

Immunology and immune-mediated diseases

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Sex differences in immune response

Women mount stronger humoral and cellular immune responses than men. In fact, a higher number of CD4⁺ T lymphocytes, stronger production of cytokines (e.g., IFN α) in response to infections and higher levels of circulating antibodies have been observed in women in comparison to men.

The higher activation of the immune response is a double-edged sword because it makes women more resistant to infections but more susceptible to inflammatory and autoimmune diseases¹. The main factors affecting the differences between the female and male immune systems are: the presence of two X chromosomes in females versus one X and one Y chromosome in males, the sex hormones, and the different responses to environmental factors (e.g., microbial exposure and diet)². Sociological differences between genders may also have a role in affecting the immune responses³.

The role of the X chromosome

In women the transcription of the genes present in both of the X chromosomes would lead to a dangerous increase in the expression of their products, which is avoided by the random inactivation of one of the two chromosomes. However, if an incomplete inactivation of one of the X chromosomes occurs then some crucial immune-related genes and microRNA can be over-expressed. In fact, several immune factors, such as *CD40L*, *CXCR3*, *FOXP3*, *TLR7*, *TLR8*, *IL-2R γ* , *BTX*, *IL-9R* are encoded by genes expressed in the X chromosome and some microRNAs present on the X chromosome are involved in the regulation of the immune response^{4,5}. Hence, the presence of a second X chromosome in females can have a significant impact on immune factors and miRNA expression levels, contributing to the dimorphism of the immune response.

The role of sex hormones

Sex hormones, such as estrogens, progesterone, and androgens can also influence immune system function and affect the incidence, activity and progression of autoimmune diseases. Generally, estrogens, in particular 17- β estradiol (E2), act as an enhancer, at least of humoral immunity, and testosterone and progesterone as natural

immunosuppressants⁶. E2 has different effects depending not only on the concentration but also on the type of target cell and the receptor subtype expressed on a given cell type. Estrogen receptors (ER) α and ER β play an opposite role in the immune function with α , respectively, pro- and anti-inflammatory activity. Regarding E2 concentrations, at periovulatory to pregnancy levels, it has mainly anti-inflammatory effects, by inhibiting production of proinflammatory cytokines, such as TNF, IL-1 β and IL-6 and by inducing an expression of anti-inflammatory cytokines favouring a Th2 phenotype, such as IL-4, IL-10 and TGF- β , and by activating regulatory T cells (Treg). At lower concentrations, E2 stimulates TNF, IFN- γ , IL-1 β and NK cells, while it enhances antibody production by B cells both at high and low concentrations.

Consistent with the effects of sex hormones on immunity, changes in the severity of autoimmune diseases are also observed during pregnancy, when estrogens and progesterone reach the highest levels⁷. Maternofoetal immune tolerance is essential to maintain a healthy pregnancy and one of the important adaptations leading to this immune tolerance is the shift, at implantation, from a pro-inflammatory Th1/Th17 response, which promotes rejection, toward a Th2/Treg cell response that promotes tolerance. Due to these adaptive changes in immune system function, pregnancy has opposite effects on some autoimmune diseases. For instance, pregnancy is associated with an increase in disease activity in Systemic Lupus Erythematosus (SLE), this effect being related to the increased Th2 response and enhanced production of pathogenic autoantibodies. On the other hand, pregnancy has a protective effect in Th1-mediated autoimmune diseases, like Rheumatoid Arthritis (RA).

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 (mRNA and protein) is higher in males than females (both in mice and in humans) and it is up regulated by androgens and down regulated by estrogens⁸.

Sex differences in rheumatoid arthritis

RA is a chronic systemic immune-mediated inflammatory disease affecting synovial tissue in multiple joints. In developed countries the prevalence of RA is 0.5 to 1.0%, with

a female:male ratio of 3:1. Interestingly, women were found to have higher disease activity scores, more pain and greater loss of function than men, both in the early and established disease¹. The reason for this gender imbalance is not clear, but both genetic and hormonal factors are thought to be involved. Estrogen levels are increased in the synovial fluid of patients with RA due to the increased activity of the aromatase enzyme which converts androgens into estrogens. In particular, 16 α -hydroxyestrone interferes with the proliferation of monocytes and the production of TNF. The severity of the RA is inversely associated with serum androgen levels; patients with RA of both sexes have reduced levels of serum androgens even a few years before the onset of disease. The level of microRNA expression localized on the X chromosome (miR-222, miR-532, miR-98, and miR-92a) is significantly different between men and women with RA. Furthermore, the single nucleotide polymorphism in the IL9R gene on the X chromosome is significantly more frequent in men with RA. To note, men seem to have a better response to treatment with DMARDs (disease modifying antirheumatic drugs) and with anti-TNF drugs than do women⁹.

Sex differences in systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a multifactorial and highly polymorphic systemic autoimmune disease that affects multiple organs including kidneys and the heart. The incidence of the disease is estimated at 20–50 cases/100,000 individuals. SLE is characterized by auto-antibody production by dysregulated B cells, a target organ infiltration by inflammatory T cells and aberrant immune cell activation. SLE is often called a “woman’s disease” because of the striking differences in prevalence related to sex¹. Pre-menopausal women have SLE incidence rates of 8:1-15:1 when compared to age-matched males; these rates decline to 3:1 in the pre-adolescent population and to 5:1 after menopause, when estrogen levels are more similar between genders. Results from different studies indicate that the use of oral contraceptives and hormone replacement therapy increases the risk of developing SLE; however, some retrospective studies suggest no increase in clinical flares with hormonal therapy¹⁰. Importantly, a reduction in the disease activity has been observed in SLE patients treated with the ER antagonist fulvestrant (Faslodex)¹¹.

X-linked genes, such as FOXP3, TNF and TLR7, have been associated with gender bias in SLE¹. Additionally, several X-linked miRNAs have been found to be upregulated in CD4⁺ T cells from female SLE patients compared to male patients, potentially contributing to the sex bias in SLE. In males, SLE has a late onset and different clinical features and outcomes, different organ involvement (e.g., more severe renal manifestations), higher frequency of pleurisy, suggesting that male-specific predisposing and/or pathogenetic factors exist. To date, there is limited evidence to suggest an altered hormonal milieu in men with lupus. Potential risk factors include X-chromosome

abnormalities (as supported by the increased incidence of SLE in patients with Klinefelter syndrome) and various somatic genetic polymorphisms.

Conclusions

The immune response in women and men is regulated by multiple factors related to sex and gender that act in succession or at the same time and which are responsible for a different susceptibility to and severity of the disease (e.g., autoimmune diseases). A greater knowledge of how these factors act and interact can contribute to a better understanding of the pathogenic mechanisms of autoimmune diseases, ultimately encouraging the development of new targeted and personalized therapeutic strategies.

References

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