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Sex Differences in Immune Responses

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Abstract

Biological sex has a significant impact on the immune system and immune-related diseases. Females exhibit a stronger immune response and are therefore more vulnerable to multiple autoimmune diseases. Males are comparatively more susceptible to specific viral, bacterial, parasitic, and fungal infections. Although sex hormones contribute to sexual differences in immune cell population composition and functions, the presence of two X chromosomes in females suggests that differential expression of a large number of X-linked immune-related genes, accompanied by abnormalities in X-chromosome inactivation, may also contribute to the sex-biased functions of innate and adaptive immune cells in health and disease. A comprehensive and multi-perspective understanding of this sex difference would have vital importance for planning and implementing personalized and precision immunotherapies.

Keywords

sex hormones, X-chromosome inactivation, adaptive immune cells, innate immune cells

1. Introduction

Proven by an avalanche of clinical and basic research over decades, immune-response patterns and disease susceptibility have significant sex differences. These studies also provide sufficient evidence that male are more vulnerable to infectious disease, with higher severity and incidence [1]. When it comes to acute viral infections, microbial infections, and infection-associated cancers, males have more severe symptoms and higher mortality. Females are shown to have stronger resistance to infectious disease; however, with their stronger overall immune responses, they are more susceptible to autoimmune diseases and certain inflammatory disorders. Besides, the long-term or chronic sequelae of infection, known as post-acute sequelae of infection, occur at higher rates in females. These sequelae have been recognized as bona fide autoimmune or inflammation-associated diseases [2], and the symptoms include, but are not limited to, diffuse pain, arthralgia, pulmonary fibrosis, and cognitive impairment. Collectively, observations in these studies reveal clinical sex differences in immune disorders and immunological responses and establish the importance of such differences in the field. Although there is a simple observation that “males and females are different.” In order to understand far beyond this, investigate the sex difference of immune system across different environments and tissues is crucial. More deeper scientific exploration of sex differences may pave the way to better disease diagnosis, treatment, and prevention, as well as the development of personalized, precision immunotherapies.

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Sex differences in the immune system originate from the combined and interacting effects of genetic, hormonal, and environmental factors. Immune cells are present in every organ and tissue, where they perform specific functions, regulate cell-cell interactions, tissue development, homeostasis, and pathological processes. Therefore, the function of each kind of immune cell must be investigated within its specific cellular microenvironment, tissue, and organ. The molecular origins of sex differences in immune responses are sex chromosomes—the X and Y chromosomes, the reproductive organs, and sex hormone levels, which change with age. Sex hormones, particularly androgens and estrogens, may have either pro-inflammatory or anti-inflammatory effects, and the expression of many immune-related genes is regulated by the presence of nuclear hormone receptor binding. Sex chromosomes provide the genetic and epigenetic basis for inherited and sex-specific differences in gene expression in immune cells. The X chromosome contains approximately 50 immune-related genes, including immune-cell identity (FOXP3); cell activation and intracellular signaling (CD40LG, TLR7, IRAK1, IL13RA1/2, NEMO, TASL, and IL-9R); leukocyte migration (CD99 and CXCR3); immune-cell differentiation and proliferation (IL-2RG and BTK); and cellular metabolism (OGT and CYBB) [3]. Therefore, the X chromosome probability acting as an important contributor to the female-biased antimicrobial responses and the molecular basis of autoimmunity.

This review summarizes the current studies on sex differences in the immune cell population composition and function, discusses the effects of immune-cell population composition, hormones, and X-chromosome-associated genetic factors on the immune system, with the destination to clarify the mechanisms underlying sex-biased immune responses; additionally, it provides a theoretical scientific reference for understanding sex differences in infections and autoimmune disease onset rates, as well as for developing personalized immunological intervention strategies.

2. Sex Differences in Immune Cells

Sex-biased differences in innate, humoral, and cellular immunity in humans accompany the differences in immune-cell population composition between males and females [3]. Circulating and tissue-resident immune cells also show significant sex differences in population composition and phenotype [4]. For example, flow-cytometric immunophenotyping of healthy European and Asia participants has shown that females have higher numbers of $CD4^+$ T cells, especially naïve T cells, which may reflect stronger thymic function in females [5, 6]. Recently, multiple whole-blood transcriptomic analyses of healthy international individuals across different continents also confirmed this similar observation: Females have a higher proportion of $CD4^+$ T cells [7]. The CD4: CD8 ratio in peripheral-blood T-cell populations is higher in females [8], and this drift is associated with enhanced immune function and autoimmune disease [8, 9]. Comparatively, the lower CD4:CD8 ratio in males is considered an immune-risk phenotype; a lower CD4: CD8 ratio is also associated with immune aging [4]. Therefore, $CD8^+$ T cells isolated in vitro from males exhibit a less activated phenotype; comparatively, $CD8^+$ T cells from females are more active [10]. These findings could also be applied to long-lived $CD8^+$ tissue-resident memory T cells (T_RM cells), they permanently colonized in various tissues and provide a first defensive line at barrier positions against infections and tumors. Studies have shown that female mice have more T_RM cells in the intestine and skin than male mice [11].

Besides, compared with males, females have higher levels of immune cells in circulating peripheral blood, including $CD19^+$ B cells, plasma cells, regulatory T cells—defined as cells with high CD25 and low CD27 expression—and mucosal-associated invariant T cells [6, 10, 12–14]. Total B-cell numbers are generally equivalent between the sexes, but B cells in females more frequently exhibit class-switched and memory phenotypes. These B cells produce antibodies more efficiently; pinpointed that females would show much stronger and broader antibody responses, particularly upon pathogen re-exposure [4]. The increase in class-switched cells in females occurs between puberty and menopause, suggesting that estrogen regulates B-cell development [15]. Humoral immunity also has sex differences; females have higher IgM antibody levels than males [16].

By contrast, females have relatively lower proportions of $CD14^+$ and $CD16^+$ monocytes, lower overall proportions of myeloid cells, and fewer natural killer cells [6, 7, 10, 12, 17]. Among innate immune cells, neutrophils are the most abundant pro-inflammatory cells in the blood, and their numbers are slightly but statistically significantly higher in females [18]. This difference is influenced by hormones: estrogen and testosterone levels are positively and negatively correlated with neutrophil counts, respectively, and

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premenopausal females have higher circulating neutrophil counts than postmenopausal females [4]. Neutrophils exposed to estradiol and progesterone show less apoptosis [19], this phenotype is associated with extended cellular lifespan and tissue residency characteristics. Estrogen can also promote neutrophil effector functions, especially the recruitment of neutrophils to inflamed tissues [4]. Comparatively, non-classical monocytes, also known as “patrolling” monocytes, may exert either anti-inflammatory or pro-inflammatory effects depending on the specific disease background. Their count in the blood of adult males is threefold higher than that in adult females [20]. Similar to the adaptive immune system, higher counts of innate immune cells do not directly indicate stronger immune or antiviral activity. Male mice have more circulating natural killer cells but lower natural killer-cell activity than female mice [21], whereas female mice secrete higher levels of the inflammatory antiviral cytokine interferon-γ (IFN-γ) following viral infection.

3. Sex Hormone-Mediated Regulation of Immune Function

Sex differences in immune-cell function come from differences in gene expression among immune-cell subsets in males and females, and sex hormones may influence these observed expression differences [3]. Transcriptomic analysis of innate and adaptive immune cells, including monocytes, naïve B cells, and various T-cell subsets, identified approximately 1,875 transcripts with sex-biased differential expression, most of them were autosomal genes [22]. Most of these transcripts exhibited sex-biased differential expression in only one immune-cell type, indicating the cell-type specificity of sex-biased differential gene expression and suggesting that sex hormones and sex chromosome-encoded trans-acting factors may broadly influence the observed expression differences [22].

Sex hormones, including estrogens, progestogens, and androgens, can regulate gene expression [23, 24]. Sex-hormone levels differ obviously between males and females and fluctuate dynamically across the life. In females, hormone levels also vary across the menstrual cycle and with the use of hormonal contraceptives or hormone replacement therapy. These dynamic changes in hormone action may contribute to the plasticity of sex differences in immune responses [4]. Estrogens have both pro-inflammatory and anti-inflammatory effects, depending on their local concentration and the immune-cell type examined [3].

Both immune and non-immune cells can respond to sex hormones. Peripheral and tissue-resident immune cells express estrogen receptor α (ERα), estrogen receptor β (ERβ), androgen receptor (AR), and progesterone receptor (PR), enabling them to respond directly to sex-hormone signaling in a cell- and tissue-specific manner. Plenty of experimental evidence supports cell-intrinsic responses of innate and adaptive immune cells to ER, AR, and PR signaling [25, 26] (Fig. 1). Overall, estrogens tend to exert immunostimulatory effects, whereas testosterone mainly exerts immunosuppressive effects; this pattern is manifest in both circulating and tissue-infiltrating immune-cell populations.

Immune-cell types in both the adaptive and innate arms of the immune system respond directly to sex hormones. Immune-cell subsets differ between the sexes in both abundance and activity.

Beyond the sex-related molecular and functional differences in immune cells, biological sex can further shape overall immune responses by modulating networks of intercellular interactions. Effective immune responses depend on coordinated activity within immune-cell networks. Consequently, sex differences observed in individual immune-cell populations and their functions tend to reflect broader sex-dependent differences in immune networks. Transcriptomic analyses have identified specific gene-set signatures that are differentially enriched between the sexes. Recent tissue-specific studies have begun to characterize these differences and have described sex-biased immune networks involving interactions among distinct immune-cell populations and between immune and non-immune cells [27].

In mice, the skin of adult females has greater cell counts of conventional T-cell subsets and resident dendritic-cell subsets [28]. Sex differences in skin T cells are also present in germ-free mice, suggesting that the sex bias in skin T-cell abundance is independent of the microbiome. The authors found that androgens, acting through androgen receptor signaling, negatively regulate type 2 innate lymphoid cells (ILC2s), which are abundant in the skin, then suppress dendritic-cell accumulation and activation, impair dendritic cell-mediated T-cell priming, and alter cutaneous immune responses [28]. Although sex differences in T-cell abundance are also present in germ-free mice, they will influence bacterial colonization in conventionally

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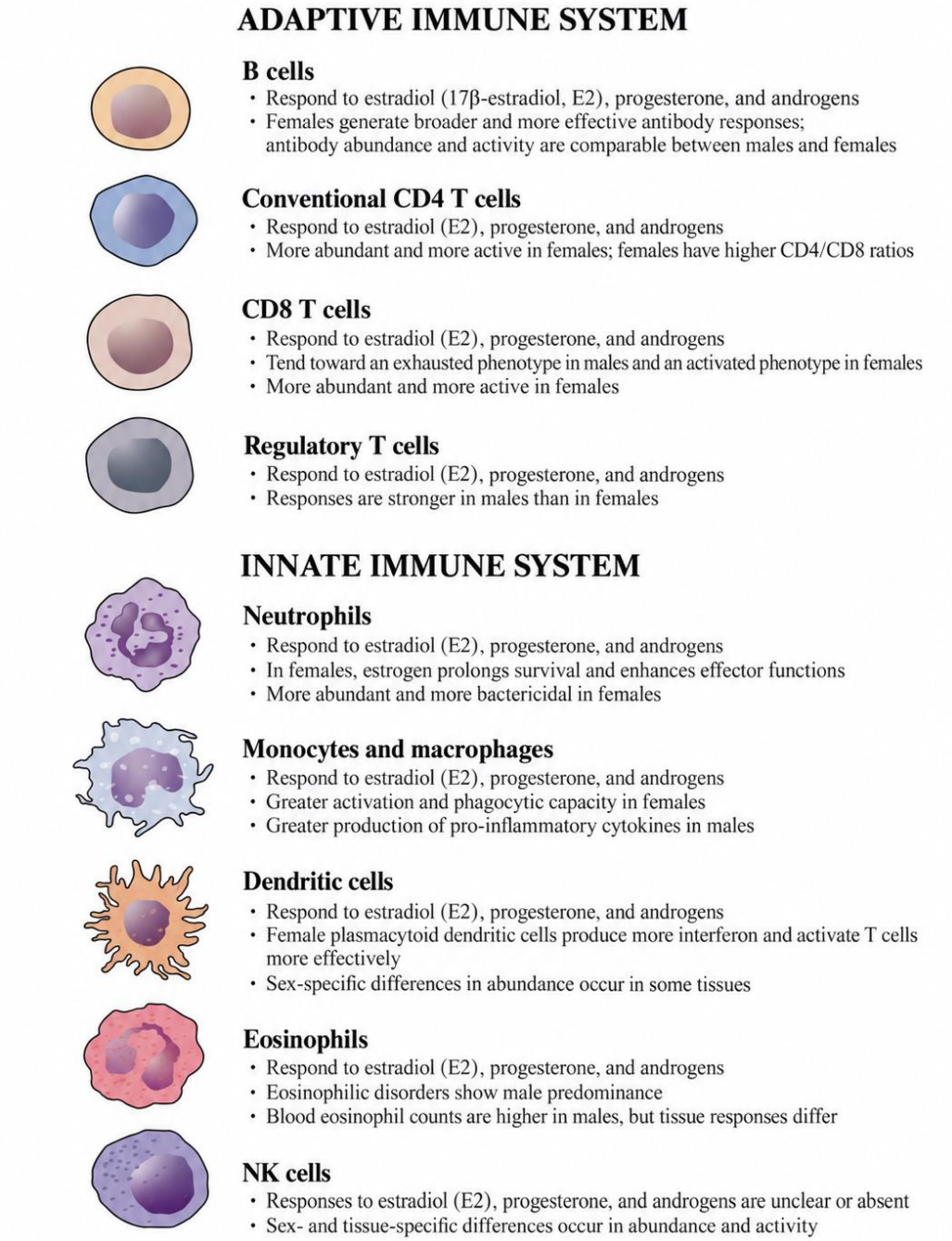
housed mice. This study therefore provides mechanistic evidence that sex-hormone signaling can directly alter host responses to commensal and pathogenic microorganisms.

Biological sex can also influence interactions between immune and non-immune cells (Fig. 1). Many non-immune cell types, including endothelial cells, adipocytes, fibroblasts, and keratinocytes, respond directly to sex hormones. Sex-hormone signaling in these cells can affect immune cells in several ways. For example, estrogen signaling in endothelial cells promotes vasodilation, thereby influencing immune-cell trafficking, and reduces the release of pro-inflammatory cytokines by endothelial cells, thereby affecting immune-cell phenotypes [29]. Sex-hormone signaling in non-immune cells can also directly influence tissue immunity. Following ERα knockdown in adipocytes, expression of the macrophage marker F4/80 increased in the adipose tissue of male mice, indicating macrophage infiltration [26]. These findings demonstrate that sex bias in immunity can also be mediated by non-immune cells.

Figure 1: Characteristics of Human Immune Cells and Their Responsiveness to Sex Steroid Hormones



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4. Sex Differences in Immunity Mediated by Escape from X-Chromosome Inactivation

Biological sex is classified according to sex chromosomes, with XX as female sex and XY as male sex. Rarer karyotypes include XXY, XYY, and XO, which have been shown to affect vulnerability to immune-mediated diseases [30]. Autoimmune diseases such as systemic lupus erythematosus, Sjögren syndrome, and scleroderma are associated with increased X-chromosome dosage, supporting a direct role for the X chromosome in regulating immune function. The human X chromosome is approximately three times as large as the Y chromosome and contains roughly 800 additional protein-coding genes that are enriched in immune-related pathways [3]. To balance X-linked gene dosage between XX females and XY males, most genes on one of the two X chromosomes in female cells are transcriptionally silenced through a process known as X-chromosome inactivation (XCI). Nevertheless, approximately 23–30% of genes on the inactive X chromosome (Xi) escape inactivation, and some genes escape in a tissue-specific manner [31, 32]. Female mammals regulate X-linked gene expression through XCI. During development, one X chromosome—the Xi—is transcriptionally silenced, and the epigenetic memory of this state is maintained through successive cell divisions and persists into adulthood [3]. A range of epigenetic modifications, together with the long noncoding RNA Xist, are enriched on the Xi and jointly maintain the transcriptional repression of most, but not all, genes on this chromosome. Xist expression is essential for establishing the Xi; loss of Xist during early development disrupts X-linked gene dosage during embryonic and placental development and therefore lethal [33]. Deletion or silencing of Xist reduces, and may completely abolish, the enrichment of heterochromatic modifications on the Xi [34]. It also causes some X-linked genes on the Xi to be reactivated, with the extent of reactivation depending on the cell type and the timing of Xist loss relative to XCI initiation.

Mouse models in which Xist is conditionally deleted from somatic cells after XCI has been established exhibit diverse phenotypes, including myeloproliferative neoplasms following deletion in hematopoietic stem cells, increased polyp formation following deletion in intestinal cells and subsequent azoxymethane/dextran sulfate sodium treatment, and no overt phenotype following deletion in neurons, B cells, epithelial cells, or enterocytes. In the latter models, the animals remain viable and have normal lifespans [35–37]. Taken together, these studies support three key conclusions: (1) the identity and number of X-linked genes reactivated following Xist deletion vary among cell types; (2) X-linked gene-dosage imbalance is tolerated to differing degrees in a cell-type-specific manner; and (3) inflammatory stress may exacerbate Xi reactivation.

Female mammals are mosaics with X-chromosome activity because each female somatic cell contains an Xi of either maternal or paternal origin. Most somatic cell types examined to exhibit similar enrichment of epigenetic features on the Xi, including Xist RNA, heterochromatic histone modifications, and the histone variant macroH2A; all of these can be observed cytologically [38–41]. Immune cells, however, lack some of the hallmark epigenetic features maintained by canonical XCI maintenance. Specifically, mouse splenic B and T cells and human circulating lymphocytes lack cytologically detectable enrichment of Xist RNA and heterochromatic marks on the Xi, although significant changes exist in Xist transcription [42–45]. Thus, Xist transcription and localization to the Xi are genetically independent processes. After in vitro activation of B and T cells, Xist RNA and heterochromatic modifications reappear on the Xi before the first cell division [42–44, 46]. Xist RNA and dynamic localization of heterochromatic marks to the Xi are also observed during lymphocyte development. Because after the common lymphoid progenitor stage, referred to the pro-B-cell and DN1 thymocyte stages, Xist RNA is lost from the Xi; Xist transcription remains stable [43, 44].

Surprisingly, non-canonical XCI maintenance mechanisms exsist in both adaptive and innate immune cells. The stability of Xist RNA relocalization to the Xi varies significantly among immune-cell types. Neutrophils and plasmacytoid dendritic cells (pDCs) lack detectable Xist RNA localized to the Xi, natural killer (NK) cells exhibit multiple Xist RNA foci within the Xi territory [45]. Bone marrow-derived macrophages stimulated with lipopolysaccharide (LPS) or CpG exhibit a diffuse Xist RNA distribution, and approximately half of the nuclei contain H3K27me3 foci that colocalize with Xist signals. Although Xist transcription is persistent, in vitro stimulation of mouse pDCs with CpG or a TLR7 agonist does not show Xist RNA localization. Both resting and in vitro-activated pDCs contain only a small number of H3K27me3 foci [45].

The deficiency of epigenetic features on the Xi in many immune cells, including lymphocyte progenitors, supports the hypothesis that Xi chromatin in immune cells is more euchromatic than that in fibroblasts and is therefore more susceptible to abnormal reactivation at certain loci [3]. The variable nature of Xi chromatin may facilitate the upregulation of pro-inflammatory X-linked genes during pathogen infection, potentially

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providing an immunological advantage on females. However, it may also disrupt self-tolerance and contribute to the development of female-biased autoimmune diseases.

5. Conclusions and Future Perspectives

Biological sex is an important determinant of immune responses and immune health, and understanding how immune cells, hormones, and genetic factors contribute to sex differences in immunity is becoming increasingly important. In 2009, more than 60% of immunology-related publications using animal models did not mention biological sex. Although more than half of human immunology publications included samples from both males and females, more than 90% of these studies lacked sex-specific analyses [3]. The proportion of immunology studies that included both male and female samples increased from only 16% in 2009 to 46% in 2019 [3]. Nevertheless, further efforts are needed to ensure that sex is adequately considered as a biological variable in future immunological research. Although previous studies have examined the effects of sex hormones on sex-specific immune-cell functions and cytokine production following infection with certain pathogens, the role of the X chromosome in sex-biased immune responses remains unclear. Future experiments investigating genes that escape XCI in specific immune-cell populations, together with genetic gain- and loss-of-function studies of immune-related X-linked genes, will help elucidate important mechanisms underlying sex differences in susceptibility to infection and disease severity. Utilizing mouse models that recapitulate the sex differences observed in clinical infection and autoimmune disease to investigate the origins of sex-biased responses may inform the development of targeted, sex-specific therapeutic strategies and thereby improve patient outcomes.

With respect to immunotherapy, research into how sex differences affect immune-cell function is still at an early stage, and the translation of this knowledge into therapeutic and clinical benefits has yet to be achieved. As immunotherapy moves away from standardized approaches toward individualized treatment— differences in therapeutic responses among individuals—key factors such as sexual dimorphism must inform decisions on the prevention, diagnosis, and treatment of immune-related diseases. Future studies should also consider interactions among sex, race and ethnicity, age, and exogenous hormone supplementation, as these factors may jointly influence immune function and therapeutic outcomes.

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Conflicts of Interest

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