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Sex hormones and gender disparity in immunity and autoimmunity

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Summary. Homeostasis of the human immune system is regulated by multiple factors whose alterations may result in pathological conditions. These factors include the sex hormones that affect both phenotype and function of immune cells through interaction with specific receptors expressed by these cells. In particular, activation of sex hormone receptors by hormone binding may impact many biological processes such as immune cell differentiation and maintenance of immune homeostasis. In turn, they are involved in the pathogenesis of a wide spectrum of diseases, including autoimmune disorders. The different regulatory activity of sex hormones in both sexes results in immune dimorphism. Although it has been suggested that estrogens may enhance immune reactions, while androgens and progesterone may reduce immune system function, the mechanisms underlying this scenario are far from being elucidated. This review discusses the regulatory activity of sex hormones on the immune system and their potential involvement in the onset, progression and outcome of autoimmune diseases.

Key words. Immunity, autoimmunity, sex hormones, estrogens, androgens, progesterone.

Ormoni sessuali e differenze di genere nell'immunità e nell'autoimmunità

Riassunto. La maggior parte delle malattie autoimmuni tende a colpire in misura maggiore le donne rispetto agli uomini. I meccanismi che sono alla base di tale differenza ancora non sono del tutto noti. Tra i fattori responsabili ci sono le differenze genetiche (cromosoma X e Y) e ambientali, ma soprattutto viene attribuita sempre maggiore importanza al ruolo svolto dagli ormoni sessuali. Infatti, gli ormoni sessuali sembrano avere una cruciale funzione di modulare il sistema immunitario influenzando sia l'insorgenza che la cronicizzazione e il decorso delle malattie autoimmuni. Le donne, fisiologicamente, presentano maggiori livelli di estrogeni e progesterone (che rappresentano gli ormoni sessuali femminili) rispetto agli uomini che al contrario hanno più elevati livelli di testosterone e dei suoi derivati (ormoni sessuali maschili). Gli ormoni sessuali femminili e maschili hanno una diretta influenza sulle cellule del sistema immunitario che esprimono recettori ormonali specifici, spesso agendo in senso opposto e modificando sia qualitativamente sia quantitativamente molte caratteristiche della risposta immune.

Parole chiave. Immunità, autoimmunità, ormoni sessuali, estrogeni, androgeni, progesterone.

Introduction

Sex-based disparity in immune responses is well documented and the interplay of sex hormones and immunity is a well-studied phenomenon[1,2]. It may be explained by intrinsic genetic differences between males and females and/or by the differential levels of specific sex hormones produced by males and females. Evidence pointing towards a significant role for sex hormones has been provided by human and animal studies on hormone manipulation. It has been shown on several circumstances that females respond better than males to pathogenic infections and vaccination programs both in mouse models and clinical studies. Moreover, women display a higher prevalence of the majority of autoimmune diseases as opposed to men (e.g., systemic lupus erythematosus, SLE), but some autoimmune diseases appear indifferently in the two sexes (e.g., Behçet disease) while only few of them are more common in males (e.g., Type 1 diabetes mellitus) (Figure 1).

Gender disparity in immune response

Women show greater antigen presenting activity and mitogenic responses, higher immunoglobulin levels and more enhanced antibody production than males[2]. The immune system in women tends to generate a Th1 response characterized by pro-inflammatory cytokines and cytotoxic T lymphocytes, except during pregnancy when the immune system shifts towards a Th2 response.

It is well established that sex hormones modulate immune response through the interaction with specific hormone receptors expressed by immune cells and also play an important role as modulators of the onset/perpetuation of autoimmune diseases. Generally, steroid hormones exert an opposite role on the immune response, with estrogens as enhancers of humoral immunity and androgens and progesterone as natural immunosuppressants. Notably, estrogens, androgens and progesterone are found in both males and females, although at different levels, and their effects depend on their concentration levels and the type of target immune cell.

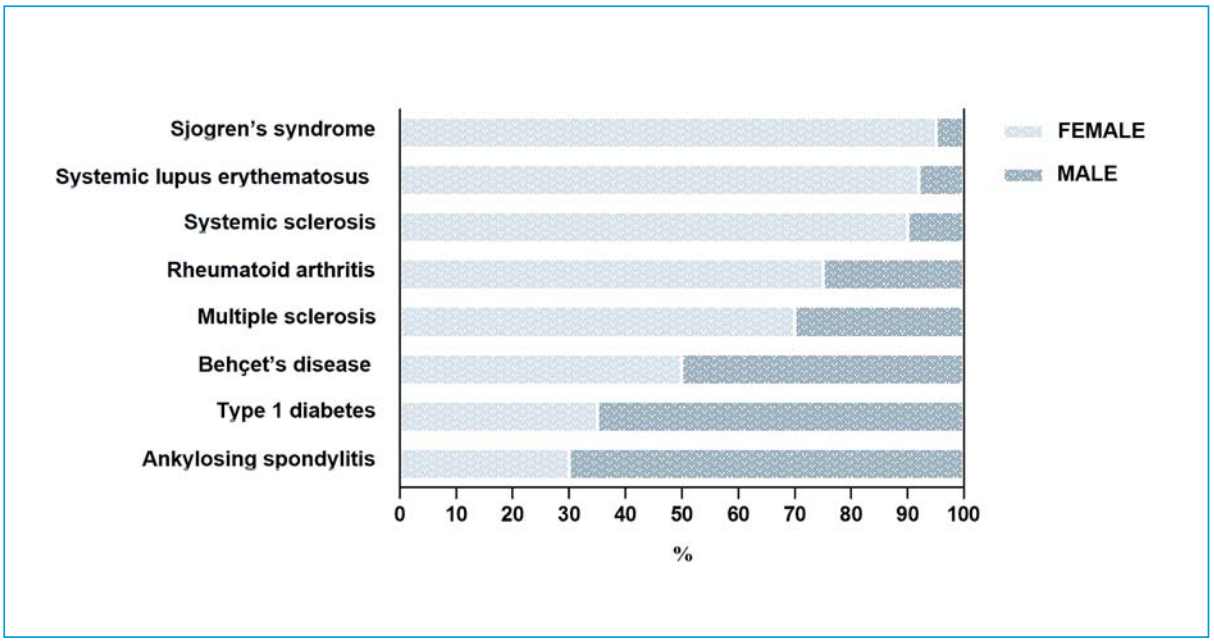

Figure 1. Sex distribution of systemic autoimmune diseases.

Androgens

Androgens act through the androgen receptor (AR), from the NR3C4 gene located on chromosome X. Intracellular ARs are present in bone marrow stromal cells[3], thymocytes[4] and immature dendritic cells (DCs)[5,6]. Splenic T cells and macrophages express a membrane form of AR[7]. The action of androgens on immune function may vary depending on the type of androgen used, the dose administered, and the timing of administration[8]. For example, some studies report immunosuppressive effects[9-11], whereas endogenous androgens are also thought to be immunostimulatory[12]. Testosterone, the primary and best known androgen, has been implicated as a regulator of the immune response to viruses, vaccines, host tissue, and cancer. Despite the relevance of these pleiotropic effects, the mechanisms underlying the activity of testosterone on the immune system are not well understood. Testosterone may suppress the expression of the pro-inflammatory cytokines TNF-α, interleukin (IL)-1β and IL-6 and potentiate the expression of the anti-inflammatory cytokine IL-10[13]. Testosterone inhibits Th1 differentiation by up-regulating type 1 protein tyrosine phosphatase (Ptpn1) in both mice and humans[14], reduces the proliferation and differentiation of lymphocytes[15-17] and may suppress immunoglobulin production, in particular IgA[12]. Supraphysiological doses of testosterone may inhibit the cytotoxic activity of natural killer (NK) cells[18-20]. Overall, these data strongly support an immunosuppressive role for androgens although, since their effects may vary considerably depending on the level of exposure, the potential role of these hormones in gender-specific immune function is still unknown.

Progesterone

Progesterone has three isoforms of receptors (PRs) PR-A, PR-B, and PR-C, from the NR3C3 gene located on chromosome 11. To date, progesterone is found to have two intracellular receptors (iPRs) and three membrane receptors (mPR) of which two isoforms of each receptor type are found in humans [iPRA, iPRB, membrane PRα (mPRα), and mPRβ][21-24]. The wide distribution of PRs in immune cells, including granulocytes, NK cells, DCs, T cells and B cells, indicates that progesterone impacts both the innate and adaptive immune systems[21]. Intracellular or nuclear progesterone receptor expression on lymphocytes was initially described in pregnant women[25]. In addition to playing a critical role in gestation, iPR, activated by low-physiologic concentrations of progesterone, is thought to suppress antibody responses in both sexes[26]. More recently, mPRα has been detected in T cells of non-pregnant women, and appears to be upregulated during the luteal phase on CD8+, but not on CD4+ T lymphocytes[23]. It is known that it suppresses Th1/Th17 and favors Th2 type cytokine secretions, inhibits the cytotoxicity of T cells and increases the differentiation of Th0 cells as T regulatory cells (Tregs). Similarly, an inhibitory effect is exerted by progesterone on the activities of NK cells, e.g., inhibition of IFN-γ production and apoptosis induction[27].

Other known effects include the inhibition of macrophage activity[28], the modulation of myeloid DC activity[29], the inhibition of glucocorticoid-mediated thymocyte apoptosis[30], the reduction of nitric oxide production[31], and the expression of toll-like receptors by macrophages[32].

Estrogens

Estrogens modulate the immune system contributing to significant modifications in immune function during the menstrual cycle and pregnancy. They also impact infectious and autoimmune diseases as well as inflammation[33-36]. Estrogens, in particular 17β estradiol (E2), are able to regulate immune responses acting at multiple levels, including cell development, proliferation, cytokine or antibody production, and apoptosis. Regulation of both proliferation and apoptosis is of particular importance in the development of an appropriate T and B cell repertoire and in the preservation of immune homeostasis, eluding abnormal clonal expansion of autoreactive immune cells[37]. E2 interacts with two receptors, estrogen receptor (ER)α and ERβ, from NR3A1 and NR3A2 genes located on chromosome 6 and 14, respectively. All immune cell types express intracellular ER and the presence of one ER subtype over the other might change estrogen effects, promoting or dampening inflammation[33,36,38,39]. ERα activation plays a predominant and immunostimulatory role[40,41] while ERβ activation appears to have a slightly immunosuppressive effect[39]. Our group has recently demonstrated the intracellular expression of both ERα and ERβ in human peripheral T and B lymphocytes, and in NK cells[42]. Notably, intracellular ER levels are not menstrual cycle-dependent and do not decrease with age in cycling females[43].

As stated above, E2 influences the development of both B and T cells. For example, it appears to favor the survival of high-affinity DNA-reactive B cells at both the immature and transitional B cell stages facilitating the maturation of a potentially pathogenic naive autoreactive B cell repertoire[44,45]. Several studies have demonstrated a role for E2 in the thymus (including thymic involution) and early T cell development[46-48]. The effects of E2 on mature immune cells are quite complex. In short, at periovulatory to pregnancy levels (500 pg/ml-50ng/ml)[49], E2 inhibits proinflammatory pathways such as tumor necrosis factor (TNF)-α, IL-1β, IL-6 production, and activity of NK cells; it is also able to stimulate antiinflammatory pathways such as IL-4, IL-10, and transforming growth factor-β production[38]. Conversely, at lower concentrations, E2 stimulates TNF-α, IFN-γ, IL-1β, and the activity of NK cells. E2 is capable of stimulating antibody production by B cells both at high and low concentrations[38]. Interestingly, a recent study showed that E2 induces in B cells the expression of activation-induced deaminase, a protein that drives antibody diversification, transforming benign antibodies into autoantibodies, thus favoring autoimmunity[50]. E2 is also able to play an immunoregulatory role, increasing the number and function of CD4+CD25+ Tregs[51,52].

The discovery of plasma membrane-associated ERα (mERα) in different cell types has greatly expanded the understanding of estrogen action[53]. Membrane ERα rapidly activates different protein kinase cascades influencing downstream transcription factors to produce non-genomic effects; at the same time it can modulate intracellular ER action through the phosphorylation of intracellular ERs and their coactivators[54]. With regard to mER expression in immune cells, previously reported data obtained using a membrane-impermeant form of E2 (i.e., E2 conjugated with bovine serum albumin) indicated that an estrogen-binding protein exists in the plasma membrane of human lymphoblastoid B cells[55-57]. The cell surface expression of a functionally active ERα isoform, but not of ERβ, has also been found in the plasma membrane of lymphocytes, demonstrating that E2 level fluctuations may be associated with a prompt lymphocyte response[42]. Recently, our research team showed the presence of anti-ERα antibodies (Abs), but not of anti-ERβ Abs, in sera from patients with two paradigmatic autoimmune diseases, characterized by a high female-to-male ratio, i.e., SLE and systemic sclerosis[58,59]. These antibodies behave as true ERα agonists activating ERK signaling and significantly correlate with disease activity and severity. Further studies are needed to gain greater insight into mER expression and its signal transduction pathways in different lymphocyte subpopulations.

Conclusions

Estrogens, progesterone and androgens are crucial regulators of the immune system. The major effects of sex hormones on immune cells have been summarized in Table 1. The mechanisms behind sex hormone influences on immune functions are attributed to their interactions with the receptors expressed on the immune cells, which affect the production, maturation, differentiation, and, ultimately, the functioning of the immune system, also influencing the development of immune-related diseases. In fact, for most autoimmune diseases there are clear sex-related differences in prevalence whereby women are gene-

Table 1. Summary of sex hormone effects on immune system.

Hormone	Receptor	Inhibition of	Induction of
Androgen	AR	• Expression pro-inflammatory cytokines (TNF-alpha, IL-1beta, IL-6) • Differentiation of Th1 • Proliferation and differentiation of lymphocytes • Cytotoxic activity of NK cells	• Expression of anti-inflammatory cytokine IL-10
Progesterone	PR	• Th1-Th17 response • Cytotoxicity of T cells • Activities of NK cells • IFN-gamma production from NK cells • Macrophage activity • Glucocorticoid-mediated thymocyte apoptosis • Nitric oxide production • Expression of toll-like receptors by macrophages • Differentiation of Th2 cells in vitro	• Th2 type cytokines secretion • Differentiation of Th0 as Tregs • Apoptosis
Estrogen (high level)	ER	• Production of TNF-alpha, IL1-beta and IL-6 • Activity of NK cells	• Production of IL-4, IL-10, TGF-beta • Expression of activation-induced deaminase in B cells
			• Activation of $CD4^+CD25^+$ regulatory T cells • Antibody production by B cells
Estrogen (low level)	ER		• TNF-alpha, IFN-gamma, IL-1beta production • Activation of NK cells • Antibody production by B cells

rally more frequently affected than men (Figure 1).

In conclusion, understanding the effects of the sex hormones on immune-mediated diseases could lead to the identification of innovative and readily available therapeutic interventions, such as hormone antagonists or agonists, to manage autoimmune diseases.

Key messages

- Sex-based disparity in immune responses is well documented.
- Incidence of autoimmune disease is generally higher in females than males.
- Immune cells express sex hormone receptors.
- Sex hormones are implicated in the immune response, with estrogens as enhancers and androgens and progesterone as natural immunosuppressants.
- Sex hormones have an impact on gender disparity in immune-related diseases.

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