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Review

Contribution of sex steroids and prolactin to the modulation of T and B cells during autoimmunity

Gabriela Recalde [a], Tamara Moreno-Sosa [b,d], Florencia Yúdica [a], Cristian A. Quintero [a], María Belén Sánchez [b], Graciela A. Jahn [b], Alexis M. Kalergis [d,e], Juan Pablo Mackern-Oberti [b,c,d,*]

[a] Universidad Juan Agustín Maza, Argentina
[b] Instituto de Medicina y Biología Experimental de Cuyo IMBECU-CCT-CONICET Mendoza, Argentina
[c] Instituto de Fisiología, Facultad de Ciencias Médicas, Universidad Nacional de Cuyo, Argentina
[d] Millennium Institute on Immunology and Immunotherapy, Departamento de Genética Molecular y Microbiología, Facultad de Ciencias Biológicas, Pontificia Universidad Católica de Chile, Santiago, Chile
[e] Departamento de Endocrinología, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

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ABSTRACT

In this review we discuss how sex steroids and prolactin affect regulation and responsiveness of B and T cells. Sex hormones exert profound effects on several physiological processes of non- reproductive tissues. In the immune system, several studies with experimental models for SLE have shown a noticeable pro-inflammatory role for ERα, contributing to disease development reflected in proteinuria and renal pathology. On the other hand, ERβ appears to have an anti- inflammatory and immunosuppressive effect. Estrogen/ERα signaling induced an increase of Th17 cells in lymph nodes as well as the expression of its correspondent chemokine receptor CCR6 during collagen induced arthritis acute phase. High levels of anti- DNA antibodies and increased mortality was observed when given high E and prolactin doses to NZB/NZW mice, as compared with mice receiving low E and prolactin doses, or high E and low prolactin doses. Intracellular progesterone receptors have been detected in $TCD4^{+}$ cells but in contrast as observed with ERs, it suppresses T cell dependent responses. Progestagen administration on female NZB/NZW mice decreased anti DNA IgG, improved survival, decreased glomerulonephritis and proteinuria.

Contents

* Corresponding author at: Instituto de Medicina y Biología Experimental de Cuyo IMBECU-CCT-CONICET Mendoza, Av. Ruiz Leal s/n Parque Gral San Martín, Mendoza, Argentina.
E-mail address: jpmackern@mendoza-conicet.gob.ar (J.P. Mackern-Oberti).

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1. Introduction

It is well known that autoimmune diseases are triggered by an immune response raised by the body directed towards its own tissues or cellular components; however, their etiology remains unknown. Although advances have been reported in the last decade in relation to their mechanisms, specific and effective therapies for autoimmune disorders have not yet been developed [1–4]. Currently, it is postulated that multiple factors participate in the onset of autoimmune diseases including genetic, environmental, infectious and hormonal components that confer greater susceptibility but are not determinant for their development [5–7]. The high incidence of autoimmune diseases in females versus males suggests that female hormonal homeostasis is a very important risk factor [8].

Sex hormones exert profound effects on several physiological processes of non- reproductive tissues. In the immune system, sex hormones have several activities, such as modulation of cytokine production by lymphocytes, cytokine receptor expression, and activation of effector immune cells [9]. By modifying dendritic cells (DCs) function, E (E) could alter T cell proliferation [10]. In contrast, incubation of DCs with Progesterone (P) decreases T cell priming and prevents the upregulation of co-stimulatory molecules after stimulation with Toll-like receptor 3 (TLR3) ligands [11]. In relation to hormonal status, it has been reported that a certain subset of Systemic Lupus Erythematosus (SLE) patients showed high prolactin (PRL) levels, which have also been associated to disease activity [12,13]. In this review, we discuss recent data relative to the role of E, prolactin and Pg in T and B cells function in immunity and autoimmune disorders.

2. Estrogens and T cells

Estrogens (E) have a complex role in inflammation [14] and most of their effects are mediated by two specific intracellular receptors, i.e., E receptor (ER) α and β, which function as ligand- activated nuclear transcription factors producing genomic effects [15]. ERα and β are the products of different genes (ESR1 and ESR2, respectively) and in the human, are located on different chromosomes (locus6q25.1 and locus 14q23–24.1, respectively) [16,17]. Human ERα and ERβ are modular proteins that belong to the nuclear receptor protein family, with a structure that can be divided into common regions, named A/B, C, D, E, and F. These regions participate in the formation of independent and interacting functional domains: the N-terminal transactivation domain, the DBD (DNA-binding domain), the dimerization domain(s), the nuclear localization sequence (NLS), and the LBD (ligand-binding domain) [18–20]. The A/B region or the N-terminal transactivation domain of ERs is involved in protein–protein interactions [21] and in transcriptional activation of target-gene expression [19,21]. Also, it contains the activation function-1 (AF-1) domain and several phosphorylation and sumoylation sites [18]. The AF-1 domain binds, directly or via co-activators/co-repressors, to some parts of the primary transcription machinery [22]. The DBD plays an important role in receptor dimerization and binding of specific DNA sequences [20]. The C-terminal E/F region of ERs include the LBD, the AF-2 domain, and part of the nuclear localization region (NLS) [20,23].

ERα and ERβ differ markedly in their tissue distribution that includes immune cells [15,24,25]. The relative expression of one ER subtype over the other might change E effects, promoting or dampening inflammation [14]. Several studies with experimental models for SLE developed in mice have showed a noticeable pro-inflammatory role for ERα, contributing to disease development reflected in proteinuria and renal pathology [26–28]. On the other hand, ERβ appears to have an anti-inflammatory and immunosuppressive effect on these mice and application of the ERβ-selective agonist diarylpropionitrile (DPN) starts a reduction of autoantibody production and a decline of albuminuria [27]. In fact, a significantly lower expression of ERβ in T cells from patients with SLE compared with healthy controls [29] has been reported. Similarly, a significant reduction of ERβ expression in peripheral blood T lymphocytes from Crohn disease and ulcerative colitis patients with active disease as compared to those in remission and healthy controls [30] has been demonstrated. These results suggest that downregulation of ERβ is found in a pro-inflammatory microenviroment.

Some evidence indicates that E can regulate pathways leading to IL-2 production, which is an important factor in determining T-cell tolerance and differentiation [31]. E increases Sp1 (specific protein 1, transcription factor) expression in human T cells [32], which increases expression of the cAMP responsive element modulator (CREM). CREM in turn binds to the IL- 2 promoter and suppresses the production of IL-2 [32]. This mechanism could potentially account for the increased expression of CREM and decreased expression of IL-2 observed in female patients with SLE when compared to male patients [33] (Fig. 1A).

The discovery of membrane-associated ERα (mERα) in different cell types, including lymphocytes [25], has greatly expanded the understanding of E effects [34]. Rapid signaling by 17β-estradiol at the membrane level is consistent with the rapid actions of numerous steroids acting at often-undefined receptors in a variety of cells [35]. Membrane ERα rapidly activates different protein kinase cascades influencing downstream transcription factors to produce non- genomic effects; at the same time, it can modulate intracellular ER action through the phosphorylation of intracellular ERs and their co-activators [36] (Fig. 1A).

The discovery of the Th17 cell as a bona fide T-cell subset led to a rekindling of interest in this cytokine in the context of autoimmunity. Many, if not most, autoimmune diseases are now connected in some manner to IL-17 or to the Th17 pathway, indeed, pre- clinical studies supporting a role for IL-17 in immune mediated diseases has led to current clinical trials designed to block IL-17, the IL-17 receptor (IL-17R) or its inducers in autoimmunity [37]. Interestingly, E/ERα signaling induced an increase of Th17 cells in lymph nodes as well as the expression of its correspondent chemokine receptor CCR6 during collagen induced arthritis acute phase [38] (Fig. 1A).

All these data highlights the potential role of E and ERs on T cell homeostasis during immune mediated diseases.

3. Estrogens and B cells

The effects of sex hormones on the immune system are not limited to T cells [39,40]. It has been demonstrated that E affect different stages of B-cell development and modify the humoral response [41–43]. In the bone marrow, E treatment decreases the number of B-cell precursors by negatively affecting differentiation, proliferation, and viability of early B-cell precursors. It regulates cytoplasmic μ^+ bone marrow pre-B cells [42], immunoglobulin (Ig) gene rearrangements, and mitotic activity of early B cells [44] (Fig. 1B). ERα has a key role in the regulation of B lymphopoiesis and Ig production [45]. E treatment induces B cell homeostasis changes, an observation that supports the importance of ERα in the regulation of B cell development [46]. ERs and its nuclear receptor family members are involved in the regulation of the functional aspects of B cells during class switch recombination. E treatment decreases B- cell lymphopoiesis in the bone marrow and this effect can be mediated through either ERα or ERβ [26,47]. The decreased lymphopoiesis has been shown to reflect an estradiol-mediated decrease in IL-7 production by bone marrow stromal cells. IL-7 responsive B cell precursors were greatly expanded in genetically hypogonadal female mice that have a secondary deficiency in gonadal steroidogenesis. E replacement in these mice resulted in a dose-dependent reduction in B cell precursors [43] (Fig. 1B).

Since E is a potent inhibitor of B-cell lymphopoiesis, physiological conditions of high E production, such as pregnancy, are associated with a reduction in B lymphopoiesis [48,49]. Conversely, ovariectomy leads to increased B lymphopoiesis [50].

In contrast, it has also been described that treatment of women with E or exposure of human peripheral blood mononuclear cells (PBMCs) to

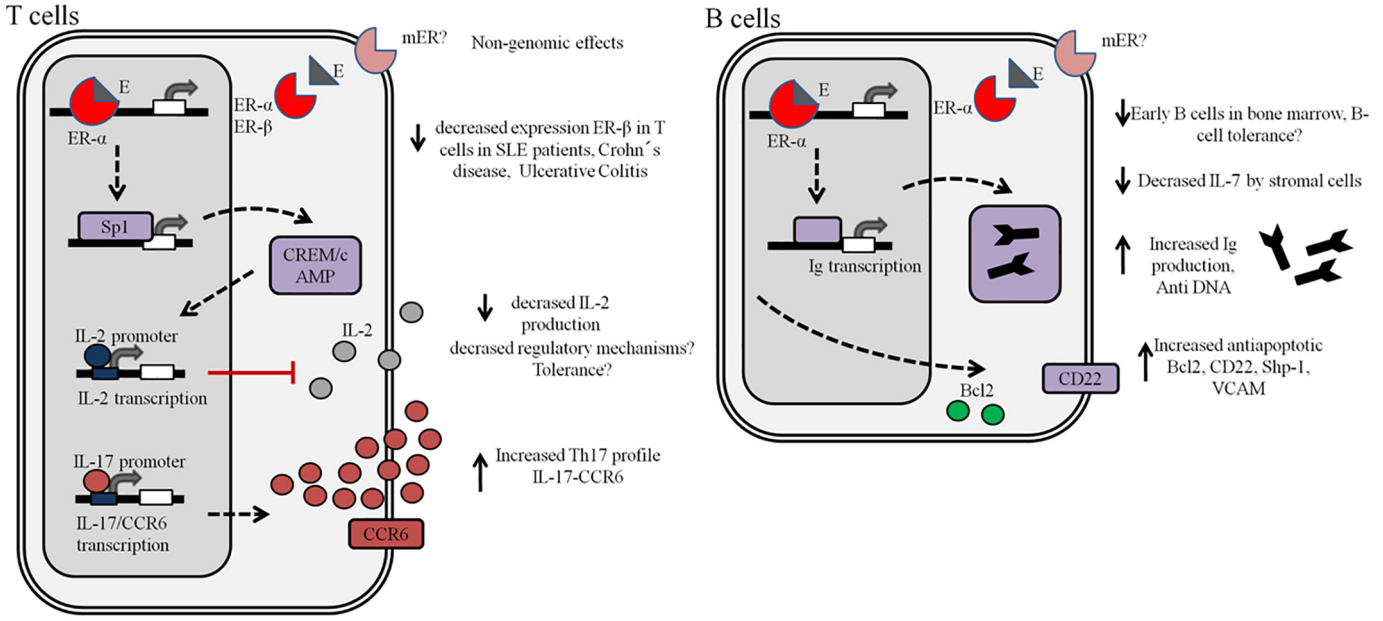

Fig. 1. Estrogen, estrogen receptor, T cells and B cells. A, a significant lower expression of ERβ in T cells from patients with SLE compared with healthy controls is reported. Estrogens (E) increases Sp1 (specific protein 1, transcription factor) expression in human T cells which increases expression of the cAMP responsive element modulator (CREM). CREM in turn binds to the IL- 2 promoter and suppresses the production of IL-2 decreased expression of IL-2 observed in female patients with SLE when compared to male patients. E/ERα signaling induced an increase of Th17 cells in lymph nodes as well as the expression of its correspondent chemokine receptor CCR6 during collagen induced arthritis acute phase. E treatment decreases the number of B-cell precursors by negatively affecting differentiation, proliferation, and viability of early B-cell precursors amd Ig production. E seems to promote survival of self-reactive B cells at peripheral checkpoints, possibly via upregulation of the prosurvival molecule, apoptosis regulator Bcl-2, the B cell surface molecule CD22, and other genes such as shp-1, and vcam-1.

E lead to significantly higher levels of Igs [51]. 17β-estradiol acts on mouse splenocytes by increasing IgM and IgE levels [52]. Interestingly, E increases the frequency of IgA-producing B cells in $\mu MT^{-/-}$ mice lacking the μ Ig heavy-chain in both bone marrow and spleen, suggesting the existence of an alternative B-cell activation pathway in response to E [53]. Short-term E treatment increases the number of Ig producing cells both in ovariectomized and intact animals [45]. On the other hand, long-term E exposure induces production of antibodies to various self-antigens, such as DNA [54], cardiolipin [55–57], phosphatidylserine, and phosphatidylinositol [56], as well as Ig deposition in renal glomeruli [58]. These data show that the duration of E exposure has a differential influence on B-cell responses (Fig. 1B).

E seems to promote survival of self-reactive B cells at peripheral checkpoints, possibly via upregulation of the prosurvival molecule, apoptosis regulator Bcl-2, the B cell surface molecule CD22, and other genes such as shp-1, and vcam-1 [58–62]. The increased survival might occur through the binding of ER to E response element (ERE) present in the bcl-2 gene [63] (Fig. 1B).

Marginal zone B cells, which are implicated in innate-like B-cell immunity [64], produced high level of anti-DNA antibodies, and deletion of CD4+ T cells did not alter their activation after E exposure [54]. As might be expected, tamoxifen downregulates the induction of *E*-modulated lupus by preventing B cells from differentiating to a marginal zone B-cell phenotype [41,54]. The recombinant inbred NZM strains of mice develop severe lupus at an early age. It has been reported that female NZM/ERα KO mice developed milder lupus diseases with improving survival compared to the wild type littermates [65]. However, NZM/ERα KO mice developed similar levels of anti DNA IgG and comparable immune complex deposition in the glomerulus [65]. Altogether, these data demonstrate that E may modulate B cell homeostasis leading to autoimmune development.

The fact that E impairs B cell lymphopoiesis while increasing Ig producing cells hinder the understanding of the immunological effects that occur in different B cell compartment and physiological conditions such as spleen, lymphoid tissues and gestation between others. Additionally, given E induce PRL secretion it is likely probable that this last hormone be partially involved in E-induced effects [66].

4. Estrogen actions on monocytes and DCs

Human monocytes express low levels of ESR1 and ESR2 mRNA [24]. Using flow cytometry analysis, it has been reported that 88% of the human peripheral blood monocyte population is positive for ER (using a monoclonal antibody that recognizes both isoforms) which localizes in the nuclei [67]. Although, the monocytic cell line U937 expressed only ERβ, when this cell line differentiates into macrophages with PMA treatment, the ER expression profile changed to high expression of ERα with decreased levels of ERβ [67]. In contrast human monocyte-derived DCs, which are mainly conventional DCs (cDCs), displayed high levels of ESR1 transcripts and low levels of ESR2 mRNA [68,69]. Although plasmacytoid DCs (pDCs) are one of the most important immune cells during SLE pathogenesis, there are few studies evaluating the expression of ERs mRNA in them [9,67,70]. It has been reported that human pDCs express both receptors, ERα and ERβ [68]. Murine cDCs express higher levels of ERα than ERβ [71]. Lambert et al. showed that cDCs from mice spleen and thioglycolate-elicited peritoneal macrophages express ERα mRNA, however neither cell type expressed ERβ [72]. Using KO mice, in vitro differentiated DCs from murine bone marrow precursors may also express ERα [73]. Recently, it has been reported that E2 may also be able to initiate fast responses independently of classical ERs. Human primary monocytes and monocyte-derived DCs express the G-protein coupled receptor 30/G-protein E receptor 1, which could bind to E2 and initiate rapid responses [74].

Interestlingly, ERα KO mice display reduced numbers of differentiated DCs from bone marrow suggesting E/ERα modulates GM-CSF mediated differentiation [75]. It is important to note that most fetal calf serum preparations possess sufficient amounts of E to promote DC differentiation [76]. Furthermore, the generation of bone marrow derived DCs is impaired without E stimulation [75]. In contrast, it has been reported that the E/ERα signaling, during Flt3 differentiation of pDCs

reduces proliferation keeping functional status [71,77]. ERα deficient DCs displayed a decreased capacity of stimulate T cell in the OVA specific transgenic T cells [75]. In contrast, E/ERα ligation induced a mature phenotype with higher levels of co- stimulatory molecules CD40 and CD86 and higher expression of IL6 and IL12 in murine BMDDCs [75,78]. In contrast, ERβ KO mice showed normal DCs differentiation suggesting that ERβ is not essential for this biological process [75].

E increases TLR-ligand activation of DCs via binding to ERα [78]. While CD40 expression was not affected in ERα KO DCs, the response to CD40L and cytokine production were reduced suggesting that DC induced T cell activation is controlled by ERα activation [75]. Additionally, E2/ERα signaling in DCs differentiated with GM-CSF promotes the activation of Interferon Regulatory Factor 4 (IRF4) which is actively involved in autoimmunity [71]. All these data suggest that the sex of the patient should be considered when targeting immune responses in cancer or autoimmunity.

5. Prolactin and T cells

In recent years the role of pituitary sex hormones such as PRL has been widely studied and it has been observed that in addition to exerting its endocrine control on reproduction, growth, metabolism, behavior and immune system, it acts as a cytokine modulating the immune response by paracrine and autocrine mechanisms [79–85]. These functions include the capacity of PRL to increase the number of immune cells in mammary gland exudates and to enhance the chemotaxis effect over T cells, memory T cells, B cells, monocytes, macrophages, neutrophils and eosinophils [86], among others. In addition, an association between hyperprolactinemia (hyperPRL) and systemic autoimmune diseases (SLE and RA), as well as organ-specific autoimmune diseases (DM1, Hashimoto's Thyroiditis and Multiple Sclerosis) has been reported [87–90]. However, no data clearly attribute a pathogenic role to PRL in human autoimmune pathology. In type 1 diabetes, a disease caused by the autoimmune destruction of pancreatic β-cells, PRL can enhance the efficacy of the anti-CD3 monoclonal antibody therapy to induce the remission of diabetes by regulating the mass and function of the β cells [91]. However, this action of PRL was not related to the proliferative capacity of T cells [91] but to a trophic action of PRL upon β-cells. Similarly, in experimental autoimmune encephalomyelitis (EAE), an animal model of MS [92–94], the combination of prolactin and a suboptimal dose of recombinant murine interferon [β] improved clinical signs of the disease [95]. The role of PRL in EAE was also seen in the delay in production of IFN-γ, IL-17A and IL-6 and the T cell proliferation induced by myelin Ag in PRL- and PRL-R KO mice [96] (Fig. 2A). These results suggest an enhancer effect of PRL in the improvement of both diseases. Prolactin also may modulate the suppressor effect of regulatory T (Treg) cells, since prolactin decreases the suppressor effect exerted by Treg cells [97] (Fig. 2A). The PRL-R is constitutively expressed on Treg cells in healthy individuals and SLE patients, and this expression is higher in SLE patients [97]. This point is interesting because both percentage and function of Treg cells are decreased in SLE patients compared to healthy individuals [97]. This fact could suggest a relationship between the prolactin signaling pathway and the SLE progression.

6. Prolactin and B cells

In addition to the pituitary production and secretion, PRL is produced by the immune system cells, which also express PRL receptors (PRL-R) [98] (Fig. 2 B). Accordingly, we can expect that PRL acts on the immune system via endocrine and paracrine/autocrine pathways [99]. Cells of the immune system in the blood and various hematopoietic organs constitutively express PRL-Rs [100].

Prolactin action is mediated by the PRL-R which exists as a long and a short isoforms; the latter resulting from alternative splicing of the intracellular cytoplasmic domain (ICD) [101,102]. The PRL-R is a member of the GH/cytokine receptor super family, which includes receptors for growth hormone (GH), leukemia inhibiting factor, leptin, several

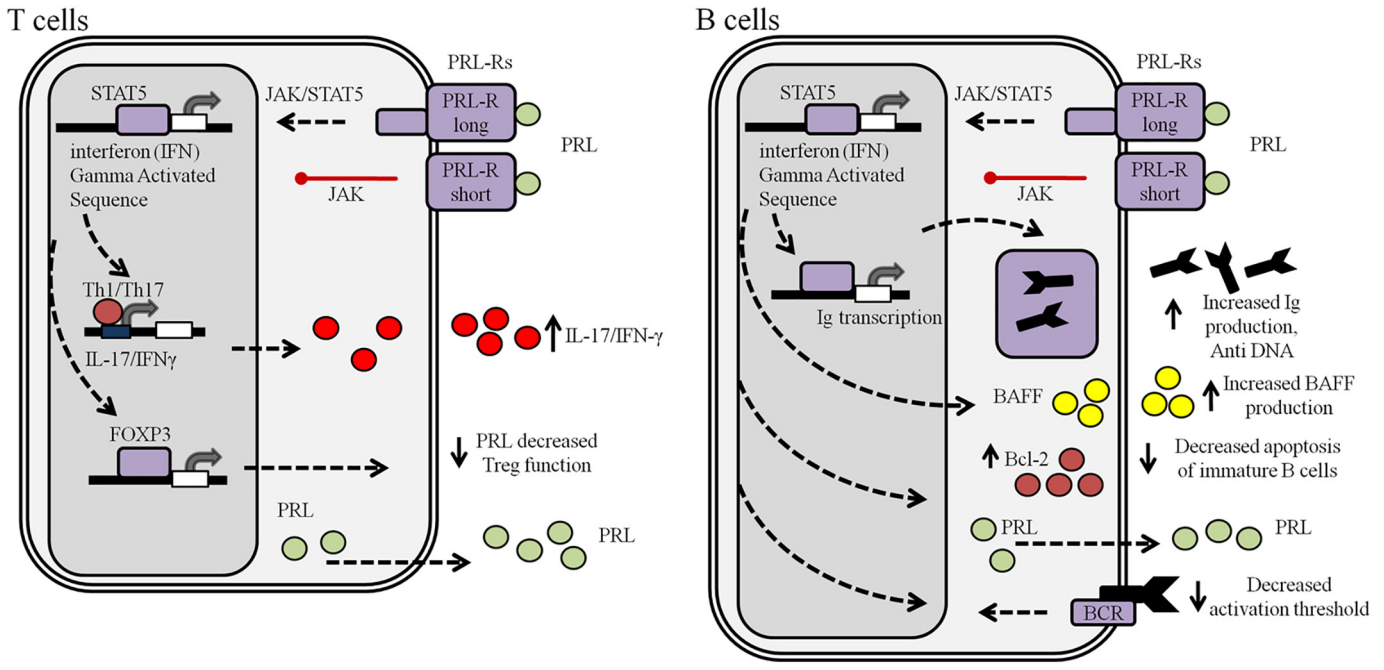

Fig. 2. Prolactin, prolactin receptor, T cells and B cells. A, PRL is produced by the immune system cells, which also express PRL receptors (PRL-R). PRL acts on the immune system via endocrine and paracrine/autocrine pathways. Prolactin action is mediated by the PRL-R which exists as a long and a short isoforms; the latter resulting from alternative splicing of the intracellular cytoplasmic domain leading to JAK/Stat pathway signaling. The role of PRL in EAE was also seen in the delay in production of IFN-γ, IL-17A and IL-6 and the T cell proliferation induced by myelin Ag in PRL and PRL-R KO mice. Prolactin also may modulate the suppressor effect of regulatory T (Treg) cells, since prolactin decreases the suppressor effect exerted by Treg cells. B, High levels of anti- DNA antibodies and increased mortality was observed when given high E and high prolactin doses to NZB/NZW mice. Activation of B cells in the presence of PRL enhanced the secretion of BAFF and Bcl-2 production. When B cells were stimulated with PRL, BCR threshold decreased displaying an increase in cell activation and proliferation.

interleukins and erythropoietin [103]. The JAK/Stat pathway is the main signaling pathway used by all members of this receptor family. To activate this pathway, PRL binds to the PRL-R causing the receptors to dimerize [104,105] that leads to the activation of PRL-R-associated JAK2 protein tyrosine kinases (PTK). Activated JAK2 then phosphorylates downstream targets on tyrosine residues, including the PRL-R ICD, Stat proteins, and other SH2-containing signaling molecules. Activated Stats form homo- or heteromeric complexes that translocate into the nucleus, bind to a conserved DNA element called interferon (IFN) Gamma Activated Sequence (GAS) and regulate target gene transcription. In addition to the JAK/Stat pathway, PRL also activates numerous parallel kinase cascades to regulate target gene expression in a tissue- and cell-type- specific manner [101] (Fig. 2 B). Activation of these cascades modulates several cell functions such as differentiation, proliferation, survival, and secretion [106]. B cells treated with E increase the expression of PRL-Rs transcripts [107]. In vivo evidence using PRL knockout mice revealed that PRL seems to be necessary for enhancing mitogen-induced T-cell proliferation under stress conditions, such as thermal injury [108]. Even though E has a critical role in the development of SLE, additional studies have demonstrated that prolactin can also induce autoimmunity and skew the maturation of autoreactive B cells towards follicular B cells [64,109]. High levels of anti-DNA antibodies and increased mortality was observed when high E and high prolactin doses are given to NZB/NZW mice, as compared with mice receiving low E and low prolactin doses, or high E and low prolactin doses [110]. Blocking pituitary prolactin secretion with the dopamine agonist bromocriptine inhibits E-induced lupus in BALB/c mice transgenic for the heavy chain of a pathogenic anti-DNA antibody [111]. This suggests that E could modulate SLE through pituitary PRL induction. Additionally it is likely possible that cell sensitivity to E(or PRL) mediated by the modulation of hormone receptors may affect lupus outcome. However, it could not be rule out that negative selection to self-antigens be modulated by E (and/or PRL).

An important study analyzed the role of the genetic interval *Sle3/5*, a genomic locus of the NZM2410 mouse strain that confers increased lupus sensitivity. When this locus was transferred to normal C57/B6 mice (B6·*Sle3/5*), the mice developed a lupus-like phenotype when treated with prolactin [112], highlighting the fact that the *Sle3/5* related factors confer sensitivity to the hormone. In a later study, this group demonstrated that the lupus susceptibility locus *Sle3*, confers responsiveness to prolactin and that prolactin-treated DCs from B6·*Sle3* mice develop IgG specific to DNA [113]. Studies of non-transgenic mice demonstrated that hyperprolactinemia interferes with several mechanisms of B-cell induction of tolerance to self- antigens [109], suggesting that prolactin, by itself, could impair tolerance checkpoints. Interestingly, PRL plays an active role in inhibiting apoptosis of immature B Cells from lupus mice. Treatment with anti-IgM F(ab')2 antibody to induce cross-linking of the BCR, a step that mimics self-antigen recognition, produces a significant decrease in the viability and increase in apoptosis of immature B-cells from wild type C57BL/6 mice and lupus MRL/lpr mice [114]. However, preincubation with prolactin prevented the effect of the anti-IgM treatment in the lupus MRL/lpr mice but had no effect on the C57BL/6 mice [114] (Fig. 2B). Thus, prolactin may increase the severity of the disease in lupus prone subjects by promoting the maturation and survival of self-reactive B cells.

Another important study reported that SLE patients presented increased circulating PRL levels when compared to normal subjects that correlated positively with anti-double-stranded DNA autoantibody production. Of note, PRL concentration was reduced during disease remission, indicating that PRL levels may predict disease severity in SLE patients [115,116]. Increased PRL levels have also been reported in association with rheumatoid arthritis, systemic sclerosis and others autoimmune diseases [117,118]. These findings have led to the proposal of PRL as a novel biomarker for autoimmune diseases [119]. Similarly, MS patients have significantly elevated levels of PRL irrespective of the stage of the disease and PRL increases the production of anti-myelin IgG in vitro [107]. Activation of B cells in the presence of PRL enhanced the secretion of BAFF and Bcl-2, and B cell receptor threshold decreased displaying an increase in cell activation and proliferation [107]. It should be pointed out that a case report shows that treating a prolactinoma resulted in the remission of a multiple sclerosis disease condition, which had developed when the patient's PRL levels were very high [120].

7. Prolactin and macrophages

Prolactin regulation of monocyte and macrophage functions is suggested by the presence of PRL-R in these cells [121,122]. Different studies show that macrophages exposed to PRL secrete higher amounts of IFN-γ, IL-1β, IL-12, chemokines like macrophage inflammatory protein (MIP)-1α, monocyte chemoatractant protein (MCP)-1 and IFN-gamma-inducible protein (IP)-10, as well as reactive oxygen species [121–123]. Additionally, PRL has been shown to play a cooperative role in the production of pro-inflammatory cytokines such as IL-6 and IL-12 in response to CD40L and TNF [124]. In rheumatoid arthritis and psoriatic arthritis patients, PRL-R expression is significantly higher in sinovial tissue compared with healthy individuals [124]. Furthermore, IFN-γ- and IL-10-treated macrophages showed an increased expression of PRL-R compared to control cells [124]. Thus, prolactin may be part of a positive feedback loop in macrophages, stimulating the production of inflammatory factors that in turn stimulate PRL- R expression, resulting in exacerbated inflammation.

8. Prolactin and DCs

As discussed above, PRL has been associated to diverse autoimmune diseases including lupus pathogenesis in human and murine models but its role on DCs has been poorly studied [113,125]. It has been reported that PRL profoundly modulates DC phenotype [126]. PRL-R is expressed in the majority of thymic DCs [127]. It has been shown that PRL promotes a mature-like phenotype in murine splenic DCs (cDCs and pDCs), increasing the expression of MHC-II and CD40 molecules [128]. Furthermore, in these cells, PRL increased the production of several pro-inflammatory cytokines such as IL-6 and IL-12 [128]. Similarly, PRL synergized with GM- CSF to promote the differentiation of human-primary monocytes into cDCs [129]. Nevertheless, PRL-treated thymic DCs displayed an increase in the immunogenicity capacity in mixed leukocyte reaction assays, cell surface expression of CD80 and MHC molecules, and production of IL-12, TNFα e IL-1β [127,129,130]. DCs exposed to high PRL concentrations show an increased antigen-presenting activity that may be of significance in the initiation of the immune response against MHC-presented self-antigens and may explain the association of hyperprolactinemia with autoimmune diseases [130]. In the B6·Sle3/5 mice, in which PRL induces a lupus-like disease [131], the hormone increases CD80 expression on cDCs [113]. Additionally, adoptive transfer of DCs (cDCs and pDCs) from PRL-treated B6·Sle3/5 mice to wild type recipients promotes the development of lupus-like disease, increasing DNA-reactive B cells and suggesting that PRL may promote rupture of the immune tolerance to DNA [113]. There is a strong relationship between DCs and Treg cells which is reflected in the higher production of IL-6 and IL-23 in vitro and in vivo by DCs when these cells are exposed to the increased prolactin levels induced by stress [126]. This higher production of cytokines by the DCs plays a critical role modifying Treg phenotypes [126].

9. Progesterone and immune cells

Progesterone (P), a sex steroid hormone, plays an immune modulator role by binding with specific receptors. The presence of membrane progesterone receptors (mPRs) has been demonstrated in human peripheral blood T cells (PAQR7, PAQR8 y PAQR5 and PGRMC1) [132] and in the resident T cell population of bovine corpus luteum [133] (Fig. 3A). Intracellular progesterone receptors (iPR) have been detected

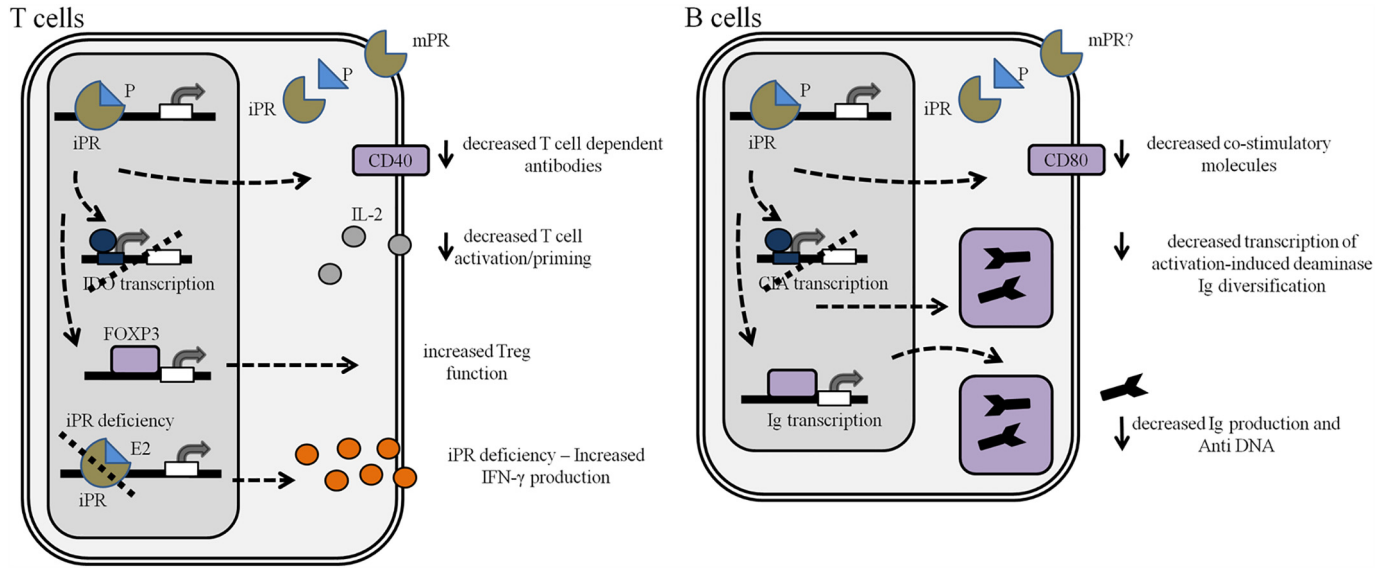

Fig. 3. Progesterone, PRs, T and B cells. A, the presence of membrane progesterone and intracellular receptors (mPRs and iPR) has been demonstrated in human T cells. P decreased T cell activation and priming. P is a potent inductor of Treg FOXP3 activity. iPR KO mice showed an increased IFN-γ production by spleen cells. B, on B cells, P decreased the expression of the co-stimulatory molecules CD80 and CD86 on B cells. P administration on female NZB/NZW mice decreased anti DNA IgG. Pg decreases transcription of activation-induced deaminase m RNA, a crucial molecule in Ig diversification.

in TCD4$^+$ cells that suppress T cell dependent (TD) antibody responses [134]. However, iPR KO mice displayed a healthy spleen cell homeostasis and normal levels of circulating IgG suggesting that this receptor may modulate immune cells only in the presence of P [134]. In contrast, iPR KO mice showed an increased IFN-γ production by spleen cells [134] (Fig. 3 A).

P is a potent inductor of Treg activity, increasing naive T cells differentiation into FoxP3$^+$T cells that are more stable under inflammatory conditions [135] (Fig. 3 A). At high concentrations, P inhibits differentiation of bone marrow murine DCs to CD11b$^+$ CD11c$^+$ and reverses the differentiation induced by E [136]. Monocytes from newborn umbilical blood expressed higher levels of mPR than adult peripheral blood monocytes, and were more susceptible to P leading to a decreased production of pro-inflammatory cytokines, such as TNF and IL-6 [137]. In canine neutrophils, it has been reported that P decreases phagocytic activity and oxidative burst [138]. In humans, some authors have shown that mPRα expressed in peripheral blood T cells during pregnancy, is mainly involved in immune response regulation, generates fetal protection and impairs fetal complications [139].

For the treatment of premature labor, which has a high rate of perinatal mortality, some authors emphasize the use of P. It has been reported that peripheral blood CD4$^+$ Treg from women with preterm labor, increase significantly after P administration when compared with a nulliparous group [139]. Moreover, Bianchi et al.; demonstrated that progesterone participates in the establishment of the tolerogenic state during gestation, impairing the expression of the enzyme indoleamine2,3-dioxygenase (IDO) in CD4$^+$ and dendritic cells [140] (Fig. 3A). In rats, during the stages where progesterone levels are high, like diestrus or metaestrus, DCs were more susceptible to the action of this hormone through binding to PRs [141]. Strikingly, P impairs the expression of several immune factors such as MHC class II, co-stimulatory molecules, production of TNF and IL-1 and reduces T cell priming in in vivo and in vitro assays [141] (Fig. 3A).

Interestingly, P also has indirect effects over B cells. It has been reported that P treated endometrial stromal cells decreased the expression of the co-stimulatory molecules CD80 and CD86 on B cells [142]. Also, P decreases transcription of activation-induced deaminase m RNA, a crucial molecule in Ig diversification [143] (Fig. 3B).

Thus, the effects of P on immune cells are mainly suppressive, in particular during pregnancy, in which this hormone plays a pivotal role towards preservation of the growing fetus by preventing its rejection by the maternal immune system, along with the maintenance of a quiescent uterus.

10. Progesterone and autoimmunity

P plays an important role in the regulation of immune mechanisms associated with autoimmune diseases such as SLE, Rheumatoid Arthritis and Experimental Autoinmune Encephalomyelitis in animals (EAE) [144,145]. During EAE, it has been reported that P administration decreases TNF-α, IL-2, and IL-17 secretion, reduces cellular infiltration in the spinal cord, increases myelinization and clinically reduces signs of illness [145]. Furthermore, some authors established that this hormone reduces the risk of SLE by antagonizing some E effects [141,146]. Addittionally, Wong et al., have reported that aged female lupus prone mice made PR KO displayed an increase in IgG anti DNA autoantibodies, leading to glomerular immune complex deposition and concomitant kidney damage [144]. Additionally PR deficiency decreases splenic Tregs and increases T follicular helper and IFN- γ production in these aged females [144] (Fig. 3A). Interestingly, PR deficient DCs showed an increased expression of the co- stimulatory molecule CD86 [144]. Similarly, continuous medroxyprogesterone acetate administration to female NZB/NZW mice decreased anti DNA IgG, improved survival, decreased glomerulonephritis and proteinuria, and lowered the expression of CD86 on DCs [147] (Fig. 3B). Unexpectedly, these authors reported that medroxyprogesterone acetate increased the expression of CD40 on B cells which is crucial for germinal center reaction [147] (Fig. 3B). In conclusion, P inhibits immune cell activation improving immunological status during autoimmunity.

11. Conclusions

In summary, E and PRL actions on the immune system are mostly stimulatory, promoting its activation and the induction of autoimmunity, while P actions are mainly suppressive, repressing autoimmunity and most importantly, rejection of the embryo by the maternal immune system. This may be another instance where the action of E and prolactin are opposed or prevented by progesterone, as observed in other physiological situations such as mammary gland function and some instances of the regulation of hormone secretion and actions.

The capacity of sex steroids and prolactin to affect not only the differentiation, regulation, and responsiveness of B and T cells, but also immune messengers, such as pro-inflammatory cytokines, add layers of complexity to the interactive molecular and cellular events that occur in inflammatory and autoimmune diseases. Intense studies are currently delineating how sex hormones impact the immune system. Deciphering the multi-faceted influences of sex hormones on the responsiveness of B lymphocytes could be critical in elucidating key pathogenic mechanisms and provide novel therapeutic strategies for those pathologies where the immune system is involved.

Abbreviations

DCs	dendritic cells
E	estrogens
EAE	experimental autoimmune encephalitis ER estrogen receptor
GC	glucocorticoids
DMPA	medroxyprogesterone acetate
P	progesterone
PR	progesterone receptor
PRL	prolactin
PRL-R	prolactin receptors
RA	rheumatoid arthritis
SLE	systemic lupus erythematosus
T1D	type 1 diabetes
TLRs	toll like receptors
Tregs	regulatory T cells

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