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Autoimmune diseases: Role of steroid hormones

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A B S T R A C T

Autoimmune diseases (AIDs) are a heterogeneous group of disorders in terms of clinical manifestations, pathogenesis, and prevalence, and there is no agreement to date on a common classification.

Adaptive immune responses are responsible for the existence of AIDs, although innate immunity is also involved in misguiding the immune response against self-antigens.

Hormones, in general, and in particular steroid hormones, play a critical role in the physiology and pathology of the immune system, especially in adaptive immunity. Hormonal factors, alone or in relation to age, sex, and reproductive status, are involved in conditioning the onset of a number of AIDs. There is a well-defined sexual dimorphism for human AIDs.

At the same time, the classic view has been that steroid hormones have well-defined effects, with one type, estrogens, being "pro-inflammatory" and the other two progestogens (progesterone and its synthetic analogs) and androgens being "anti-inflammatory."

Although this view has been considered too simplistic and seems contradicted by numerous observations, it remains valid: progestogens and androgens are immunosuppressive and therefore

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protective against AIDs, whereas estrogens are immune-stimulatory and therefore pathogenic in AIDs.

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Introduction

Autoimmune diseases (AIDs) represent a heterogeneous group of disorders in terms of pathogenesis, clinical manifestations, and prevalence; their classification has varied with time but, unfortunately, without a common agreement to date on classification criteria. Hayter and Cook [1] have proposed an assessment of prevalence, spectrum, and case definition on the basis of a number of features, which has led to their identification of 81 AIDs. Fortyfive of them have been associated with well-defined autoantigens. Among these, half are rare with a prevalence of $<1/10^4$ and a female bias is present in the high prevalence ones such as Multiple Sclerosis (MS), in which the gender bias could be related to a possible hormonal association [2]. Autoimmunity is the mirror image of tolerance, reflecting the loss of tolerance to "*self*" that can take place in several different ways, as there is no single cause responsible for autoimmunity. The breakdown of tolerance, which should discriminate between "*self*" and "*non-self*" at the earliest stage of adaptive immunity development, can lead to an attack of the body's own structures as if they were foreign through various mechanisms. Sometimes "*self*" cells may display "*non-self*" antigens (Ags), such as intracellular viruses, *Plasmodium falciparum,* or drugs, which are unavoidably destroyed in the process of eliminating the intruder.

Molecular mimicry can take place in the presence of particular viral and bacterial components and families of phylogenetically highly conserved proteins such as heat shock proteins. They are expressed in prokaryotic and eukaryotic cells under physiological conditions, and in response to various forms of stress, they can trigger an aberrant immune reaction to common antigenic epitopes in persistent chronic infections in which cross-reactive cells are generated [3]. Alteration of "*self*" proteins and structures by various agents such as oxidative stress can lead to modifications that result in transformations, where "*self*"-Ags are no longer ignored by the immune system but seen as foreign, thus triggering immune reactions [4]. Occasionally, late developing or sequestered "*self*" Ags such as lens, sperm, and myelin, come into contact with the immune system only at a later stage and are treated as "*non-self*" structures [5]. Furthermore, Ag presentation by non-professional Antigen-presenting cells can give rise to self-reactivity. Self-reactive B cells can be stimulated by "polyclonal activators," which override the usual triggering requirements [6]. Moreover, a deficiency in the regulatory pathway can represent a crucial key point for allowing autoimmune reactions [7,8]. Finally, autoimmunity can phenocopy Mendelian inherited disorders characterized by mutations of autoantigens, and a common feature of these proteins is the presence of repeat and coiled-coil domains and their frequency is in contrast with random samples of the human proteome spectrum [1].

Adaptive immune responses are the protagonists responsible for the existence of AIDs, although innate immunity is also involved in the aberrant immune response against "*self*"-Ags.

Both humoral response and cell-mediated immunity are involved in autoimmune processes that take place in a large variety of autoimmune reactions. T helper (Th) cells are the directors of both antibody-mediated and cell-mediated responses. Because a high degree of complexity and sophistication underlies most immunological phenomena, their network has become much larger than the initial Th1/Th2 paradigm [9] including several other T cell subsets such as Th17 [10], T regulatory (Treg) populations [11], and T follicular helper (Tfh) cells [12], which are also involved in regulating autoimmune processes. In contrast to the classic Th1 and Th2 cells, which represent a rather stably polarized T cell subset, $CD4^+$ Th cell differentiated subpopulations are characterized by a remarkable grade of heterogeneity and plasticity, which implies that their initial differentiation does not represent an endpoint in their development. This plasticity can be a key feature in the development of autoimmune reactions [13].

B cells play a crucial role in protecting against pathogens and can also contribute to harmful immune responses in many autoimmune diseases by producing antibodies (Abs) directed toward "*self*"-Ags, by

presenting "*self*"-Ags, and by producing pro-inflammatory cytokines. Human and mouse Systemic Lupus Erythematous (SLE) studies have shown that hyper-responsiveness of B cells due to defects in the regulation of B cell antigen receptor signaling or increased signaling through the nuclear-sensing Toll-like receptors can alter the selection of autoreactive B cells and promote the production of pathogenic auto-Abs [14]. CD22 contributes to the regulation of autoimmunity. Some recent data suggest that targeting CD22 can suppress pathogenic B cell responses. Genetic variants of CD22 or enzymes involved in the glycosylation of ligands of CD22 have been linked to susceptibility to human AIDs [15]. Autoimmunity is also connected with the cytokine and chemokine pathways that trigger and regulate the type of innate and acquired immune response along with a multiplicity of genetic influences at the level of T cell and B cell subsets and of the hormonal influence on the immune system [16].

Role of steroid hormones

Hormones play a critical role in the physiology and pathology of the immune system, especially in adaptive immunity (Table 1). The classic view is that female steroid hormones have well-defined effects, with estrogens being "pro-inflammatory" and progesterone (P) and synthetic progestins being "anti-inflammatory"; this view is too simplistic, and contradicted by numerous observations [17].

Indeed, estrogens can interact with modifiable environmental factors. For example, in experimental autoimmune encephalomyelitis (EAE), the mouse model of MS, vitamin D3 (D3) acts in an estrogen-dependent manner: ovariectomy eliminates and 17β-estradiol (E2) can restore D3-mediated EAE protection. In addition, E2 and D3 interact synergistically within $CD4^{+}$T cells to prevent this demyelinating disease through a cooperative amplification loop involving E2 and calcitriol [18,19].

Table 1
T Helper Cells and Immunity.

T HELPER CELLS AND IMMUNITY
• **Th1 cells** are mainly involved in immunity against intracellular pathogens and autoimmunity. They are induced by IL-12 during naive T cell priming through the activation of their STAT-1, which, in turn, activates T-bet, the master regulator of Th1 cell differentiation. They secrete IFN-γ, IL-2, TNF-α, and TNF-β (LTα) [65–68] and are responsible for cell-mediated inflammatory reactions, delayed-type hypersensitivity, and tissue injury in infectious and autoimmune diseases.
• **Th2 cells** arise during naive T cell priming in the presence of IL-4 through the activation of STAT-6, which, in turn, activates GATA-3, the master regulator of Th2 cell differentiation. They are mainly involved in immunity against extracellular pathogens, allergy, and atopy and also play a role in autoimmunity. They secrete amphiregulin and cytokines IL-4, IL-5, and IL-13 [45,65,67,69,70] and are associated with B-cell antibody production.
• **Th17 cell** priming of naive T cells is regulated by the activation of STAT-3 in the presence of IL-6 and TGF-β, which, in turn, activates RORγt, the main regulator of Th17 cell differentiation. They are involved in immune responses against extracellular pathogens and autoimmunity [71]. They secrete GM-CSF, IL-17A, IL-17AF, IL-17F, IL-21, and IL-22 and display strong cell plasticity in the presence of IL-17/IFNγ double-producing cells [72,73]. Plasticity and functional variability of Th17 and Treg cells imply a relationship between Th17 and Treg cells. Both Th17 and Tregs are reciprocally related to each other; for example, TGF-β links the development of Th17 cells to that of FoxP3+Tregs. It was shown that TGF-β induces the differentiation of Tregs, whereas the combination of Tregs with IL-6 or IL-21 results in the induction of Th17 cells and inhibition of Treg differentiation [74], thereby giving rise to autoimmunity.
• **Treg cells** are induced by the presence of TGF-β, which primes naive T cells activating STAT-5, which, in turn, activates Foxp-3, their X-linked master transcription factor. Tregs are involved in maintaining the immune homeostasis and tolerance; therefore, they are vitally important in preventing autoimmunity [75,76]. They secrete IL-10 and TGF-β, and they rule out the immunoregulatory processes of immune responses. Treg cells, like Th17 cells, display a high grade of plasticity, and this feature enhances the risk for autoimmunity. In addition, female gender and hormonal influences regulate Foxp-3 expression, which is critical for the gender bias of AIDs [77]. A strictly regulated balance between T effector cells and Tregs is at the basis of a finely regulated immune response [50,78,79].
• **Tfh cells** are primed by IL-6 and IL-21 from naive T cell with the induction of STAT-3 that activates Bcl-6, their main lineage transcription factor. These cells are found in the periphery within B cell follicles of secondary lymphoid organs. Within the germinal centers of lymph nodes, they play a critical role in mediating the selection and the survival of B cells that proceed to differentiate into either plasma cells capable of producing high-affinity Abs or memory cells and are implicated in auto-Ab production in AIDs [80–82]. They secrete IL-21, which activates B cells and promotes Ab production.

Abbreviations: STAT-1 = Signal transducer and activator of transcription, T-bet = T-box transcription factor TBX21, IL = Interleukin, IFN = Interferon gamma, TNF = Tumor Necrosis Factor alfa, LTα = Lymphotoxin alfa, RORγt = RA-related orphan receptor gamma, GM-CFS = granulocyte macrophage colony stimulating factor, FoxP3 = forkhead box P3, Bcl-6 = B-cell lymphoma 6 protein.

In addition, there is clinical and experimental evidence that estradiol confers protection against HIV and other sexually transmitted infections, through the enhancement of $CD4^+$ T cell antiviral immunity [20].

However, P, despite being one of the major players in creating pregnancy immunotolerance, sustains cytokine expression, thereby enhancing proliferation of immune cells. Indeed, a recent investigation probed the respective role of P and E2 in regulating IL-15 messenger RNA (IL-15 mRNA) and its secretion in human endometrial stromal cells (ESCs) *in vitro*. IL-15 stimulates lymphocyte proliferation and migration and seems to be involved in regulating the proliferation and differentiation of uterine natural killer cells (NKs). When ESCs were treated with P alone or P plus E2, there was a significant increase in IL-15 mRNA levels, whereas E2 alone was not able to increase IL-15 mRNA expression [21].

Hormonal factors, alone or in relation to age, sex, and reproductive status, are involved in conditioning the onset of a number of AIDs. There is a well-defined sexual dimorphism for human AIDs (Table 2) [22], e.g., SLE, MS, and autoimmune thyroid diseases (ATDs) seem to affect women primarily during reproductive years; however, the highest incidence of Rheumatoid Arthritis (RA) is seen after menopause. Experimental and epidemiological evidence indicates that in humans, sex steroids can modulate the genetic risk of AIDs [23]. In specific diseases such as Hashimoto's thyroiditis, differences in the sex-related prevalence may be observed in almost every age group [24]. In other instances, such as MS, female-to-male ratios seem to increase with age. In 2006, Orton et al. [25] carried out a longitudinal study of MS and proposed that the disproportional increase in incidence *per se* and with age in women might have an environmental origin, although probably associated with interactions between genetic and environmental factors. This trend has been confirmed by more recent studies [26–28].

Over 30 years ago, Grossman [29] described some of the interrelationships between the immune and reproductive systems, involving pituitary, gonadal steroid, and thymic hormones. Grossman quoted early experimental evidence showing that transplantation of gonads in castrated rats of both sexes produced immune suppression [30]. In 1994, Van Vollenhoven and McGuire [31] reported that, as sex hormones possess marked immunomodulatory properties, attempts have been made at treating AIDs with various steroids (Table 3). Unfortunately, estrogen therapy has not shown promise in RA,

Table 2
Sex Differences in Human Autoimmune Diseases. Adapted from Mc Combe et al., 2009 [42].

Disease	Female:Male Ratio
Systemic	
SLE (388)	13.1:1 (African American), 8.7:1 (white)
Sjogren's Syndrome	4:1 (Israel); 8.7:1 (Denmark)
Endocrine	
Type 1 diabetes	0.5:1 (Sweden); 0.8:1 (Denmark)
Grave's disease	3.5:1
Hashimoto's thyroiditis	5.2:1
Gastrointestinal and liver	
Ulcerative colitis	1:1
Crohn's disease	1.3:1
Primary biliary cirrhosis	9:1
Celiac disease	1.8:1
Rheumatological	
Ankylosing spondylitis	1:3
Rheumatoid arthritis	2.7:1
Psoriatic arthritis	1:1
Neurological	
Multiple sclerosis	1.9:1 (Canada); 2,4:1 (Japan); 4.3:1 (Wales)
Myasthenia gravis	2:1
Guillain-Barré syndrome	0.9:1
CIDP	0.6:1
Skin	
Psoriasis	0.8:1 (Italy); 1.1:1 (Denmark)
Scleroderma	4:1

despite epidemiological data suggesting possible benefits. However, testosterone supplementation in men has produced mild improvements.

As recently noted by Hughes and Choubey [32], the mechanisms through which an AID leads to loss of immune tolerance are not necessarily the same as those involved in subsequent immune-mediated injury. Thus, sex hormone action may produce different effects depending on disease risk and disease activity. Hence, the observed contrasting results may be due to the fact that dimorphism in the manifestations of AIDs seems to involve not only immunomodulation by sex steroids but also non-hormonal factors encoded by genes on the X and Y chromosomes [33].

Both androgens and estrogens regulate the balance of the cytokine-related AIDs. Estrogens in general have immunostimulatory roles, in particular suppressing T and B cell lymphopoiesis and activating B cell functions [34]. However, androgens and progestogens are immunosuppressive and are able to counteract pathways affected by estrogens [35,36]. Specifically, P affects $CD4^+$ T cell differentiation and cytokine production, leading to an increase in IL-4 production and Treg differentiation as well as reduced Interferon-γ (IFN-γ) production, reduced T cell proliferation, and T cell-dependent Ab production [37].

Estrogens

Several investigations have addressed in detail the effects of estrogens on AIDs. In two comprehensive early reviews, Grossman [29] and Grossman et al. [38] expressed the opinion that estrogens depress specific subsets of thymocytes, thereby depressing several cell-mediated immune responses. Grossman and Grossman et al. further suggested that estrogens downregulate thymocyte function by decreasing the release of thymic polypeptides, leading to the depression of T lymphocyte activity. They concluded that estrogens "*depress most, if not all, the major functions attributed to the cell-mediated immune system.*"

In 2006, the topic was again reviewed by Cutolo et al. [39], starting from the premise that estrogens enhance humoral immunity, whereas androgens, progestogens, and glucocorticoids suppress humoral immunity. They pointed out the complexity of the situation because a number of conditions may affect either ovarian or placental estrogen production or its peripheral conversion rate. These include not only physiological situations (such as the two phases of the menstrual cycle, pregnancy, the postpartum, and peri- and postmenopause) but also other conditions (such as age, chronic stress, altered circadian rhythms, and inflammatory conditions) and the effects of medications (corticosteroids, oral

Table 3
Recommended use of sex hormones in rheumatic diseases. Adapted from Van Vollenhoven and McGuire, 1994 [31].

Disease	Hormone intervention	Recommendations and observations
Rheumatoid arthritis	Estrogen-containing oral contraceptive therapy	Recommended
	Estrogen replacement therapy	Strongly recommended
	Therapeutic use of estrogen	Investigational
	Therapeutic use of testosterone	Investigational; might be considered in men with low serum testosterone
Systemic lupus erythematosus	Estrogen-containing oral contraceptive therapy	To be avoided or used with caution under close monitoring
	Progesterone-only oral contraceptive therapy	Recommended, except when hypercoagulability or history of thromboembolic disease exists
	Estrogen replacement therapy	May be used in most patients; relatively contraindicated in active systemic lupus erythematosus but cautiously recommended in inactive systemic lupus erythematosus
	Danazol	Modest benefits in systemic lupus erythematosus-related cytopenias
	Nortestosterone	Not indicated in men; investigational in women, probably no benefit
	Dehydroepiandrosterone	No studies to date in men; investigational in women, probable benefit
Ankylosing spondylitis	Human chorionic gonadotropin	Investigational, possible benefit for men
	Estrogen	Investigational, possible benefit for women
	Bromocriptine	Investigational, possible benefit

contraceptives, and hormonal steroid replacement). They reported that in some AIDs (e.g., RA and SLE), there is an enhanced peripheral conversion of androgens [testosterone, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEAS)] to estrogens. Their view is supported by studies showing low circulating androgen levels in women with SLE [40] and RA [41] that have been interpreted as indicating accelerated peripheral conversion to estrogens, through a pathogenic mechanism involving inflammatory cytokines that are able to stimulate peripheral aromatase expression.

Without negating the effect of estrogens, McCombe et al. [42] have argued that if the increased prevalence of autoimmunity in women was entirely due to sex hormones, then estrogens *per se* should predispose to autoimmunity, but this is not the case. Estrogen receptors (ER) are present on many cells of the immune system. Consequently, estrogens could theoretically modulate damage caused by autoimmune injury. The enhancement of Th2 responses induced by the estradiol-driven conversion of $CD25^-$ to $CD25^+$ Treg cells may, at high doses, improve the clinical picture in Th1-mediated AIDs. Moreover, certain mechanisms (such as estrogen-enhanced Ab production in response to Ag immunization) can differ among different estrogens [43].

Laffont et al. [44] have focused their attention on estrogens or ER agonists as potent neuroprotective as well as anti-inflammatory agents, in EAE. Estradiol-mediated protection from EAE may be exercised through two non overlapping mechanisms: an anti-inflammatory effect, when the hormone is administered before the disease is induced, and a neuroprotective action, once the disease has progressed.

In a very recent, comprehensive review, Moulton [45] again stressed that progesterone and androgens are immunosuppressive and therefore protective against AIDs, whereas estrogens are immune-stimulatory and therefore pathogenic in AIDs. Aire, a key molecule in central tolerance, has been found to be present at lower levels in postpubertal females than in males; therefore, estrogen-mediated regulation of the T cells repertoire selection is important in central tolerance and contributes to autoimmunity [46]. Moreover, estrogens influence $CD4^+$ T cell activation, cytokine production, differentiation, and regulatory functions with an impact on physiological processes and AIDs [47]. Different studies show that the effect of estrogens on immune responses depends on specific concentrations and expression of specific receptor subtypes, thus indicating a tissue-specific targeting. The role of estrogens in autoimmunity is complex and presents an intriguing dichotomy regarding its effects on different AIDs. SLE worsens during pregnancy, while MS, RA, ATD, and others improve due to the maternal shift from Th1 to Th2 immune response. The Th1 to Th2 shift has been reported to provide protection from immune rejection and enhancement of antibody production for passive transfer of immunity to the fetus. In SLE, the shift to a Th2 immune response enhances autoantibody production [48]. In postmenopausal women, estrogen deficiency is crucially involved in the chronic inflammatory reaction mediated by IL-17, which leads to osteoporosis. IL-17 is also implicated in the pathogenesis of inflammatory arthritis including RA, and estrogen administration is able to reverse IL-17-mediated bone destruction [49]. Furthermore, lower numbers of Tregs are found in the postmenopausal period of estrogen decline, indicating an impaired Treg-mediated suppressive function on T effector cells and protective effects on bone metabolism [50].

The dichotomy of the role of estrogens in autoimmunity can explain contribution of estrogen to SLE pathogenesis, worsening the disease in humans and murine models, while offering immune protection in other AIDs such as MS and RA [51].

Progestogens

The basic effects of progestogens on the immune systems will be considered in another chapter of this issue [52]. The action of progestogens is only mentioned here for ease of reference. Overall, P and C_{21} synthetic progestins exert a suppressive action on the immune system. Forty years ago, it was suggested that P is responsible for the decreased immune responses observed during pregnancy [53]. P also influences Abs production, especially of those that are asymmetrically glycosylated and therefore unable to trigger immune effector mechanisms. Asymmetric Abs are thought to be self-protective [54]. The immunomodulatory effects are generally considered as anti-inflammatory; they differ from those of estrogens and androgens and may confer protection from injury in general [55].

Hughes [30] has pointed out that both P and synthetic progestins impact on the risk of immune-mediated injury and do so in a number of ways depending on their concentrations,

affinity for receptors expressed in immune organs, and the immune cells or tissues targeted by immune attack. Whereas at physiological levels, P may enhance pathways related to SLE pathogenesis, at the concentrations found during gestation, it may suppress disease activity in RA and MS.

Androgens

Androgens have also been implicated in regulating the immune system and in modulating the immune response. Almost all the actions of androgens are considered to be immunosuppressive [36,56]. Androgens modulate the development of B cell populations and regulate the function of immuno-competent T cells by depressing the T lymphocyte response [31]. Different androgens probably act differently on the immune system [31], which may have relevance when discussing progestogens, as some progestogens that are used clinically have androgenic activity, as shown in Table 4.

An example of how complex the situation may become is illustrated with cyproterone acetate (CPA), a progestin with marked antiandrogenic activity. An early report [57] found that CPA exerts a strong immunosuppressive effect in mice. This may seem paradoxical because, as an antiandrogen, CPA would be expected to stimulate immune function. However, cyproterone also has marked progestational activity; therefore, it may be that – at least in mice – the immunosuppressive action of the progestin dominates. In addition, despite the progestational properties, CPA has a pharmacological profile similar to that of the antiprogestin mifepristone [58].

Overall, it can be stated that testosterone administration in mice causes thymic atrophy, and male mouse castration produces thymic hypertrophy [59,60].

In Moulton's review [45], there is updated information of the mechanism of action of androgens on the immune system, stressing that low testosterone levels are associated with high levels of B cells and antibody responses. Moulton [45] concluded that androgens promote B lymphopoiesis through either an intrinsic mechanism on B cells or a direct action on bone marrow stromal cells. Androgens also act to limit the peripheral lymphoid compartment and their suppression leads to an increase in peripheral lymphoid populations.

Clinically, there is evidence that androgens can protect against autoimmune diseases. Androgens also have different effects in both sexes. In men with MS, transdermal testosterone treatment significantly reduced delayed-type hypersensitivity skin recall responses and decreased the proportion of $CD4^+$ T cells, while increasing NK cell levels [61,62]. However, in females, transdermal testosterone administration in mild-to-moderate SLE did not significantly affect disease activity, quality of life, or sexual functioning. However, the authors stated that the increased use of steroids in the placebo group may have confounded the results [63].

Another androgen assessed in SLE is DHEA. In 2007, a Cochrane review of seven RCTs (842 participants; 839 women and only 3 men) concluded that DHEA had little clinical effect on disease activity in patients with mild/moderate AID. However, one trial showed evidence of stabilization or improvement in 8.3% more patients than those treated with placebo [64].

Table 4
Relative potencies of synthetic progestins. Adapted from Greer et al., 2005 [83].

Progestin (1 mg)	Progestational Activity	Androgenic Activity[a]
Norethisterone	1.0	1.0
Norethisterone acetate	1.2	0.6
Ethynodiol diacetate	1.4	1.6
Levonorgestrel	5.3	8.3
Dl norgestrel	2.6	4.2
Norgestimate	1.3	1.9
Norelgestromin	1.3	1.9
Desogestrel	9.0	3.4
Drospirenone	1.5	0.0

[a] Progestational and androgenic activity are relative to 1-mg dose of norethisterone.

Conclusions

The modulatory effect of steroid hormones on the immune system has been well established, although the simple view that estrogens have a stimulatory action, while progestogens and androgens are immunosuppressive, is no longer acceptable.

The situation is complicated by the fact that different classes of synthetic progestins have different, sometimes opposite, additional activities (androgenic, antiandrogenic, glucocorticoid, anti-glucocorticoid, etc.).

Finally, estrogens seem to have a double role in autoimmunity, contributing to worsening SLE pathogenesis, while offering immune protection in other AIDs such as MS and RA.

Conflict of interest statement

The authors declare to have no conflict of interest with the content of this review.

Practice points

- Autoimmune disorders represent a heterogeneous group of diseases in terms of clinical manifestations, pathogenesis, and prevalence. At present, there is no agreement on a common classification.
- Autoimmunity is the mirror image of tolerance. Loss of tolerance to one's own substances can take place in several different ways; therefore, there is no single cause responsible for autoimmunity. The breakdown of tolerance can lead to an attack of the body's own structures, as if they were foreign through various mechanisms.
- Sex steroid hormones may positively or negatively influence the course of an autoimmune disease, depending on the type of immune mechanism involved in its pathogenesis.
- Steroid hormones play a critical role in the physiology and pathology of the immune system, especially in adaptive immunity. The classic view that female steroid hormones have well-defined effects, with estrogens being "pro-inflammatory" and progesterone and synthetic progestins being "anti-inflammatory," is presently considered too simplistic.
- Hormonal factors, alone or in relation to age, sex, and reproductive status, are involved in conditioning the onset of a number of human autoimmune diseases, with a female-to-male ratio of 2:1.
- Overall, estrogens seem to play a double role in autoimmunity. While in SLE pathogenesis they contribute to the worsening of the disease, they provide immune protection in other AIDs such as MS and RA.

Research agenda

- Progesterone and synthetic progestins are considered both anti-inflammatory and immunosuppressant. At the same time, synthetic progestins belong to at least 4 different families with different estrogenic, anti-estrogenic, androgenic, anti-androgenic, or glucocorticoid-like activities. Given this reality, it is important to evaluate the effects of individual classes of progestins on autoimmune diseases.
- Estrogens are considered pro-inflammatory and immunostimulant. Classic studies refer to the effect of estradiol and presently several new estrogens are being utilized clinically. The effect of these new compounds on autoimmune diseases should be investigated.
- There is insufficient information of the effect of androgens on autoimmune diseases in women.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bpobgyn.2019.03.001.

References

[1] Hayter SM, Cook MC. Updated assessment of the prevalence, spectrum and case definition of autoimmune disease. Autoimmun Rev 2012;11:754–65.
[2] Avila M, Bansal A, Culberson J, Peiris AN. The role of sex hormones in multiple sclerosis. Eur Neurol 2018;80:93–9.
[3] Benagiano M, D'Elios MM, Amedei A, Azzurri A, van der Zee R, Ciervo A, et al. Human 60-kDa heat shock protein is a target autoantigen of T cells derived from atherosclerotic plaques. J Immunol 2005;174:6509–17.
[4] Stemme S, Faber B, Holm J, Wiklund O, Witztum JL, Hansson GK. T lymphocytes from human atherosclerotic plaques recognize oxidized low density lipoprotein. Proc Natl Acad Sci USA 1995;92:3893–7.
[5] Wucherpfennig KW. Autoimmunity in the central nervous system: mechanisms of antigen presentation and recognition. Clin Immunol Immunopathol 1994;72:293–306.
[6] Hammarström L, Smith E, Primi D, Möller G. Induction of autoantibodies to red blood cells by polyclonal B-cell activators. Nature 1976;263(5572):60–1.
[7] Phan GQ, Yang JC, Sherry RM, Hwu P, Topalian SL, Schwartzentruber DJ, et al. Cancer regression and autoimminity induced by cytotoxic T lymphocytes-associated antigen 4 blockade in patients with metastatic melanoma. PNAS 2003;14:8372–7.
[8] Freyschmidt EJ, Mathias CB, Diaz N, MacArthur DH, Laouar A, Manjunat N, et al. Skin inflammation arising from cutaneous regulatory cell deficiency leads to impaired viral immune response. J Immunol 2010;185:1295–302.
[9] Hirahara K, Nakayama T. $CD4^+$ T-cell subsets in inflammatory disesase: beyond the Th1/Th2 paradigm. Int Immunol 2016;28:163–71.
[10] Bettelli E, Korn T, Oukka M, Kuchroo VK. Induction and effector functions of T(H)17 cells. Nature 2008;453:1051–7.
[11] Josefowicz SZ, Lu LF, Rudensky AY. Regulatory T cells: mechanisms of differentiation and function. Ann Rev Immunol 2012;30:531–64.
[12] Vinuesa CG, Linterman MA, Yu D, McLeannan ICM. Follicular helper T cells. Ann Rev Immunol 2016;34:13.1–13.34.
[13] Vahedi G, Poholek CA, Hand TW, Laurence A, Kanno Y, O'Shea JJ, et al. Helper T-cell identity and evolution of differential transcriptomes and epigenomes. Immunol Rev 2013;252:24–40.
[14] Green NM, Marshak-Rothstein A. Toll-like receptor driven B cell activation in the induction of systemic autoimmunity. Semin Immunol 2011;23:106–12.
[15] Angata T. Associations of genetic polymorphisms of Siglecs with human diseases. Glycobiology 2014;24:785–93.
[16] Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol 2016;16:626–38.
[17] Wang L, Wang FS, Gershwin ME. Human autoimmune diseases: a comprehensive update. J Intern Med 2015;278:369–95.
[18] Pedersen LB, Nashold FE, Spach KM, Hayes CE. 1,25-dihydroxyvitamin D3 reverses experimental autoimmune encephalomyelitis by inhibiting chemokine synthesis and monocyte trafficking. J Neurosci Res 2007;85:2480–90.
[19] Nashold FE, Spach KM, Spanier JA, Hayes CE. Estrogen controls vitamin D3-mediated resistance to experimental autoimmune encephalomyelitis by controlling vitamin D3 metabolism and receptor expression. J Immunol 2009;183:3672–81.
[20] Anipindi VC, Bagri P, Roth K, Dizzell SE, Nguyen PV, Shaler CR, et al. Estradiol enhances CD4+ T-cell anti-viral immunity by priming vaginal DCs to induce Th17 responses via an IL-1-dependent pathway. PLoS Pathog 2016;12:e1005589.
[21] Okada H, Nakajima T, Sanezumi M, Ikuta A, Yasuda K, Kanzaki H. Progesterone enhances interleukin-15 production in human endometrial stromal cells in vitro. J Clin Endocrinol Metab 2000;85:4765–70.
[22] Whitacre CC. Sex differences in autoimmune disease. Nat Immunol 2001;2:777–80.
[23] Rubtsov AV, Rubtsova K, Kappler JW, Marrack P. Genetic and hormonal factors in female-biased autoimmunity. Autoimmun Rev 2010;9:494–8.
[24] Volpe R, Clarke PV, Row VV. Relationship of age-specific incidence rates to immunological aspects of Hashimoto's thyroiditis. Can Med Assoc J 1973;109:898–901.
[25] Orton SM, Herrera BM, Yee IM, Valdar W, Ramagopalan SV, Sadovnick AD, et al. Sex ratio of multiple sclerosis in Canada: a longitudinal study. Lancet Neurol 2006;5:932–6.
[26] Trojano M, Lucchese G, Graziano G, Taylor BV, Simpson Jr S, Lepore V, et al., MSBase STUDY Group and the New Zealand MS Prevalence Study Group. Geographical variations in sex ratio trends over time in multiple sclerosis. PLoS One 2012;7:e48078.
[27] Bove R, Chitnis T. The role of gender and sex hormones in determining the onset and outcome of multiple sclerosis. Mult Scler 2014;20:520–6.
[28] Boström I, Stawiarz L, Landtblom AM. Age-specific sex ratio of multiple sclerosis in the National Swedish MS Register (SMSreg). Mult Scler 2014;20:513–4.
[29] Grossman CJ. Regulation of the immune system by sex steroids. Endocr Rev 1984;5:435–55.
[30] Graff RJ, Lappé MA, Snell GD. The influence of the gonads and adrenal glands on the immune response to skin grafts. Transplantation 1969;7:105–11.
[31] Van Vollenhoven RF, McGuire JL. Estrogen, progesterone, and testosterone: can they be used to treat autoimmune diseases? Cleve Clin J Med 1994;61:276–84.
[32] Hughes GC, Choubey D. Modulation of autoimmune rheumatic diseases by oestrogen and progesterone. Nat Rev Rheumatol 2014;10:740–51.
[33] Ngo ST, Steyn FJ, McCombe PA. Gender differences in autoimmune disease. Front Neuroendocrinol 2014;35:347–69.
[34] Savino W, Mendes-da-Cruz DA, Lepletier A, Dardenne M. Hormonal control of T-cell development in health and disease. Nat Rev Endocrinol 2016;12:77–89.

[35] Hughes GC. Progesterone and autoimmune disease. Autoimmun Rev 2012;11:A502–14.
[36] Gubbels Bupp MR, Jorgensen TN. Androgen-induced immunosuppression. Front Immunol 2018;9:794.
[37] Tan IJ, Peeva E, Zandman-Goddard G. Hormonal modulation of the immune system – a spotlight on the role of progestogens. Autoimmun Rev 2015;14:536–42.
[38] Grossman CJ, Roselle GA, Mendenhall CL. Sex steroid regulation of autoimmunity. J Steroid Biochem Mol Biol 1991;40:649–59.
[39] Cutolo M, Capellino S, Sulli A, Serioli B, Secchi ME, Villaggio B, Straub RH. Estrogens and autoimmune diseases. Ann N Y Acad Sci 2006;1089:538–47.
[40] Lahita RG, Bradlow HL, Ginzler E, Pang S, New M. Low plasma androgens in women with systemic lupus erythematosus. Arthritis Rheum 1987;30:241–8.
[41] Bijlsma J, Straub RH, Masi AT, Lahita RG, Cutolo M. Neuroendocrine immune mechanisms in rheumatic diseases. Trends Immunol 2002;23:59–61.
[42] McCombe P, Greer JM, Mackay IR. Sexual dimorphism in autoimmune disease. Curr Mol Med 2009;9:1058–79.
[43] da Silva JA. Sex hormones and glucocorticoids: interactions with the immune system. Ann N Y Acad Sci 1999;876:102–17.
[44] Laffont S, Garnier L, Lélu K, Guéry J-C. Estrogen-mediated protection of experimental autoimmune encephalomyelitis: Lessons from the dissection of estrogen receptor-signaling in vivo. Biomed J 2015;38:194–205.
[45] Moulton VR. Sex hormones in acquired immunity and autoimmune disease. Front Immunol 2018;9:2279.
[46] Bakhru P, Su MA. Estrogen turns down "the AIRE." J Clin Invest 2016;126:1239–41.
[47] Dragin N, Bismuth J, Cizeron-Clairac G, Biferi MG, Berthault C, Serraf A, et al. Estrogen-mediated downregulation of AIRE influences sexual dimorphism in autoimmune diseases. J Clin Invest 2016;126:1525–37.
[48] Pernis AB. Estrogen and CD4+ T cells. Curr Opin Rheumatol 2007;19:414–20.
[49] Tyagi AM, Srivastava K, Mansoori MN, Trivedi R, Chattopadhyay N, Singh D. Estrogen deficiency induces the differentiation of IL-17 secreting Th17 cells: a new candidate in the pathogenesis of osteoporosis. PLoS One 2012;7:e44552.
[50] Luo CY, Wang L, Sun C, Li DJ. Estrogen enhances the functions of CD4+CD25+Foxp3+ regulatory T cells that suppress osteoclast differentiation and bone resorption in vitro. Cell Mol Immunol 2011;8:50–8.
[51] Khan D, Ansar Ahmed S. The immune system is a natural target for estrogen action: opposing effects of estrogen in two prototypical autoimmune diseases. Front Immunol 2016;6:635.
[52] Szekeres-Bartho J, Schindler AE. Progestogens and immunology. Best Pract Res Clin Obstet Gynaecol 2019;60:17–23.
[53] Clemens LE, Siiteri PK, Stites DP. Mechanisms of immunosuppression of progesterone on maternal lymphocyte activation during pregnancy. J Immunol 1979;122:1978–85.
[54] Canellada A, Blois S, Gentile T, Margni Idehu RA. In vitro modulation of protective antibody responses by estrogen, progesterone and interleukin-6. Am J Reprod Immunol 2002;48:334–43.
[55] Tait AS, Butts CL, Sternberg EM. The role of glucocorticoids and progestins in inflammatory, autoimmune, and infectious disease. J Leukoc Biol 2008;84:924–31.
[56] Trigunaite A, Dimo J, Jørgensen TN. Suppressive effects of androgens on the immune system. Cell Immunol 2015;294:87–94.
[57] Vicklicky V, Polackova M, Vojtiskova M, Draber P, Kolida ME. Immuno-suppressive effect of an antiandrogen steroid (cyproterone acetate) in mice. Folia Biol (Praha) 1977;21:145.
[58] Honer C, Nam K, Fink C, Marshall P, Ksander G, Chatelain RE, et al. Glucocorticoid receptor antagonism by cyproterone acetate and RU486. Mol Pharmacol 2003 May;63:1012–20.
[59] Sutherland JS, Goldberg GL, Hammett MV, Uldrich AP, Berzins SP, Heng TS, et al. Activation of thymic regeneration in mice and humans following androgen blockade. J Immunol 2005;175:2741–53.
[60] Hince M, Sakkal S, Vlahos K, Dudakov J, Boyd R, Chidgey A. The role of sex steroids and gonadectomy in the control of thymic involution. Cell Immunol 2008;252:122–38.
[61] Sicotte NL, Giesser BS, Tandon V, Klutch R, Steiner B, Drain AE, et al. Testosterone treatment in multiple sclerosis: a pilot study. Arch Neurol 2007;64:683–8.
[62] Gold SM, Chalifoux S, Giesser BS, Voskuhl RR. Immune modulation and increased neurotrophic factor production in multiple sclerosis patients treated with testosterone. J Neuroinflammation 2008;5:32.
[63] Gordon C, Wallace DJ, Shinada S, Kalunian KC, Forbess L, Braunstein GD, et al. Testosterone patches in the management of patients with mild/moderate systemic lupus erythematosus. Rheumatology (Oxford) 2008;47:334–8.
[64] Crosbie D, Black C, McIntyre L, Royle PL, Thomas S. Dehydroepiandrosterone for systemic lupus erythematosus. Cochrane Database Syst Rev 2007;(4):CD005114. https://doi.org/10.1002/14651858. CD005114. pub2.
[65] Mosmann TR, Coffman RL. Heterogeneity of cytokine secretion patterns and functions of helper T cells. Adv Immunol 1989;46:111–47.
[66] Trinchieri G. Interleukin-12 and its role in the generation of TH1 cells. Immunol Today 1993l;14:335–8.
[67] Mosmann TR, Sad S. The expanding universe of T-cell subsets: Th1, Th2 and more. Immunol Today 1996;17:138–46.
[68] Szabo SJ, Kim ST, Costa GL, Zhang X, Fathman CG, Glimcher LH. A novel transcription factor, T-bet, directs Th1 lineage commitment. Cell 2000;100:655–69.
[69] Romagnani S. Regulation of the development of type 2 T-helper cells in allergy. Curr Opin Immunol 1994;6:838–46.
[70] Zheng W, Flavell RA. The transcription factor GATA-3 is necessary and sufficient for Th2 cytokine gene expression in CD4 T cells. Cell 1997;89:587–96.
[71] Bettelli E, Oukka M, Kuchroo VK. T(H)-17 cells in the circle of immunity and autoimmunity. Nat Immunol 2007;8:345–50.
[72] Benagiano M, Munari F, Ciervo A, Amedei A, Rossi Paccani S, Mancini F, et al. Chlamydophila pneumoniae phospholipase D (CpPLD) drives Th17 inflammation in human atherosclerosis. PNAS 2012;109:1222–7.
[73] Verstappen GM, Corneth OBJ, Bootsma H, Kroese FGM. Th17 cells in primary Sjögren's syndrome: pathogenicity and plasticity. J Autoimmun 2018;87:16e25.
[74] Kleinewietfeld M, Haflera DA. The plasticity of human Treg and Th17 cells and its role in autoimmunity. Semin Immunol 2013;25:305–12.
[75] Li MO, Rudensky AY. T cell receptor signalling in the control of regulatory T cell diffrentiation and function. Nat Rev Immunol 2016;16:220–33.

[76] Kitagawa Y, Sakaguchi S. Molecular control of regulatory T cell development and function. Curr Opin Immunol 2017;49:64–70.
[77] Nie J, Li YY, Zheng SG, Tsun A, Li B. FOXP3+ Treg cells and gender bias in autoimmune diseases. Front Immunol 2015;6:493.
[78] Prieto GA, Rosenstein Y. Oestradiol potentiates the suppressive function of human CD4 CD25 regulatory T cells by promoting their proliferation. Immunology 2006;118:58–65.
[79] Arruvito L, Sanz M, Banham AH, Fainboim L. Expansion of CD4+CD25+and FOXP3+ regulatory T cells during the follicular phase of the menstrual cycle: implications for human reproduction. J Immunol 2007;178:2572–8.
[80] Weinstein JS, Herman EI, Lainez B, Licona-Limón P, Esplugues E, Flavell R, Craft J. Follicular helper T cells progressively differentiate to regulate the germinal center response. Nat Immunol 2016;17(10):1197–205.
[81] Blanco P, Ueno H, Schmitt N. T follicular helper (Tfh) cells in lupus: activation and involvement in SLE pathogenesis. Eur J Immunol 2016;46:281–90.
[82] Park H-J, Park H-S, Lee J-U, Bothwell ALM, Choi J-M. Gender-specific differences in PPARγ regulation of follicular helper T cell responses with estrogen. Sci Rep 2016;6:28495.
[83] Greer JB, Modugno F, Allen GO, Ness R. Androgenic Progestins in Oral Contraceptives and the Risk of Epithelial Ovarian Cancer. Obstet Gynecol 2005;105:731–40.