Helper T cells: A potential target for sex hormones to ameliorate rheumatoid arthritis? (Review)

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Abstract. Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease whose etiology is not fully understood. Defective peripheral immune tolerance and subsequent mis-differentiation and aberrant infiltration of synovium by various immune cells, especially helper T (Th) cells, play an important role in the development of RA. There are significant sex differences in RA, but the results of studies on the effects of sex hormones on RA have been difficult to standardize and hormone replacement therapy has been limited by the potential for serious side effects. Existing research has amply demonstrated that cellular immune responses are largely determined by sex and that sex hormones play a key role in Th cell responses. Based on the aforementioned background and the plasticity of Th cells, it is reasonable to hypothesize that the action of sex hormones on Th cells will hopefully become a therapeutic target for RA. The present review discussed the role of various Th cell subsets in the pathogenesis of RA and also explored the role of sex hormones on the phenotype and function of these aberrantly regulated immune cells in RA as well as other pathologic effects on RA.

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1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease with chronic polyarticular inflammation as the main clinical manifestation. The pathogenesis of RA is associated with the production of autoantibodies such as anti-immunoglobulin G (IgG) and citrullinated proteins (1). The main pathological features of RA are synovial hyperplasia of the joint cavity, thickening of the lining layer, formation of vascular opacities and infiltration of a variety of autoimmune cells and activated inflammatory cells, which in turn cause the destruction of cartilage and bone tissues, ultimately leading to joint deformity and loss of function (2,3).

The pathogenesis of RA involves dysregulation of both intrinsic and adaptive immunity. In adaptive immunity, T cells and B cells are involved to varying degrees in the pathogenesis of RA. B cells accumulate in the synovium of inflamed RA and secrete rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), which are involved in the inflammatory process (4). Helper T (Th) cells are a diverse group of CD4+ T cell subsets that play a crucial role in the immune system. Intrinsic defects in the naive CD4+ T cells cause cellular mis-differentiation, leading to irreversible tissue-tolerant destruction as a key pathogenesis of RA (2).

A systematic analysis of global, regional and national burden studies of RA from 1990-2017 showed that the global age-standardized point prevalence and annual incidence of RA in 2017 were 246.6 [95% uncertainty interval (UI) of 222.4-270.8] and 14.9 (95% UI of 13.3-16.4), respectively, which increased by 7.4% (95% UI 5.3-9.4) and 8.2% (95% UI 5.9-10.5) from 1990, respectively (all estimates presented as counts and age-standardized rates per 100,000 population) (5). The data in this systematic analysis also showed that the prevalence of RA was highest in developed countries, followed by India and South America, and appeared to be lower in rural areas compared with urban settings, suggesting that population characteristics, socioeconomic or environmental risk factors influence the prevalence of RA (5). Women make up the majority of patients with RA, with a ratio of up to 4:1 or more to men (6-8). The influence of specific events such as menopause, the number of parturiency and breastfeeding on the risk of developing RA, as well as the sex ratio of patients with RA, all contribute to the role of sex hormones in RA. This role has been explored from as early as the last century and clinical trials have confirmed the anti-inflammatory effects

of sex hormones in RA and the significant improvement of symptoms (9). However, hormone replacement therapy (HRT) has since declined substantially due to potentially serious side effects such as increased risk of coronary heart disease, breast cancer and stroke (10,11). Currently glucocorticoids are widely used with the treatment of RA, but sex hormones have not been included in the treatment regimen for RA. A recent study of female patients with RA treated with tocilizumab, an IL-6 receptor antibody and/or traditional disease-modifying anti-rheumatic drugs found that exogenous sex hormone use appeared to be associated with higher remission rates (12). Although epidemiologic investigations and mechanistic studies remain contradictory, the effect of sex hormones on RA is evident. Few articles have looked at Th cells to illustrate the role of sex hormones in RA and repairing Th cell defects during asymptomatic autoimmunity may be the next cutting-edge intervention in RA. Exploring the effect of sex hormones on RA from Th cells may be another research proposal for using sex hormones to treat RA.

2. Materials and methods

The present study used 'rheumatoid arthritis', 'T cells' and 'sex hormone' as the key words and collected relevant information from different databases, including PubMed (https://pubmed.ncbi.nlm.nih.gov), Web of Science (https://ras.cdutcm.edu.cn:7080/s/cn/clarivate/webofscience/G.https/wos/woscc/basic-search), Springer (https://link.springer.com), Science Direct (https://www.sciencedirect.com), ACS (https://pubs.acs.org/?locale=zh_CN), Wiley (https://onlinelibrary.wiley.com) and CNKI (https://www.cnki.net). Inclusion criteria were: Clinical studies, laboratory studies (including purely experimental animal studies or *in vitro* cellular studies, combined animal and *in vitro* cellular studies), meta-analyses and bioinformatics studies validated with clinical or laboratory data, regardless of the languages of publication. Exclusion criteria were: Studies that were repeatedly published, clinical trials from which no relevant data could be extracted, newspapers, conferences, comments and other information without experimental data, studies that were low quality or had incorrect assertions or conclusions and different reports on the same issue (these have been retained for comparison and discussion purposes).

3. Immunology of RA

The immunopathogenesis of RA spans decades and is characterized by defective immune responses, primarily involving pro-inflammatory cytokines and alterations in peripheral immune tolerance, especially Th cells (13,14). Genetic and environmental factors are major risk factors for RA and shared epitope-positive HLA-DRB1 alleles and PTPN22 variants are associated with the development of RF and ACPA (15,16). Although these studies have taken less account of the effect that other factors have on this process, they have revealed the relationship between these genes and autoantibodies and the effect of this process on RA. T cells recognize citrullinated antigens in the context of HLA-DRB1*04 and B cells respond by producing large amounts of citrullinated proteins (17,18). B cells can also play an important role as antigen-presenting cells (APCs) to self-reactive T cells (19,20). There are several important stages in the transition from a healthy state to clinical RA, which a high-quality review from *Nature Immunology* categorized as the systemic breakdown of self-tolerance, the transition from asymptomatic autoimmunity to tissue inflammation and the transition from acute synovitis to prolonged chronic synovitis (2).

Specifically, individuals with genetic and environmental risks begin with the recognition of modified protein antigens and the appearance of autoantibodies (phase I). Following a prolonged period of asymptomatic autoimmunity and immune system remodeling, cell-intrinsic changes in metabolic networks and DNA instability drive T cell differentiation to tissue-invasive short-term effector T cells and protective macrophage failure, followed by disruption of tissue tolerance and the development of early synovitis (phase II). The transformation of synovial stromal cells to self-invasive effector cells transforms synovitis from acute to chronic destructive, leading to destruction of articular cartilage and bone (phase III). In the vast majority of cases, the destruction of tissue tolerance is irreversible (2).

Th cells in RA background. The second phase of RA is clinically marked by synovial inflammation, which is closely related to cell-intrinsic defects in CD4+ T cells, caused by mis-differentiation during the conversion of initially resting CD4+ T cells into memory T cells and effector T cell (21-23). Specifically, naive CD4+ T cells are transformed into highly proliferative, tissue-invasive and pro-inflammatory T cells rather than relatively quiescent memory T cells; initial self-tolerance is disrupted, the disease process shifts localization and a variety of immune cells infiltrate the synovium (Fig. 1). Activated CD4+ T cells make up a large proportion of inflammatory cells in synovial tissue and are involved in the pathologic process of RA. A reduced naive CD4+ T cell frequency is the strongest predictor of the development of synovitis in patients with ACPA-positive populations (24).

Naive CD4+ T cells are activated and differentiated into various Th cell subpopulations in response to antigenic stimulation and cytokine signaling and their differentiation process is dependent on the expression of specific transcription factors induced by specific cytokines. These Th cells exert varying degrees of disease-promoting or protective effects.

Role of Th cell subsets in the pathogenesis of RA and experimental arthritis

Th1 cells. Initially, Th1 cells were hypothesized to play a dominant role in the development of RA due to the high expression levels of interleukin-12 (IL-12) and interferon-gamma (IFN-γ) found at sites of inflammation and the positive correlation of IL-12 levels with disease activity observed in the serum and synovial fluid of a significant proportion of patients with RA (25,26). In addition, most CD4+ T cells infiltrating the synovium express IFN-γ, which subsequently activates macrophages and induces tumor necrosis factor-alpha (TNF-α) production (25). However, the Th1 phenotype does not explain the full mechanism of RA development because of the higher susceptibility to collagen-induced arthritis (CIA) in IFN-γ-deficient mice and IFN-γ receptor-deficient mice (27,28), as well as the lack of

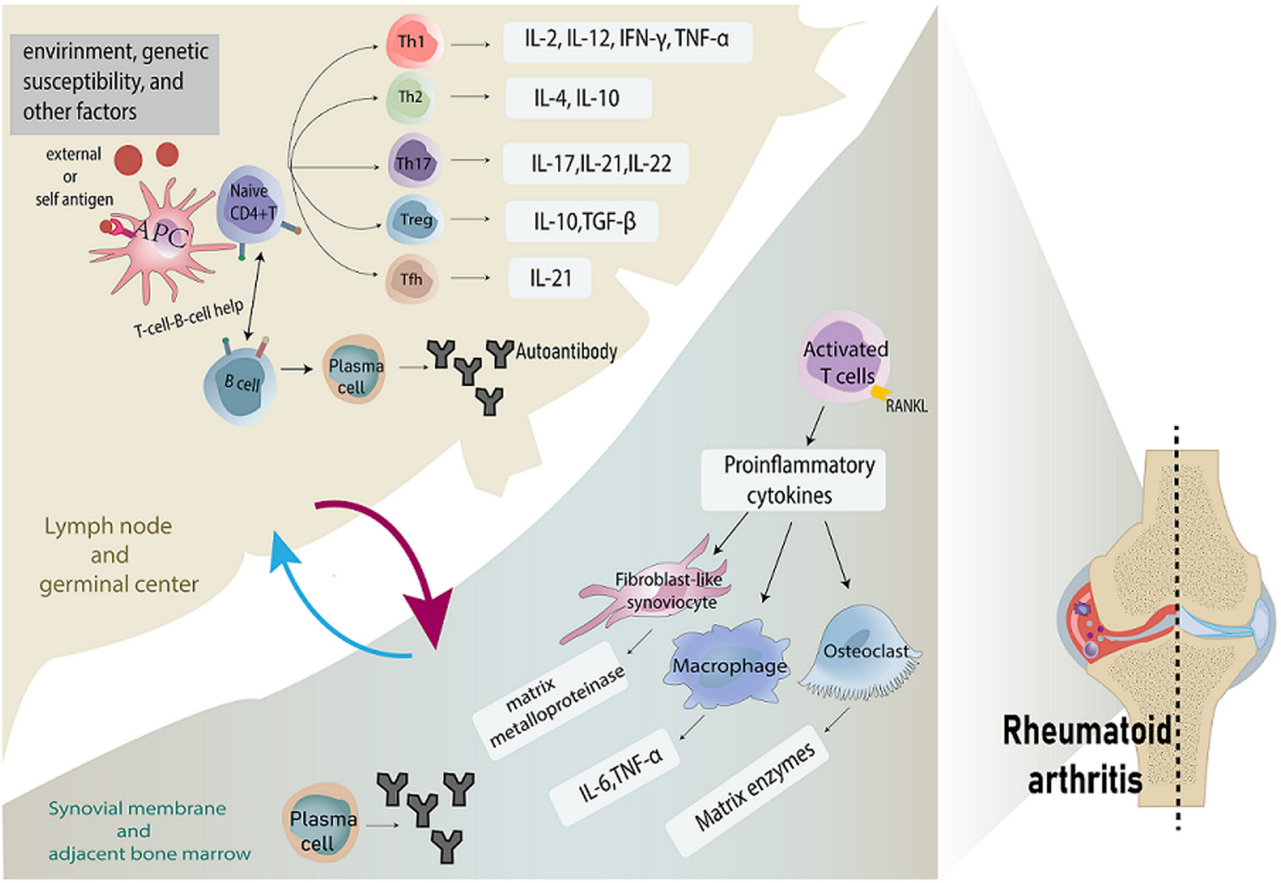

Figure 1. Th cells in RA. In the pathogenesis of RA, environmental, genetic and other factors lead to defective self-tolerance and subsequently the naive CD4+ T cells are activated and differentiated into various Th cells that produce various cytokines when stimulated by antigens presented by APCs as well as specific cytokines. There is also co-stimulation between B cells and T cells and the B cells are activated to differentiate into plasma cells and produce autoantibodies. These immune cells infiltrate the joints and produce pro-inflammatory cytokines and associated antibodies involved in the inflammatory process of RA, which in turn causes destruction of cartilage and bone tissue, ultimately leading to joint deformity and loss of function. Th, helper T; RA, rheumatoid arthritis; APCs, antigen-presenting cells; IL, interleukin; IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor-α; TGF-β, transforming growth factor-β; RANKL, receptor activator of NF-κB ligand.

efficacy of IFN-γ monoclonal antibodies in the majority of patients with RA (29).

Th2 cells. The proposed Th1/Th2 model was used to explain RA pathology in early studies. In arthritis dominated by Th1 cells, IL-4 secreted by Th2 cells prevents disease and induces a switch from a Th1-type to a Th2-type response. IL-4 deficiency is essential for disease induction in animal models of CIA (30). Treatment of CIA mice using mesenchymal stem cells (MSC) in combination with IL-4 restored synovitis symptoms to the level of healthy controls (31). Later, the hypothesis that the Th1/Th2 model is dominant began to change due to the emergence of anti-inflammatory regulatory T (Treg) cells that produce growth transformation factor-beta (TGF-β) and pro-inflammatory Th17 cells that produce IL-17 (32).

Th17 cells. Multiple molecules are involved in the differentiation process of Th17 cells and the combination of these molecules with each other generates pathogenic and non-pathogenic Th17 cell subpopulations with varying degrees of pro- and anti-inflammatory properties (33,34). In patients with RA, both *in vivo* and *in vitro* anti-TNF-α treatment induced the production of the anti-inflammatory factor IL-10 by Th17 cells, suggesting that TNF-α may have an inhibitory effect on IL-10 production by Th17 cells (35). Although Th17 cells and their effector molecules play a positive role in the maintenance of immune homeostasis in the body, they are also involved in the pathology of a variety of autoimmune diseases. Peripheral blood mononuclear cells (PBMC) from patients with RA had a large number of Th17 cells and their proportion correlated with the progression and activity of RA (36,37). IL-17-deficient and blocked mice exhibited resistance to CIA while ameliorating disease severity in a mouse model of CIA (38,39). IL-22 is an important cytokine produced by Th17 cells and IL-22(-/-) mice had severely reduced splenic germinal centers and their CIA severity was also significantly reduced (40).

Th17 cells expressing the receptor activator of NF-κB ligand (RANKL), an osteoclast-activating factor, stimulate localized bone resorption by regulating the migratory state and functional changes of mature osteoclasts through cell-to-cell contacts and this may be the mechanism by which Th17 cells mediate inflammatory bone destruction (41). As IL-17 blockade has therapeutic potential for RA and clinical trials have been conducted to explore the feasibility of this treatment approach. For instance, a study has shown that IL-17 blocking drugs such as secukinumab and ixekizumab are effective in the treatment of RA, but their efficacy appears to be inferior

to that of already existing biologics such as anti-TNF-α and anti-IL-6 (42).

Treg cells. Treg cells play a crucial role in maintaining autoimmune tolerance by secreting the anti-inflammatory cytokine IL-10 and the immunosuppressive molecule TGF-β (43,44). However, the number of Treg cells in the synovial fluid of patients with RA with persistent joint inflammation is significantly increased, suggesting that Treg cell function is altered in patients with RA (45). This is supported by other studies which have found that Treg cell regulation is reduced in both peripheral blood and synovium in patients with RA (46-48). Forkhead box protein 3 (Foxp3) is a key transcription factor for Treg cells and TNF-α dephosphorylation inhibits the transcriptional activity of Foxp3, disabling Foxp3+ Treg cells in patients with RA (46). In arthritic conditions, CD25(lo) Foxp3(+) T cells lose Foxp3 expression and transdifferentiate into inflammatory Th17 cells (49). The regulatory capacity of Treg cells in an inflammatory environment is reduced or lost, so that Treg cells isolated from active patients with RA cannot prevent effector T cells from secreting pro-inflammatory cytokines such as IFN-γ and TNF-α (47,48), which may be a vicious cycle. In addition, studies have shown that MSC has a favorable effect on the regulatory function of Treg cells in the context of RA (50,51).

T follicle helper (Tfh) cells. Tfh cells are characterized by high expression of the chemokine receptor C-X-C motif chemokine receptor 5, the transcription factor Bcl6, inducible co-stimulatory molecule and the co-inhibitory molecule programmed cell death protein 1 (PD-1). Once the naive CD4+ T cells are activated by APCs, IL-6 and IL-21, they differentiate into Tfh cells (52). Tfh cells help B cells produce relevant antibodies in patients with RA. Transplantation of MSC into CIA mice prevented the progression of arthritis by suppressing the number and function of Tfh cells (53). patients with RA express high levels of IL-21 in serum (54,55) and the percentage of Tfh cells is also positively correlated with disease activity (55). After 1 month of drug treatment, the percentage of PD-1+ Tfh cells was significantly decreased in drug-responsive patients with RA (55). In the synovium of IL-21R-deficient RA model mice, fewer Tfh cells and more Th17 cells were found in comparison with the control, as well as low levels of RANKL expression, suggesting that IL-21 plays an important role in the disease process of RA through Tfh cell proliferation and RANKL induction rather than Th17 cell function (56,57).

4. Sex hormones and Th cell response

The thymus is a key site for the production of a number of types of T cells and the effects of sex hormones on the thymus were recognized as early as the last century when it was observed that the thymus is enlarged in male castrated mice and shrinks following the administration of androgens (58). Compared with men, women have a higher absolute number of CD4+ T cells and show stronger T-cell responses and B-cell responses to antigens, which contributes to autoimmunity (59). Women are more inclined to develop T-cell-mediated autoimmune diseases, whereas men are more susceptible to cancer and infectious diseases (60), which has been commonly described as an immunostimulatory effect of estrogens and an immunosuppressive effect of androgens, which is clearly an oversimplified description. The effect of sex hormones on the immune system and immune disorders is complex and can be influenced by a combination of factors such as genetics, the relative expression of hormone receptor subtypes, hormone concentrations, the tissues in which they are found and the stage of life (Table I).

Estrogen. Women have three main natural estrogens, estrone, estradiol (E2) and estriol, with E2 being its most potent form. In studying the role of estrogen in autoimmune diseases, Cutolo *et al* (61) conclude that estrogen may promote B-cell-driven diseases, while T-cell-driven diseases may be inhibited by estrogen. Estrogen is mainly mediated by two specific intracellular receptors namely estrogen receptors (ER) α and β and a membrane G-protein coupled receptor. There are significant differences in the distribution of ERα and ERβ in immune cells and tissues and the complex effects of estrogen on the immune system are partly due to the fact that the expression of one receptor relative to the other may alter the action of estrogen (62). For example, in a mouse model of systemic lupus erythematosus (SLE), ERα has significant pro-inflammatory effects, whereas ERβ exhibits anti-inflammatory and immunosuppressive effects (63-65). ERβ expression is also significantly reduced in T cells from patients with SLE and inflammatory bowel disease (66,67). In addition, it has been found that ERα controls the production of autoantibodies to prevent autoimmunity by inhibiting the reaction of Tfh cells (68), while ERβ enhances immunosuppression by promoting the differentiation of Treg cells (69).

In peripheral T cells, low concentrations of E2 induce T cells to express T-box transcription factor expressed in T cells (T-bet) and IFN-γ to promote the Th1 response and ERα, but not ERβ, is required for this process (70). E2 levels are consistently elevated during pregnancy and high concentrations of E2 affect CD4+ T cell polarization by enhancing the expression of Th2-related genes (GATA3 and IL-4) and Treg-related genes (Foxp3, IL-10 and TGF-β), while inhibiting the expression of Th1-related genes (T-bet, IL-2, TNF-α and IFN-γ) and Th17-related genes (ROR-γ T, IL-6, IL-17 and IL-23) expression (71-74). By contrast, the decline in ovarian function and rapid decline in circulating estrogen during menopause are associated with an increase in pro-inflammatory cytokines such as IL-6, TNF-α and IL-1β (75,76). The addition of E2 at ovulation level to PBMC of postmenopausal women *in vitro* can inhibit the release of these pro-inflammatory factors (77).

Androgens. Androgens mainly include testosterone, dihydrotestosterone and dehydroepiandrosterone (DHEA) and the biological actions of androgens are mediated by the androgen receptor (AR) (78). Androgens have recognized immunosuppressive effects, in large part because of their ability to inhibit cytokine production and impair T cell effector activity (79,80).

The autoimmune regulatory gene (AIRE) provides strong protection against autoimmune disease and the effect of androgens on them is stronger in males than in females (81). Androgens recruit AR to the AIRE promoter region, enhancing AIRE transcription, improving immune tolerance and producing more effective negative selection of self-reactive T cells (82). By contrast, estrogen promotes

Table I. Sex hormones and Th cell response.

First author/s, year	Sex hormone	Object of study	Medicine	Concentration and time	Key results	(Refs.)
Kim *et al*, 2019	Estrogens	CD4-ERα knockout mice	/	/	ERα inhibits the Tfh cell response and GC reaction to control autoantibody production.	(68)
Guo *et al*, 2019		Naïve CD4+T cells isolated from the spleen and MLNs of C57BL/6 mice	ERB041 (an ERβ specific agonist)	100 nM,60 min	ERβ activation enhanced Treg differentiation and TGF-β1/Smad signaling in CD4 + T cells and promoted immunosuppression.	(69)
Maret *et al*, 2003		Ovariectomized (OVX) mice, ERα and ERβ genes destroy mice	E2	0.1 mg/60 days (Subcutaneous implants release particles)	E2 administration in OVX mice resulted in a T cell proliferative and Th1 cell response and IFN-γ and T-bet production. ERα, but not ERβ, was necessary for the enhanced E2-driven Th1 cell responsiveness.	(70)
Lambert *et al*, 2005		Naïve CD4+T cells isolated from the spleen of OVX mice and ERα-deficient mice	E2	10^{-9}M (272.4 pg/ml), 12-16 h	E2 increased IL-4 and GATA-3 mRNA levels from CD4+ T cells, which is dependent on Erα.	(71)
Polanczyk *et al*, 2005		E2-treated mice; pregnant mice	E2	2.5 mg/60 days (subcutaneous implants release particles)	E2 enhances the expression of FoxP3 and the inhibitory function of Treg cells in pregnant mice.	(72)
Tai *et al*, 2008		E2-treated mature OVX and immature mice; pregnant mice	E2	100 ng/per mouse (subcutaneous injection)	E2 expanded Treg cells in different tissues and increased the expression of Foxp3 gene and IL-10 gene.	(73)
Haghmorad *et al*, 2014		E2-treated OVX mice; pregnant mice	E2	15 mg/21 days (subcutaneous implants release particles)	Pregnancy and gestational levels of estrogen decrease the expression levels of Th1 and Th17 cell transcription factors T-bet and ROR-γt and the expression levels of Th1 and Th17 cytokines IFN-γ, TNF-α, IL-17 and IL-23 in the spleen of mice.	(74)
Dragin *et al*, 2016		ERα-knockout mice; healthy human thymus tissue	E2	200 μg/day	Estrogen upregulates the number of methylated CpG sites in the AIRE promoter via ERα, causing AIRE expression to fall below the threshold, thereby increasing the susceptibility of women to autoimmune diseases.	(83)
Zhu *et al*, 2016	Androgens	AR deficient mice; human neonatal thymus tissue	Dihydrotestosterone	0-10 mg/60 days (subcutaneous particles); 100 mg/per mouse (subcutaneous injection)	In mice and humans, the expression of AIRE in the thymus is higher in males than in females.	(82)

Table I. Continued.

First author/s, year	Sex hormone	Object of study	Medicine	Concentration and time	Key results	(Refs.)
					Androgens recruit AR to the AIRE promoter region, enhancing AIRE transcription, improving immune tolerance and producing more effective negative selection of self-reactive T cells.	
Gandhi *et al*, 2022		AR-deficient mice, oxp3 fate-mapping mice	5α-dihydrotestosterone	15 mg/60 days (subcutaneous implants release particles)	Androgen can increase Foxp3 expression and stabilize the suppressive function of Treg cells through AR signaling.	(85)
Vargas-Villavicencio *et al*, 2006		Male mice with gonadectomy	/	/	IL-4 and IL-10 mRNA levels were markedly decreased in response to castration, compared with intact unaffected mice.	(86)
Xia *et al*, 2022		Rats with allergic asthma	5α-dihydrotestosterone	0.5 mg/kg/3 day (oral)	Androgen decreased the high levels of IL-4, IL-5 and IL-33 in bronchoalveolar lavage fluid.	(87)
Kalidhindi *et al*, 2021		CD4 cells isolated from castrated mice	/	/	AR binds a conserved region within the phosphatase, PTPN1 and consequent up-regulation of PTPN1 then inhibits IL-12 signaling in CD4 T cells and inhibits Th1 cell differentiation.	(88)
Quispe Calla *et al*, 2015	Progestational hormone	DC isolated from human peripheral blood mononuclear cells	medroxyprogesterone acetate	$2x10^{-3}$ M, 24 h	The ability of medroxyprogesterone acetate-treated DC to promote CD4(+) and CD8(+) T cell proliferation was reduced.	(94)
Mao *et al*, 2010		Mature and immature female mice; pregnant mice	Pg	2 mg/mouse (subcutaneous injection)	Midterm pregnancy doses of Pg increased CD4(+)CD25(+) Treg cell proportion and IL-10 expression and also enhanced their inhibitory function. Pg has the ability to transform CD4(+)CD25(-) T cells intoo CD4(+)CD25(+) Treg cells.	(95)
Hierweger *et al*, 2019		Spleen cells from non-pregnant and pregnant mice	Pg	10^{-6} M; 48 h	Pg induced conventional CD4+T cell death, but had no lethal effect on CD4+ Treg cells.	(96)
Hughes *et al*, 2009		SLE model mice	Depot medroxyprogesterone acetate	10 mg/6 weeks, 30 weeks (subcutaneous injection)	Progestational hormone reduces the accumulation of pathogenic antibodies associated with nephrogenic Th1 cells.	(98)

Table I. Continued.

First author/s, year	Sex hormone	Object of study	Medicine	Concentration and time	Key results	(Refs.)
Carreno *et al*, 2005	PRL	13 days old fetal liver cells, 15 days old fetal thymus cells	PRL	10 ng/ml, 7 days	PRL induces thymus T cell development and hepatic lymphoid progenitor cell survival, proliferation and differentiation.	(100)
Legorreta-Haquet *et al*, 2016		Treg cells and effector T cells isolated from PMBC of SLE patients	PRL	50 ng/ml, 5 days	The percentage and function of Treg cells are decreased in SLE patients compared with healthy individuals. PRL decreased the inhibition of Treg cells and increased IFN-γ secretion.	(101)
Dimitrov *et al*, 2004		Whole blood cells from healthy individuals	PRL	20 ng/ml	PRL promotes CD4+T and CD8+ T cells to produce more TNF-α, IFN-γ and IL-2.	(102)
Lentz *et al*, 2022	HCG	Naïve CD4+T cells isolated from the spleen and inguinal and para-aortic lymph nodes of CBA/J mice	urine-derived HCG (uHCG), recombinant HCG (rHCG)	uHCG:250 IU/ml rHCG:100 IU/ml, both 24h	HCG increased the frequency of Treg cells. With the involvement of IL-2, both interfere with the differentiation of CD4 + T cells into pro-inflammatory Th17 cells and induces anti-inflammatory characteristics in already differentiated Th17 cells.	(104)
Diao *et al*, 2017		CD4+T cells isolated from PMBC of women with recurrent implantation failure	human urinary HCG	50 IU, 72 h	HCG increased the proportion of FoxP3+ Tregs cells expressing TGF-β.	(106)
Sha *et al*, 2017		Patients with unexplained recurrent spontaneous abortion	Combinati on therapy of HCG plus IG	Before 14 weeks gestation: IG 0.3 g/3 weeks; HCG 2000 U/2 days (intramuscular injection). After 13 weeks of gestation: The HCG dose was gradually reduced and eventually discontinued	Combined therapy resulted in decreased Th17/Treg ratio and Treg bias in peripheral blood and increased levels of Treg cells and related cytokines IL-10 and TGF-β1.	(105)
Iqbal *et al*, 2006	FSH	Bone marrow and macrophages in C57BL6J mice	FSH	100 ng/ml, 18 h	FSH directly stimulates the production of TNF-α by myeloid granulocytes and macrophages.	(108)

Table I. Continued.

First author/s, year	Sex hormone	Object of study	Medicine	Concentration and time	Key results	(Refs.)
Qian *et al*, 2020		The periodontal ligament cells in a healthy person	FSH	30 ng/ml, 24 h	FSH significantly increased the expression and secretion of pro-inflammatory cytokines IL-1β, IL-6 and TNF-α in human periodontal ligament cells.	(109)

Th, helper T; ER, estrogen receptor; Tfh, T follicle helper; MLNs, mesenteric lymph nodes; TGF-β, growth transformation factor-beta; Treg, regulatory T; OVX, ovariectomized; E2, estradiol; GATA-3, GATA binding protein 3; Foxp3, Forkhead box protein 3; IL, interleukin; T-bet, T-box expressed in T cells; ROR-γt, retinoic acid receptor-related orphan receptor γt; IFN-γ, interferon-γ; CpG, cytosine-phosphate-guanosine; AIRE, autoimmune regulatory gene; RA, rheumatoid arthritis; RANKL, receptor activator of NF-κB ligand; DC, dendritic cells; Pg, progesterone; SLE, systemic lupus erythematosus; PRL, prolactin; TNF-α, tumor necrosis factor-alpha; HCG, human chorionic gonadotropin; u, urine-derived; r, recombinant; PMBC, peripheral blood mononuclear cell; IU, international unit; IG, immunoglobulin; FSH, follicle-stimulating hormone.

autoimmunity by decreasing AIRE expression through ERα upregulation of AIRE methylation (83). The number of Treg cells is significantly higher in men than in women (84) and the androgen/AR pathway can stabilize the inhibitory function of Treg cells by enhancing Foxp3 expression (85). In addition, androgens regulate Th2 cytokine production and mRNA levels of IL-4 and IL-10 are reduced in gonadectomized male mice (86), but in Th2 cell-mediated allergic asthma, the androgen/AR pathway restricts Th2 cytokine release (87,88). Androgens/AR may inhibit the differentiation of CD4+ T cells into Th1 cells through a direct increase in protein tyrosine phosphatase non-receptor type 1, a phosphatase that inhibits Th1 differentiation, thus effectively preventing male autoimmunity (89). Androgen deficient men also showed higher levels of IL-1β, IL-2, TNF-α and CD4+/CD8+ T cell ratios (90). In turn, TNF-α has been shown to have an inhibitory effect on testosterone synthesis in the testis by inhibiting important enzymatic steps in the adrenal and gonads (91).

Other sex hormones. Progesterone (Pg) is a female sex hormone that plays a key role in establishing and maintaining the pregnancy process and has powerful immunomodulatory properties (92). T cells express Pg receptors (PR-a, PR-b and PR-c) and membrane Pg receptors (mPRa, mPRb and mPRg) (93). Pg reduces T cell proliferation by impairing the ability of dendritic cells to stimulate T cell proliferation (94). In mouse experiments, administration of a comparable dose of Pg in midgestation promotes CD4+CD25+ Treg cell proliferation and enhances the inhibitory function of CD4+CD25+Treg cell by increasing IL-10 expression (95). High levels of Pg during pregnancy selectively induce conventional CD4+ T cell death and CD4 + Treg cell enrichment (96). In human studies, Pg enhances anti-inflammatory responses and immune tolerance by inducing Th2 and Treg cell subsets during pregnancy (97). In addition, Pg inhibits the differentiation of naive CD4+ T cells to Th1 and Th17 cells (98,99).

Prolactin (PRL) is also involved in immunomodulation and has been shown to favor the survival and differentiation of T-cell progenitors (100). PRL reduces the inhibitory function of Treg cells (101) and SLE patients have elevated PRL receptor expression in Treg cells but decreased Treg cell percentage and function (100). It was observed that co-culturing T cells with PRL led to more production of Th1-related cytokines such as TNF-α, IFN-γ and IL-2 (102).

Human chorionic gonadotropin (HCG) peaks in early pregnancy. Studies demonstrate that HCG regulates Th1/Th2 balance (103), interferes with Th17 differentiation and induces its anti-inflammatory profile, increases the frequency of Treg cells (104) and enhances the inhibitory capacity of Tregs by increasing the secretion of IL-10 and TGF-β (105-107). Follicle stimulating hormone (FSH) is closely related to female ovulation and its level directly reflects the ovarian function status. Studies have found that FSH promotes the high expression of pro-inflammatory cytokines IL-1β, IL-6 and TNF-α (108,109).

5. Effects of sex hormones on RA

Globally, RA occurs more commonly in women (6-8). The ratio of female to male prevalence is >4 before the age of 50 years and after the age of 60 years, this value decreases to <2 (110). Disease activity and progression is also usually more severe in women than in men (111), but pregnancy puts female patients in remission. The sex differences in the prevalence of RA have led to the investigation and study of the role of sex hormones in the pathologic process of the disease, which has evolved from initial comparisons of prevalence between men and women to later studies of the specific mechanisms of the role of specific reproductive factors in RA; however, the effect of such factors on RA has not yet been fully elucidated.

Estrogen. Regardless of sex, decreased androgen levels and increased estrogen levels are found in the synovial fluid of patients with RA (112,113). This phenomenon may be due to the activation of peripheral tissue aromatase stimulated by elevated inflammatory factors (TNF-α, IL-6 and IL-1) in the

synovium and promotes the peripheral conversion of androgens to estrogens (114,115). Injection of glucocorticoids into the joints suppresses their serum estrogen androgen levels compared with baseline before injection therapy, but this tends to be reversible (116). Other studies have shown that in synoviocytes from patients with RA, estrogen hydroxylated metabolites have pro-inflammatory activity and pathogenic effects that cause synovial hyperplasia (117,118). Although these reports show a pro-RA effect of estrogen, a growing body of research suggests that the protective effect of estrogen on RA is dose-dependent and that estrogen deficiency is more likely to bring about joint inflammation and cause bone erosion. For example, estrogen deficiency induces T cell proliferation and prolongs active T-cell lifespan via IFN-γ, which leads to bone loss (119). Ovariectomized (OVX) mice have normal T cell numbers in the bone marrow, but have more RANKL-expressing CD3+ T cells and B cells (120). In MRL/lpr mice (with a genetic susceptibility similar to human RA), estrogen deficiency may induce the activation of RANKL-carrying CD4+ T cells, leading to osteoclastogenesis and bone resorption (121). Treatment of CIA mice with E2 led to a decrease in the number of Th17 cells and IL-17(+) γδ T cells in the joints but an increase in the number of Th17 cells and IL-17(+) γδ T cells in the draining lymph nodes, suggesting that E2 mediates the prevention of migration of these two types of cells from the lymph nodes to the joints (122). In addition, estrogen antagonizes acid-sensing ion channel 1α-induced mitochondrial stress and protects against cartilage damage in OVX rats with adjuvant arthritis (123).

As aforementioned, the immunizing effects of estrogen are closely related to the relative expression of ER. The expression of ER mRNA in synovial tissues of patients with RA was significantly higher than that in healthy non-inflammatory synovial tissues and the relative expression ratio of ERα/ERβ mRNA was significantly lower (124). Treatment with E2 improved synovial inflammation and joint destruction in mice with arthritis and reduced the number of Th17 cells in the joints, both of which are dependent on Erα (125,126). Recent studies have also revealed the effects of ERβ on bone. Xu *et al* (127) show that bone mass decreases in male mice with osteoblast ERβ deletion, but has no effect on bone mass in female mice, suggesting that the mechanism by which osteoblast ERβ regulates bone modeling varies by sex.

Androgens. Androgens are generally considered to be a natural anti-inflammatory agent with immunosuppressive effects (79,80). Serum androgen levels and synovial androgen metabolism levels are decreased in patients with RA regardless of sex (113,128) and serum androgen levels are negatively correlated with RA disease activity (129,130). Therefore, the deficiency of androgen regulating the immune system is considered to be related to the onset of RA. Androgen deprivation has been found to increase the risk of RA when androgen deprivation is administered to patients with prostate cancer (131,132) and the longer the duration of treatment deprivation, the higher the risk (131). In terms of improving clinical and chemical indicators of immune response in men with RA, several studies have demonstrated the beneficial effects of testosterone therapy (129,133). Animal studies have also shown that both physiologic and pharmacologic concentrations of testosterone produce anti-inflammatory effects on joint inflammation in rats (134,135). In addition, polarization of RA synovial macrophages activates intracellular androgens, which contribute to the suppression of local inflammation (136). Anti-TNF-α and anti-IL-6 treatment of synoviocytes from patients with RA both attenuate androgen suppression (137,138) and methotrexate (MTX) treatment also improves testosterone levels in rats with adjuvant-induced arthritis (139).

Other studies have also provided evidence that androgens ameliorate RA, such as the study by Stark *et al* (140) which found that the cytochrome B5 type A (CYB5A) single nucleotide polymorphism (SNP) increases androgens in women and is associated with a reduced genetic risk of RA in women, but the CYB5A SNP is not associated with RA risk in men. Overexpression of CRF6-interacting factor 1, a nuclear protein that interacts with the AR, was found by Park *et al* (141) to attenuate activation of Th17 cells and osteoclast differentiation and reduce arthritic symptoms and histological manifestations in CIA mice. By inhibiting cellular immunity and autoantibody formation, exogenous DHEA ameliorated the severity of acute and chronic antigen-induced arthritis in mice (142). However, DHEA treatment at 50 mg/day for 12 consecutive weeks did not show any greater improvement in patients with RA compared with the placebo group (143).

Other sex hormones. Studies using next-generation sequencing show that Pg-induced transcriptomic changes are significantly enriched in genes associated with pregnancy-regulated diseases (for example, multiple sclerosis, RA and psoriasis), suggesting a potential role for Pg in the immunomodulation of pregnancy-induced diseases (144). Experimental studies have demonstrated the inhibitory effect of Pg on matrix metalloproteinase activity produced by fibroblast-like synoviocytes (145). M2000 is a novel nonsteroidal anti-inflammatory drug with immunosuppressive effects that improves clinical symptoms and increases serum Pg levels in patients with RA (146).

Luteinizing hormone (LH) levels are significantly lower in both male and postmenopausal female patients with RA compared with healthy controls (147-149), but are not associated with disease activity (148). In a study using the gonadotropin-releasing hormone antagonist ASP1707 in combination with MTX for the treatment of RA, a 90% decrease in plasma LH concentrations was found in 90% of patients treated with ASP1707, but no clinical benefit was demonstrated and there were no significant changes in levels of TNF-α, matrix metalloproteinase 3 and IL-6 (150).

FSH levels increase during the perimenopausal period due to negative feedback in the gonadal axis (151) and FSH secretion promotes the production of TNF-α, which increases the number of osteoclast precursors in the bone marrow (103), but this does not affected osteoclastogenesis (152). High FSH levels have been found to be associated with an increased risk of RA and are positively correlated with RA disease activity (153). However, earlier studies have shown that serum FSH is significantly lower in postmenopausal women with RA compared with healthy controls (149).

PRL has a well-recognized immunostimulatory effect (154); increased serum PRL has been reported in patients with RA (155,156) and breastfeeding may exacerbate the condition of patients with RA through PRL effects (154).

6. Influence of special periods and special events of women on RA

Menopause. Following menopause, estrogen levels plummet and testosterone levels begin to decline and postmenopausal women have a higher pro-inflammatory immune status (157). The peak incidence of RA in women is roughly during their menopausal years (158) and menopausal status is associated with the progression of joint function decline and deterioration (159). Early age at menopause has long been recognized to be associated with an increased risk of RA (160,161) and women with menopausal age in their 40s have more than double the risk of RA (160). Postmenopausal women are at increased risk of ACPA-positive RA, especially in early menopause when estrogen plummets (162,163). Treatment with E2 in postmenopausal women with RA significantly increased the salivation of crystallizable fragments of IgG and induced its capacity for anti-inflammatory effects (164).

Pregnancy. Pregnancy has been found to have a protective effect on the development and disease activity of RA, with any number of births being significantly associated with a reduced risk of RA, but no such protective effect was found in nulliparous women (165), which, as previously described, is perhaps associated with high estrogen and Pg concentrations (166,167). A large population-based Swedish study showed that ACPA-positive patients are unlikely to experience disease improvement from pregnancy (168), possibly because pregnancy in ACPA-positive patients failed to cause elevated ACPA-IgG galactosylation (169). CD4+CD25+ Treg cell levels are significantly higher in patients with RA during pregnancy than at 8 weeks postpartum and CD4+CD25+ Treg cell frequency is negatively correlated with RA disease activity in both periods (170). Experimental studies demonstrate that pregnancy protects mice from CIA, with Treg cells playing a considerable role and that transfer of Treg cells from pregnant 'protected' mice is sufficient to confer protection to non-pregnant mice (171). Fertility is affected in patients with RA (172,173) and anti-Müllerian hormone is currently the most reliable biomarker of ovarian reserve. A number of studies have demonstrated that serum anti-Müllerian hormone levels are not reduced in patients with RA compared with healthy controls (174,175), suggesting that reduced fertility in patients with RA may not be caused by decreased ovarian reserve function.

Breastfeeding. Studies on the role of breastfeeding in RA show conflicting results. The incidence of RA is significantly higher in postpartum breastfeeding women, with ~90% of patients experiencing an onset in the first 3 months postpartum and a decrease in the following 9 months, which also suggests that elevated PRL is associated with episodes and recurrences of RA (154,176). However, prolonged breastfeeding (>12 months) has been found to be associated with a reduced risk of RA (177,178). A subsequent systematic review and meta-analysis covering 1,672 RA cases from six studies show that breastfeeding is associated with a lower risk of RA regardless of whether breastfeeding is longer or shorter than 12 months (179). Hormone levels fluctuate greatly in postpartum women, with a sudden drop in estrogen and Pg and an increase in PRL levels and coupled with the fact that PRL has been little studied in RA, there is still a large gap to be filled in terms of the effects of breastfeeding on RA and its causes.

HRT and oral contraceptive (OC). A study based on an epidemiologic survey of RA evaluating the relationship between postmenopausal HRT use and RA risk showed a reduced risk of ACPA-positive RA but no association with ACPA-negative RA in postmenopausal women who used HRT compared with those who did not (180). OC has also shown a protective effect against ACPA-positive RA only and the earlier the first exposure to OC, the lower the odds ratio for RA (180,181). No correlation with the risk of ACPA-negative RA is found for either HRT or OC (180,182) and these differences suggest the existence of different hormone-related etiologic pathologies for ACPA-positive and ACPA-negative RA. However, these results have not been fully harmonized, as a meta-analysis of 17 studies showed that OC did not provide protection against the risk of RA in women (183) and a number of large cohort studies have failed to identify an association between OC or HRT use and the risk of RA (177,184,185).

7. Conclusion and future research prospects

The present study found that androgens and Pg had a more definite inhibitory effect on immune response and RA compared with other sex hormones, whereas the protective effect of estrogen on RA appears to be dose-dependent, but the sex differences and specific mechanisms of action of these hormones remain to be investigated. These hormones regulate immune and inflammatory responses by modulating CD4+ T-cell differentiation to promote the balance between Th1/Th2 and Th17/Treg cells and altering Th-cell function and alleviate the joint symptoms of RA by modulating the balance between osteoclasts and osteoblasts to ameliorate bone destruction. From epidemiologic investigations of female-specific events on the risk of RA and mechanistic studies of RA-hormones, it is not difficult to find a common feature that an acute decline in ovarian function and estrogen drives RA progression. However, the role of estrogen combined with Pg in RA is controversial, as not all studies have shown favorable results (9,181,186). Finally, little is known about the role of hormones such as LH and FSH in the RA disease process; are their effects and mechanisms of action on RA worthy of attention?

In addition, studies of hormone therapy for RA are quite limited and the findings are inconclusive. Regardless of sex, androgen-assisted treatment of RA has a limited effect on disease activity, but brings improvements in quality of life (143,187-189). The addition of estrogen to pre-existing therapy in postmenopausal women with RA seems to bring some relief from the disease, but this is associated with serum estrogen levels (9,190) and more studies show that estrogen is well suited to ameliorate bone loss and increase bone density in postmenopausal women with RA (9,191-193). In addition, two studies of the gonadotropin-releasing hormone antagonist, cetrorelix, for the short-term treatment of RA found that cetrorelix has a rapid anti-inflammatory effect, but it is only in patients with RA and with high gonadotropin levels that adjunctive treatment with cetrorelix can show a rapid improvement in the disease (194,195).

Differences in hormone levels and regulation between men and women, as well as multiple life stages and specific events

in women, have made the study of sex hormones in disease difficult and complicated the findings, with high or low levels of a particular hormone appearing to be associated with disease. In addition, the level of expression of the hormone receptor proteins may also cause the hormones to act differently and it needs to be verified whether these differences in action have an effect on RA pathogenesis or, conversely, whether RA activity causes changes in the expression of the hormone receptor proteins.

The failure of T cell tolerance is attributed to endogenous cellular abnormalities already present in the naive T cells that shift the differentiation program to favor the production of short-term effector T cells over long-lived memory T cells. Current therapeutic strategies for RA are focused on controlling inflammation and by recognizing that RA undergoes a period of relatively stable impaired immune tolerance prior to the onset of inflammation and the associated molecular features of this period, it is possible to identify upstream therapeutic targets that can abort the disease process before irreversible tissue damage occurs. The role of sex hormones in the immune system was recognized at an early stage and it is now clear that Th cell responses are regulated by sex hormone levels and that sex hormones not only directly affect T cell transcriptional profiles, but also influence T cell responses and alter CD4+ cell differentiation by controlling gene expression in thymic epithelial cells and regulating innate immune cells (196). However, despite the a number of advances in the study of the effects of sex hormones on T cells, there are still a number of unanswered questions, especially in RA, where epidemiologic investigations are still contradictory and controversial and the study of the mechanisms of sex hormone effects on Th cells has not been carried out extensively or intensively.

Nonetheless, existing research has also revealed new areas for combating RA. Future studies may be able to devise a way to limit the targets of action of sex hormones to make T cell differentiation more stable or to correct mis-differentiation, which would be an important step in the effective use of sex hormones as an immunotherapy, but also a lengthy process that needs to be precisely controlled.

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Competing interests

The authors declare that they have no competing interests.

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