al. 1985; Gomez et al. 2001). In contrast to E2, Pg decreased the expression of FcγR2 which may partially explain the differences in the severity of autoimmune diseases, such as RA and SLE during pregnancy (Gomez et al. 1998). Similar to Pg, Cortisol, prednisone, and Dex prevent in vivo the clearance of IgG-coated erythrocytes which would be mediated by a decreased expression of FcγRs on splenic macrophages (Ruiz et al. 1991). However, it has been reported that chronic administration of Dex to lupus MRL/lpr mice increased the expression of FcγRs on resident peritoneal macrophages

but keeping controlled the pathogenesis of lupus (Zuckerman et al. 1997).

Modulation of Co-Stimulatory Molecules by Estrogen

In susceptible hosts, the autoimmune reactions are triggered when antigen-presenting cells capture self-antigens and present them to self-reactive T cells that have escaped from tolerance mechanisms (Gratz et al. 2014). Co-stimulatory molecules expression on cDCs and pDCs represents an essential event in the self-reactive T cell activation, and their intervention may ameliorate disease progression (Bhardwaj et al. 1993). In this review, it has been previously described the potential effect of E2/ER-α in MHCII, CD86 and CD40 expression on DCs (Douin-Echinard et al. 2008; Jiang et al. 2008; Siracusa et al. 2008) (Fig. 1). However, the role of estrogen as a modulator of the expression of other co-stimulatory and MHC-like molecules such as CD1d, OX40 ligand (OX40L) and SLAM/CD150 on cDCs and pDCs has not been elucidated (Beckman et al. 1994; Burgess et al. 2004; Witsch et al. 2002). Interestingly, it has been demonstrated that E2 promoted the expression of CD40 in murine cDCs

(BMDDCs) through MCM6 factor (Xie et al. 2011). Conversely, ICOS-ligand may have no changes after estriol (E3) stimulation (Papenfuss et al. 2011). Furthermore, patients with lupus showed an altered expression of MCM6 suggesting that an altered expression of this protein may play an active role during lupus pathogenesis and partially explain the sex-biased susceptibility of SLE to female (Xie et al. 2011).

Furthermore, the role of E2/ER-α in modulating the inhibitory interaction between DCs and T cells, PD-1 on T cells and its ligand PD-L1 on DCs has been less assessed (Gianchecchi et al. 2013; Papenfuss et al. 2011; Yamazaki et al. 2002; Yogev et al. 2012). It has been shown in in vitro assays that PD-L1 expression on cDCs inhibits T cell activation and promotes Tregs development by modulating crucial signaling molecules such as PTEN and mTOR (Dilek et al. 2013; Francisco et al. 2009; Keir et al. 2007). Susceptible mice lacking PD-1 develop a lupus-like syndrome displaying glomerulonephritis and lymphoproliferation (Nishimura et al. 1999). Similar to data observed with activating co-stimulatory molecules, in vivo E3 treatment of wild-type mice induces the expression of several inhibitory co-stimulatory molecules such as PD-L1, PD-L2, B7-H3, and B7-H4 on cDCs which may partially explain the protective role of estrogens in the development of EAE (Papenfuss et al. 2011) (Fig. 1). On the other hand, TIM-3 has been shown to be an inhibitory molecule present on murine and human cDCs and pDCs but, similar to other co-stimulatory molecules, it is unknown whether E2/ER-α could modulate TIM-3 (Chiba et al. 2012). Due to no single co-stimulatory molecule being immunogenic or tolerogenic, research on the complex molecular networks between E2 and ER-α that modulate DCs immunogenicity is crucial for understanding SLE pathogenesis and drug-resistance mechanisms.

Hormonal Milieu and IFN Signature in SLE

Role of E/ER-α Pathway on IFN Signature

The IFN signature, corresponding to an increase in the expression of genes regulated by IFN is associated with lupus (Banchereau and Pascual 2006). Furthermore, it is widely accepted that lupus progression is associated with IFN-α production by pDCs (Watarai et al. 2008). These cells produce high amounts of IFN-α after stimulation with immune complexes containing DNA or RNA (Barrat and Coffman 2008). In addition, the administration of adenovirus expressing IFN-α to SLE NZB/NZW mice accelerated disease onset, increasing the serum levels of anti-dsDNA antibodies and which is related to increased serum levels of B cell activating factor (BAFF), IL-6 and

TNF-α (Liu et al. 2011). Interestingly, pDCs from healthy females produce higher amounts of IFN-α than men, after stimulation with TLR7 ligand (Berghofer et al. 2006). However, increase in the IFN-α production by female pDCs was not observed after stimulation with TLR9 ligand, suggesting a privileged and sex-restricted IFN-α production by female TLR7 signaling (Berghofer et al. 2006). In addition, only female pDCs exhibit an increased in the IRF5 protein expression and is associated with the amounts of IFN-α-secreted by pDCs, which would explain the TLR7-induced IFN-α response in females (Griesbeck et al. 2015) (Fig. 1).

In the NZM2410 lupus murine model, the ER-α deficiency decreased IFN-α production by pDCs from spleen, which is accompanied by a lower disease severity (Scott et al. 2015) (Fig. 2). Interestingly, using conditional KO mice for ER-α in DCs, it has been reported that pDCs showed decreased the IRF5 mRNA expression and IFN-α production after of the stimulation with TLR7 ligand when compared to wild-type mice, suggesting that E2/ER-α signaling modulates pDCs function (Griesbeck et al. 2015) (Fig. 2). In addition, the ER-α mRNA expression correlates with IRF5 mRNA levels in human female pDCs underscoring the potential role of E2/ER-α signaling during lupus pathogenesis (Griesbeck et al. 2015) (Fig. 1).

Role of Pg on IFN Signature

In contrast to the effect of E2, Pg impaired the production of IFN-α by human and mouse pDCs after TLR9-ligand stimulation (Hughes et al. 2008). Pg also impairs IRF-7 activation in pDCs after CpG stimulation in in vitro assays (Hughes et al. 2008). Furthermore, Pg inhibits the IL-12 production from human and mouse pDCs after CpG treatment (Hughes et al. 2008). In mice, in vivo administration of Pg (DMPA) inhibited the increased expression of CD86, MHCII and CCR7 on pDCs from spleen after of the infection with vesicular stomatitis virus (RNA virus) (Hughes et al. 2008).

DC and B Cell Interactions

B cells produce antibodies after B cell receptor engagement by the specific antigens (Fagarasan and Honjo 2000). During lupus pathogenesis, the role of B cells is crucial and targeting these immune cells is a current therapy for RA but fails in SLE patients (Gregersen and Jayne 2012). Regulatory B cells from SLE patients showed an altered phenotype displaying an altered function and producing small amounts of IL-10 (Blair et al. 2010). Of note, it has been shown in in vitro assays that human DCs (dendritic Langerhans cells—cDCs) may modulate and induce IgA

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class switch on CD40-activated naive B cells (Fayette et al. 1997). Similarly, it has been demonstrated that murine activated splenic DCs (cDCs and pDCs) enhanced B cell proliferation, migration and antibody production in lupus-prone mice (Wan et al. 2008). Human pDCs can also induce plasma cell differentiation increasing the secretion of antibody through IFN-α and CD70 expression (Shaw et al. 2010). BAFF, one of the most important B cell survival factors could be produced by B cells, T cells, NK cells, monocytes and DCs and correlated with IFN-α production and disease activity in SLE patients (Panchanathan and Choubey 2013; Vincent et al. 2014). New biological agents targeting BAFF are continuously being tested in pre-clinical and clinical trials with SLE patients in which the treatment with these drugs decreased antinuclear antibody levels (Isenberg et al. 2016).

Modulation of BAFF Expression by E2/ER-α

Interestingly, BAFF expression was higher in splenic DCs (cDCs and pDCs) and macrophages from wild-type female mice spleen compared to male cells (Panchanathan and Choubey 2013) (Figs. 1, 3). Furthermore, in vitro treatment of B cells and macrophages with E2 increased BAFF mRNA and protein levels while in ER-α-deficient mice the BAFF levels were deeply affected (Panchanathan and Choubey 2013). Similar to E2, IFN-α also increased BAFF levels in B cells and macrophages in in vitro assays, meanwhile in IRF5-deficient mice the BAFF levels were markedly affected (Panchanathan and Choubey 2013). Of note, in the lupus-prone mice Nba2 and MRL^{lpr}, p202 expression, which is an IFN-inducible protein, correlates with ER-α and BAFF levels in female mice, highly suggesting a pivotal crosstalk between IFN-related genes and ER-α signaling partially explaining higher susceptibility of SLE in female patients (Panchanathan and Choubey 2013) (Fig. 3).

Modulation of the Interaction Between DCs and B Cells by PRL During Lupus

Interestingly, it has been described that the transfer of splenic DCs (cDCs and pDCs) from lupus mice treated with PRL to wild-type mice induced several changes in the number of transitional (T1 and T2) B cells which may reflect a B cell escape from central tolerance (Gonzalez et al. 2013). Furthermore, mice receiving PRL-treated cDCs, displayed an increased expression of MHCII and CD40 on B cells that may lead to an enhanced antibody response (Gonzalez et al. 2013).

These data highlight the interplay of hormonal milieu and DCs in B cell modulation and underscored the need to continue evaluating several conditions in which pathologies are associated to female hormones such as RA and SLE.

Conclusions

Although much progress has been made in understanding the mechanism of autoimmune diseases, the role of hormonal milieu in DCs signaling is still a major goal of rheumatologists. The immunomodulatory effects of estrogen and other hormones to DCs function may affect T and B cells immune response which in turn may play an active role during lupus pathology. E2, PRL, Pg, and GC affect the DCs phenotype leading to a more immunogenic or, in contrast, to a tolerogenic status. Between all hormones, E2 has been reported to produce a mature phenotype on DCs with the production of several pro-inflammatory cytokines such as IL-6, IL-12 and TNF-α and increasing the expression of CD40, CD86 and MHCII molecules. Furthermore, E2 treatment to lupus-prone mice such as MRL/lpr, B6.Sle1, NZB/W F1 and NZM2410 promotes the development of immunopathogenesis. Of note, in lupus-prone mice, ER-α deficiency decreased the expression of MHC II by pDCs from spleen suggesting an active role in DCs. The IFN signature, which is associated with lupus, may also be modulated by E2/ER-α signaling, especially on pDCs response after TLR7 ligation. Similarly, DCs-B cells' interactions may also be modulated by E2/ER-α by the fact that BAFF expression was higher in splenic DCs from female mice. However, it is not clear whether E2/ER-α signaling modulates immune mediators through direct or indirect effects. All these data uncover a potential role for estrogens and other hormones in modulating DCs' immune functions, which may account for sex-based susceptibility to develop autoimmune diseases.

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