Immune response and autoimmune diseases: a matter of sex

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Summary. Immune response differs between women and men at many levels. In general, females mount stronger innate and adaptive immune responses in comparison to males. In particular, women show more effective phagocytosis and antigen presentation, stronger production of inflammatory cytokines, higher absolute number of CD4+ T cells, higher levels of circulating antibodies, in comparison to men. Genetic, epigenetic, hormonal and environmental factors contribute to sex differences in immune response. The strong immune response in women, on one hand, appears to be beneficial, leading to the reduction of pathogen load and accelerating pathogen clearance, but, on the other hand, it can be detrimental by causing autoimmune or inflammatory diseases. Accordingly, most autoimmune diseases are more prevalent in women than in men and symptoms, disease course and response to therapy may also differ between males and females. In this review, we discuss possible mechanisms for sex-specific differences in autoimmunity with a special focus on rheumatoid arthritis, Sjögren's syndrome, primary biliary cirrhosis, antiphospholipid syndrome, systemic sclerosis, multiple sclerosis and systemic lupus erythematosus.

Key words. Immunity, autoimmune diseases, sex, gender, sex hormones.

Differenze di sesso nella risposta immunitaria e nelle malattie autoimmuni

Riassunto. In generale, le donne presentano risposte immunitarie innate e adattative più forti rispetto agli uomini. Le donne mostrano rispetto agli uomini una più efficace fagocitosi e presentazione dell'antigene, una più forte produzione di citochine infiammatorie, un numero più elevato di linfociti T CD4+ e livelli più alti di anticorpi circolanti. Fattori genetici, epigenetici, ormonali e ambientali contribuiscono alle differenze nella risposta immunitaria tra i due sessi. La più forte risposta immunitaria nelle donne, da un lato, sembra essere vantaggiosa, favorendo l'eliminazione degli organismi patogeni, ma, dall'altro, può essere dannosa causando malattie autoimmuni. Infatti molte malattie autoimmuni sono più frequenti nelle donne rispetto agli uomini e differenze tra i due sessi esistono nei sintomi, nel decorso della malattia e nella risposta alla terapia. In questa review sono descritti i possibili meccanismi responsabili delle differenze tra i due sessi nelle principali malattie autoimmuni quali l'artrite reumatoide, la sindrome di Sjögren, la cirrosi biliare primitiva, la sindrome anti-fosfolipidi, la sclerosi sistemica, la sclerosi multipla e il lupus eritematoso sistemico.

Parole chiave. Immunità, malattie autoimmuni, sesso, genere, ormoni sessuali.

Introduction

In general, females mount stronger innate and adaptive (humoral and cellular) immune responses in comparison to males[1,2]. The factors responsible for the stronger immune response in females than males are of biological origin (e.g., differential organization of chromosomes, reproductive organs, sex steroid levels), called "sex differences", and of psychosocial, cultural and economic origin, called "gender differences"[3]. This review focuses on the sex differences in immunity, taking into account the role of genetic and epigenetic factors, sex hormones, and gut microbiota. Finally, sex differences in epidemiology, clinical manifestations and outcomes of the most common autoimmune diseases, i.e., rheumatoid arthritis (RA), Sjögren's syndrome (SS), primary biliary cirrhosis (PBC), antiphospholipid syndrome (APS), systemic sclerosis (SSc), multiple sclerosis (MS) and systemic lupus erythematosus (SLE) are described.

Genetic factors

X chromosome. Women have two copies of the X chromosome, one derived from each parent, in each cell, whereas men possess one maternal X and one paternal Y chromosome. The transcription of the genes present in both X chromosomes would lead to a dangerous increase in the expression of their products. This is avoided by the random inactivation of one of the two X chromosomes in the early stages of embryogenesis, but this mechanism is incomplete and about 15% of the genes escape inactivation, leading to overexpression of some X-linked genes in females[4,5]. It is worth noting that the X chromosome contains the largest number of immune-related genes in the entire human genome, such as CD40 ligand,

chemokine receptor CXCR3, forkhead box P3 (FOXP3), toll-like receptor (TLR)7, TLR8, IL-2 receptor gamma, tyrosine-protein kinase BTK, and IL-9 receptor (IL-9R), whose overexpression may influence the immune response in a sex-dependent manner[6,7].

Y chromosome. Growing evidence indicates that the Y chromosome also contributes to immune responses and susceptibility to autoimmunity and infection. In the course of evolution, the Y chromosome became unique from all other chromosomes due to the acquisition of a dominant sex-determining gene. The remainder of the Y chromosome is largely heterochromatic and composed of multicopy genes, repeat sequences, and transposable elements[8]. Interestingly, the susceptibility of autoimmune diseases in animal models has been observed to be correlated with the natural variation in copy number of the multicopy genes Sycp3-like Y-linked (Sly) and RNA-binding motif, ChrY (Rbmy). An inverse correlation exists between the number of Sly and Rbmy multicopy genes and the number of significantly upregulated genes in immune cells suggesting that a mechanism of chromatin remodeling occurs whereby the multicopy genes may sequester proteins involved in chromatin dynamics resulting in decreased euchromatic DNA regions and transcriptional activity.

Autosomal genes. Many autosomal genes are differentially expressed in males and females. The transcription factor vestigial-like family 3 (VGLL3) was recently found to be upregulated in females, for example in ovaries, uterus, adipose tissue, and smooth muscle. VGLL3 is located on chromosome 3 and contributes to the differential expression of hundreds of genes in males and females. Genes of interest regulated by VGLL3 include B-cell activating factor (BAFF), integrin alpha M (ITGAM), IL-7, intercellular adhesion molecule 1 (ICAM-1), matrix metallopeptidase 9 (MMP-9), and ETS1 transcription factor. These sex biased genes are associated with susceptibility to autoimmunity and inflammatory processes[9].

Epigenetic factors

microRNA (miRNA). miRNA are small endogenous noncoding molecules of RNA (20-22 nucleotides) that are involved in the post-transcription regulation of gene expression, repressing the translation of target messenger RNA, or inducing its degradation. They play a crucial role in maintaining cellular homeostasis and are expressed differently in women and men. The X chromosome contains an unexpectedly high number of miRNA, at present 118, in comparison with only two miRNA localized on Y chromosome, and with an average of 40-50 miRNA on the autosomes. Some miRNA present

on the X chromosome are involved in the regulation of the immune response. The presence of a second X chromosome in females can have a significant impact on miRNA expression levels because some genes can escape X inactivation, contributing to the dimorphism of the immune response[10,11]. Accordingly, in patients with active SLE several X-linked miRNA have been observed to be more expressed in CD4+ T cells by women compared to men[12].

Gene methylation. The DNA methylation pattern of autosomes is different between males and females. Singmann et al. identified 1184 CpG sites with different methylation levels, between males and females, in peripheral blood cells[13]. In particular, two genes, cytokine inducible SH2 containing protein (CISH) and Ras-related protein RAB23, which are involved in the JAK-STAT pathway essential for regulatory T cell (Treg) function, displayed different expression in males and females associated with different DNA methylation[14].

Sex hormones

Sex hormones, such as androgens, progesterone, prolactin, and estrogens, are crucial regulators of the immune system[15-17].

Androgens. Androgens, in particular testosterone, may suppress the expression of the pro-inflammatory cytokines TNF-α, IL-1β and IL-6, and potentiate the expression of the anti-inflammatory cytokine IL-10[18]. Testosterone inhibits T helper (Th) 1 differentiation by upregulating type 1 protein tyrosine phosphatase (Ptpn1) in both mice and humans, reduces the proliferation and differentiation of lymphocytes and may suppress immunoglobulin production, in particular IgA. Supraphysiological doses of testosterone may inhibit the cytotoxic activity of NK cells.

Progesterone. Progesterone suppresses Th1/Th17 favoring Th2 type cytokine secretions, inhibits the cytotoxicity of T cells and increases the differentiation of Treg[19]. Progesterone inhibits the activities of NK cells, in particular inhibiting IFN-γ production and inducing apoptosis. Other known effects include the inhibition of macrophage activity and the modulation of myeloid dendritic cells activity.

Prolactin. Prolactin has a bioactive function acting as a hormone and as a cytokine. It interferes with immune system modulation, mainly inhibiting the negative selection of autoreactive B lymphocytes[20]. It is capable of changing Th1 and Th2 type cytokine production, promoting IL-6 and INF-γ secretion, and playing a regula-

tory role on IL-2 levels. Furthermore, prolactin increases immunoglobulin production, stimulates the development of antigen-presenting cells expressing major histocompatibility complex class II, and upholds the co-stimulatory molecules CD86, CD80, and CD40.

Estrogens. Estrogens, in particular 17-β estradiol (E2), have different effects depending on their concentration. At periovulatory to pregnancy levels, E2 has mainly anti-inflammatory effects, by inhibiting the production of pro-inflammatory cytokines, such as TNF-α, IL-1β and IL-6 and by inducing the expression of anti-inflammatory cytokines favoring a Th2 phenotype, such as IL-4, IL-10 and TGF-β, and by favoring Treg function[21]. At lower concentrations, E2 stimulates TNF-α, IFN-γ, IL-1β production and NK cell activity, while it enhances antibody production by B cells both at high and low concentrations. It is worth noting that estrogen receptors (ER)α and ERβ play an opposite role in the immune function with a pro- and anti-inflammatory activity, respectively. Hence, the effects of E2 depend also by the ER subtype expressed by target cells[15].

Endocrine disrupting chemicals

Endocrine disrupting chemicals, e.g., DDT, polychlorinated biphenyls, bisphenol A, polybrominated diphenyl ethers, and a variety of phthalates potentially impact immune response, displaying both estrogenic and anti-estrogenic properties, reducing androgen production and influencing epigenetic regulation[22].

Autoimmune regulator (AIRE)

Sex hormones act on the immune system by also regulating the expression of AIRE. AIRE is a nuclear protein that regulates the expression of specific tissue antigens in thymic epithelial cells, contributing to the negative selection of autoreactive T cells. AIRE expression is greater in males than in females (both in mice and in humans) and it is up-regulated by androgens and down-regulated by estrogens[23].

Gut microbiota

The gut microbiota is the community of microbes (bacteria, viruses, fungi and protozoa) that lives in an individual's gastrointestinal tract. Gut microbiota carries out several functions: i) protection against the aggression of environmental pathogens; ii) metabolic functions; iii) development of the innate and acquired immune system and maintenance of immune tolerance. Microbiota com-

position depends on various factors, such as age, diet, and sex. The composition of gut microbiota in male and female mice is similar before puberty and then becomes significantly different after puberty because of the hormonal changes that affect its composition. In turn, the gut microbiota influences the hormonal levels of the host by producing enzymes involved in the synthesis of sex hormones (e.g., the hydroxysteroid dehydrogenase involved in the conversion of glucocorticoids into androgens)[24,25]. To determine the contribution of the intestinal microbiota to sex differences in the immune system, Fransen et al.[26] performed experiments to transfer the intestinal microbiota from male or female mice to germ-free recipients of the same sex or opposite sex. The authors showed that the intestinal microbiota can influence the differentiation of T-cell precursors in the thymus and the differentiation of T cells in the gut associated lymphoid tissue (GALT) in a sex-specific way. In male recipients, the female microbiota induced less RORγt+Foxp3+ T cells in GALT compared to male microbiota. This cell population has recently been shown to be induced by the microbiota and to inhibit Th2-associated pathology[27]. Thus, the female microbiota might be less efficient in preventing allergies.

Autoimmune diseases differ between the sexes

Autoimmune diseases include more than 80 chronic disorders that affect nearly 5% of the population in Western countries. They are characterized by an exaggerated immune response leading to damage and dysfunction of specific or multiple organs and tissues.

The etiology of autoimmune diseases is still unknown, but the available evidence points to an interaction between genetic, hormonal, environmental and life style factors in disease development.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic chronic joint inflammatory disease affecting about 1% of the population. RA is characterized by systemic inflammation, persistent synovitis, and destruction of synovial joints, leading to severe disability and premature mortality. Relatively little is known about disease pathogenesis and etiology.

RA is more frequent in women than men with a female to male ratio of 3:1 at age of 45–55 years, dropping to 2:1 ratio in the age range from 55 to 65 years, and shifting to a male predominance in people over 70[2]. The high prevalence of RA in women as compared to men could suggest that estrogens may contribute to its onset[28,29]. However, the observations that i) RA develops

more frequently in postmenopausal than premenopausal women and ii) no relationships between oral contraceptive or hormone replacement therapy and RA onset exist[30,31] suggest that other factors are involved in disease development. In this regard, differences between men and women with RA in the expression level of some miRNA localized on the X chromosome (miR-222, miR-532, miR-98, and miR-92a) could play a role[32]. Additionally, an association between RA and single nucleotide polymorphisms of the X-encoded tissue inhibitor of metalloproteinases 1 (TIMP1) and IL-9R genes has been described. Interestingly, the IL-9R polymorphism was found to be more frequent in men with RA as compared to women[33].

Regarding disease activity and progression, RA tends to spontaneously improve in the majority of women in pregnancy, whereas delivery is followed by disease flares[34]. Interestingly, some reports suggest that disease severity tends to be worse in women than in men[35,36]. Women are more likely to acquire conditions such as thyroid dysfunctions, fibromyalgia, osteoporosis and depression than their male counterparts, while the impact of sex on cardiovascular risk is still controversial[37]. In addition, women have a worse response than men to synthetic and biological disease modifying antirheumatic drugs[38-41]. These data suggest a complex role for sex hormones in RA severity. Notably, serum androgen levels are reduced even some years before the onset of disease in both female and male RA patients and the severity of RA is inversely associated with androgen levels[42] thus suggesting a protective role for androgens. Interestingly, estrogens are significantly elevated in peripheral tissues of RA patients due to a high activity of aromatase, induced by locally produced inflammatory cytokines, that converts androgens to estrogens. In particular, high levels of estrogen metabolites, such as 16 alpha-hydroxyestrone, that interfere with monocyte proliferation and TNF-α secretion have been demonstrated in the synovial fluid of RA patients, suggesting pro-inflammatory effects of estrogen metabolites[43-45]. Finally, recent studies reported high levels of prolactin in serum and synovial fluid in female and male patients with RA[46].

Sjögren's syndrome

Sjögren's syndrome (SS) is a systemic chronic inflammatory disorder characterized by lymphocytic infiltrates in exocrine organs. Most individuals with SS present with sicca symptoms, such as xerophthalmia (dry eyes), xerostomia (dry mouth), and parotid gland enlargement.

Aside from the exocrine targets, SS also affects the lungs, kidneys, thyroid, muscle, and skin and manifests with symptoms of fatigue, pain, depression, cutaneous lesions, and mild arthritis.

One unexplained but characteristic feature of this syndrome is its skewed gender distribution, with a female to male ratio of 16:1. Women often contract their disease at the time of menopause, when they are 50-55 years old[47]. Female predominance and disease onset following a major stressful event and/or following menopause in SS patients suggest that the endocrine system and sex hormones are involved in the pathogenesis of disease.

In general, estrogen protects against SS prior to menopause and low E2 levels correlate with dry mouth and ocular dryness. Accordingly, aromatase deficient mice, in which the conversion of androgens to estrogen is prevented, develop an SS-like disease with increased inflammation of exocrine glands[48]. The reduced levels of estrogen with menopause could increase inflammation leading to increased apoptosis of glandular cells. Oral dryness in SS patients has also been associated to low androgen levels. In particular, dehydroepiandrosterone (DHEA) protects against SS and its levels decrease following menopause when most SS cases occur[49]. Salivary glands from SS patients have also been found to have reduced levels of DHEA that is needed, like estrogen, for regeneration of the acinar cells of the salivary glands. Thus, both estrogen and androgens are needed for normal exocrine gland function[50].

Actually, two peaks for the onset of SS have been reported, far more frequently shortly after menopause, but also during child-bearing years. Several studies have found an association between elevated prolactin levels and SS[51]. Prolactin released during pregnancy may increase premenopausal SS cases[52]. Prolactin may work together with high estrogen levels to increase the risk for SS in premenopausal women, increasing autoantibody levels and in particular Ro/SSA and La/SSB autoantibodies[51].

Comparing clinical features in women and men with SS, some studies reported higher exocrine gland inflammation and a more frequent association with other autoimmune diseases (like RA, thyroiditis, and Raynaud's phenomenon) in women compared to men. On the contrary, lymphoma occurs more frequently in men with SS. Ocular objective tests seem to be less frequently altered in men[53]. Higher frequency of lymphopenia and leucopenia, but lower thrombocytopenia were reported in women[54].

Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) is a cholestatic liver disease of autoimmune origin, characterized by the destruction of small intrahepatic bile ducts. The disease has an unpredictable clinical course but may progress to fibrosis and cirrhosis[55]. The diagnostic hallmark of PBC is the presence of disease-specific antimitochondrial antibod-

ies (AMA), which are pathognomonic for the development of PBC. The disease overwhelmingly affects females, with some cases of male PBC being reported. Epidemiological studies estimate that approximately 7-11% of PBC patients are males and men with PBC are older than women[56]. As such, few studies have taken into account PBC in men from a pathogenic as well as clinical viewpoint.

Genetic, epigenetic, environmental, and infectious factors have been considered important for the development of PBC and/or its progression from early stages to more advanced, life-threatening, biliary epithelial cell destruction. Several risk factors have been indicated including a history of recurrent urinary tract infection, smoking, and family history of PBC, as well as estrogen deficiency[57]. No specific risk factors were identified for males.

Some sex differences were reported in the biochemical and clinical features of PBC. As regards antinuclear antibodies (ANA), one study reported anticentromere antibodies more prevalent in women than in men, whereas no differences between males and females in AMA reactivity were found. Males as compared to females are at higher risk of life-threatening complications such as gastrointestinal bleeding and hepatoma. Abdominal pain, constitutional symptoms, and pruritus as a single symptom seem to be more frequent in females than males. More females than males also experienced sicca symptoms, scleroderma, and Raynaud's phenomenon[56].

Antiphospholipid syndrome

The antiphospholipid syndrome (APS) is defined by recurrent venous or arterial thrombosis and/or fetal loss in the presence of antiphospholipid antibodies (aPL) and/or lupus anticoagulant (LA)[58]. Patients with APS who do not suffer from lupus and other autoimmune disorders are defined as patients with 'primary' antiphospholipid syndrome (PAPS).

In PAPS, the female to male ratio is 2:1 to 5:1. This ratio is lower than in SLE. Jara et al.[59] analyzed clinical differences at diagnosis and during follow-up between male and female patients with PAPS. Central nervous system involvement, especially stroke/transient ischemic attack, was reported to be more prevalent in female than in male patients. Mesenteric thrombosis was more prevalent in male than female patients. No differences between male and female patients were reported in other manifestations, such as thrombocytopenia, and skin, renal or cardiac involvement. Peripheral vascular thrombosis and pulmonary embolism remained the most common manifestation in women and men.

More recently, de Carvalho[60] evaluated differences between males and females in the clinical and biochemical manifestations of PAPS and found that the duration of disease was similar for females and males, but the prevalence of pulmonary thromboembolism was higher in females than in males. Interestingly, positivity for IgM anticardiolipin is higher in females than in males.

Systemic sclerosis

Systemic sclerosis (SSc) is a multisystem autoimmune disease characterized by three key pathophysiologic features: vasculopathy with endothelial dysfunction, immune system activation and dysregulation, collagen overproduction with fibrosis.

SSc has an overall female to male ratio of 3:1 but this ratio increases to 10:1 during the child-bearing years. Sex differences are also involved in the severity of SSc. Some studies reported that male SSc patients have more severe disease than females[61]. Furthermore, interstitial lung disease and pulmonary arterial hypertension, the main causes of death in SSc, were reported to be more frequent and more severe in males[62].

Peoples et al.[63] analyzed sex differences in SSc, taking into account clinical features, serologic status, and outcomes. Female SSc patients were younger at disease diagnosis compared to males. Females more frequently had limited cutaneous SSc and overlap with SLE, whereas males more frequently had diffuse cutaneous SSc and overlap with myositis. Peripheral vascular involvement was more frequent in female SSc patients, but in males it was more severe. Males with SSc appeared to be more exposed to environmental exposures and were more frequently cigarette smokers than females. Interstitial lung disease or pulmonary fibrosis were more frequent and more severe in men than women. As regards the serological status, anti-centromere antibodies were more frequent in women and anti-topoisomerase I and anti-U3RNP antibodies in men. Finally, as for disease outcome, men with SSc had reduced survival and the most frequent causes of death were interstitial lung disease in men and pulmonary hypertension in women.

17-β estradiol induces fibroblast dysfunction and the development of a fibrotic phenotype, both *in vitro* and *ex vivo*, in human skin. Serum E2 levels are significantly elevated in postmenopausal female patients with early diffuse cutaneous SSc compared to healthy postmenopausal female controls, with neither group having received any hormone replacement therapy[64]. High prolactin and low DHEA levels were observed in patients with SSc[65], but their effects in the pathogenesis of SSc are still unknown. Genetic factors are also involved in the sex differences of SSc, involving the X chromosome. Skewed chromosome X inactivation and rate of monosomy X in peripheral blood mononuclear cells were significantly more frequent in female patients with SSc compared to healthy donors[66,67].

Multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system. It affects 2.5 million individuals worldwide, mainly young adults, and 1 in 1000 people in Western countries. MS pathology is characterized by inflammatory demyelinating disorder, breakdown of myelin sheaths, axonal degeneration and neuronal damage, which leads to large focal lesions in the white matter of the brain and spinal cord[68,69]. MS is characterized by bouts and remissions (relapsing-remitting) followed by a secondary progressive course. Less frequently, MS has a progressive course right from the onset.

MS affects three times more women than men in most parts of the world and the onset of the disease occurs later in men than in women[70,71]. The sex ratio in MS appears to be rising; this trend is noted primarily in relapsing-remitting MS and is associated with a latitudinal gradient strongly indicating that a complex interaction among sex hormones, genetic and epigenetic factors, environmental (sunlight, vitamin D, smoking, stress), and cultural factors occurs[72-74].

Even though men have a lower risk of developing MS as compared to women, many studies suggested that male sex is associated with a poorer clinical outcome in relapse-remitting MS and a more rapid accumulation of disability compared to female sex[75].

Pregnancy seems to be accompanied by a decreased MS activity, followed by a rebound in the first 3 months postpartum[76-78]. The impact of breastfeeding, oral contraceptive use, menopause and hormone replacement therapy on MS risk and course is less understood. Recent data suggest that MS disease severity may worsen after menopause[79]. The most widely accepted theory to explain the protective effect of pregnancy on the relapse rate and disease activity in women with MS is that, during pregnancy, estriol and progesterone induce immunological changes favoring a Th2 (anti-inflammatory cytokines) over a Th1 (pro-inflammatory cytokines) profile; the opposite occurs in the postpartum period.

From a genetic point of view, the human leukocyte antigen (HLA) complex on chromosome 6p21.3 was the first MS risk locus identified[80] and remains the most important one by far[81]: in particular, HLA class II region has the largest influence with HLA-DRB1*15:01 conferring a threefold increase in MS risk[82]. It is worth noting that the HLA-DRB5*0101–HLA-DRB1*1501–HLA-DQA1*0102–HLA-DQB1*0602 extended haplotype is more common in female than in male patients. Interestingly, Kiselev et al.[83] demonstrated, in women, an association between i) miRNA223 and miRNA146A genetic variants and MS susceptibility and ii) miRNA499A and miRNA196A2 genetic variants and MS severity. More recently, Wawrusiewicz-Kurylonek et al.[84] ob-

served that FOXP3 rs3761547 gene polymorphism was associated with the increased risk of MS development in male patients.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that affects multiple organs, including the kidneys and heart, and tissues, such as skin, muscle and joints[85]. The incidence of the disease is estimated on average 40 cases every 100,000 individuals. To date, the etiology of SLE remains unknown, but multiple genetic, environmental (e.g., infectious agents, UV light, drugs and cigarette) and hormonal factors are likely to be involved in disease onset and progression.

SLE is characterized by i) abnormal immune cell activation, ii) over-production of autoantibodies, and iii) organ infiltration by inflammatory T cells. The autoantigen-autoantibody interaction triggers the formation of immune complexes, which, once deposited, cause tissue injury[86]. Since 90% of patients with SLE are females in reproductive age, estrogens are considered important pathogenic players. Indeed, before puberty the female-to-male ratio is 3:1, during the childbearing years the ratio increases and ranges from 8:1 to 15:1, and after menopause, it declines again to 5:1[2].

Clinical and experimental data clearly point to the role of E2 in the development of SLE. The use of oral contraceptives and hormone replacement therapy have been observed to increase the risk of SLE onset[87]. It is worth noting that, in SLE patients, aromatase activation leads to an accelerated metabolic conversion of androgen to E2, in part elucidating the increased E2 availability in this disease[88]. A clinical trial on patients with SLE treated with fulvestrant (Faslodex®), a selective estrogen receptor downregulator, suggested benefits of this drug[89]. In lupus mice models, an E2 pathogenic effect, in terms of production of autoantibodies, development of proteinuria and decreased survival, has been observed to be mediated by ERα activation whereas ERβ activation seems to have immunosuppressive effects[90]. Accordingly, serum autoantibodies specific to ERα, detected in a large percentage of SLE patients, act as E2 agonists through ERα binding and activation, and their serum levels significantly correlate with disease activity[91]. On the other hand, ERβ expression levels in T lymphocytes of patients with SLE have been observed to be inversely correlated with disease activity[92].

Several immune-linked genes located on the X chromosome, including TLR7, FOXP3 and TNF-α, have been associated with SLE pathogenesis[7]. A Chinese study found that the polymorphism rs2234693 in ERα gene (ESR1) increases the risk of SLE in smoker patients compared to non-smokers[93].

Regarding gender differences in clinical presentation and severity of SLE, women have in general more frequent relapses of disease, whereas men have a late onset of the disease, higher disease severity and serious comorbidities. Cardiovascular and renal manifestations and infections have been observed to be more common in males, while mucocutaneous and musculoskeletal manifestations appear to be more frequent in females[94,95].

Conclusions

The immune response in women and men is regulated by multiple factors related to sex and gender, which, whether acting in succession or at the same time, are responsible for a different susceptibility and severity of autoimmune diseases. A better understanding of how these factors act and interact, contributing to gender differences in immunity, can lead to a better understanding of the pathogenic mechanisms of autoimmune diseases, ultimately encouraging the development of new targeted and personalized therapeutic strategies. For this purpose, there is an unconditional necessity of directing research in a gender perspective, paying attention to the difference in health demand that characterizes men and women.

Key messages

- Females have stronger immune responses than males. Thus, the frequency of various infectious diseases is higher in males than in females whereas females are more likely to develop autoimmune diseases.

- Biological factors that contribute to sexual dimorphism in immunity and autoimmunity include sex hormones, genetic, and epigenetic factors.

- Sex hormones have different effects depending not only on the concentration but also on the receptor subtype. Generally, estrogens and prolactin act as enhancers at least of humoral immunity, and testosterone and progesterone as natural immunosuppressants.

- Differences between males and females with autoimmune diseases are not just about the prevalence of the diseases, but also symptom severity, disease course, and response to therapy.

- It is a critical priority to consider all sex-related biologic factors in developing novel therapeutics for autoimmune diseases.

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