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REVIEW

Sex differences in immune responses to infectious diseases

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Abstract
Purpose The influence of sex hormones is recognized to account for the susceptibility and distinct outcomes of diverse infectious diseases.
Methods This review discusses several variables including differences in behavior and exposure to pathogens, genetic, and immunological factors.
Conclusion Understanding sex-based differences in immunity during different infectious diseases is crucial in order to provide optimal disease management for both sexes.

Keywords Sex · Immunity · Infectious diseases

Introduction

Sex-based differences on the outcome of numerous infectious diseases are evident from many clinical studies [1]. In general, females show stronger humoral and cellular immune responses to infection or antigenic stimulation than the males [2, 3]. This enhanced level of immunity is a double-edged sword: on one hand, it can provide protection against several pathogens. On the other hand, this can lead to an aberrant pathogenic inflammatory response and therefore is a risk factor for autoimmune diseases [4]. The underlying mechanisms for these sexual differences are diverse, which includes genetic, epigenetic, and hormonal determinants of immunity. In this review, we will first discuss our current understanding of the differential immunity between the sexes. In the second part, we will review the current knowledge on sex-based differential immunological responses during various infections.

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Biological background, effects of sex hormones on immunity

The X chromosome

Differential immunological responses observed in women and men are attributed to the biased response from X chromosome. The X chromosome is known to harbor majority of the immune-related genes [3, 5]. The human X chromosome encodes for a number of critical genes involved in the regulation of immunity, such as Toll-like receptors (TLR) 7 and 8 that play a central role in sensing viral pathogens; FOXP3, a transcription factor for regulatory T cells and CD40L (CD154) [6]. The X chromosome also codes for crucial microRNAs (miR) that regulate immunity. Among the X-linked microRNAs, miR-233 is widely studied and has been shown to regulate neutrophil differentiation. Similarly, miR-106A, miR-424, miR542, and miR-503 have been shown to negatively regulate monocyte differentiation [7]. Further, a large number of X-linked miRNAs are reported to downregulate negative regulators of immunity; such as forkhead box P3 (FOXP3), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death 1 (PDCD1) and members of casitas B-lineage lymphoma (CBL) and suppressors of cytokine signaling

(SOCS) family. This is considered to be a cause for prevalent autoimmune disorders observed in women [8].

Females harbor two X chromosomes, whereas males carry one X and one Y chromosome. In order to prevent excessive responses from the X chromosome, the female mammals have evolved a complex mechanism termed as X-inactivation. Through this process one of the X chromosomes is transcriptionally silenced during the development process of a female. This leads to cellular mosaicism; which means that either the X chromosome from paternal or maternal origin is expressed in different cell populations. As a result, gene mutation in X-linked chromosome is expressed in part of the cells in females, whereas all the cells in males will exhibit the mutation. Cellular mosaicism has proven to provide immunological advantage for the females. Diseases such as X-linked severe combined immunodeficiency (XSCID) and immune dysregulation [9, 10], polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) harbor mutations in genes that are linked to the X chromosome [11]. X-inactivation allows part of the cells to express the wild type genes in females compared to none of the cells in males. Therefore, these genetically inherited diseases are more prevalent in males. In mouse models of microbial sepsis, animals exhibiting cellular mosaicism for Interleukin-1 receptor-associated kinase 1 (IRAK1) expression and NADPH oxidase 2 (NOX2) have shown improved clinical phenotype in survival and bacterial clearance. Taken together, inactivation of X chromosome equips females with a wide reserve of proteins, which provide diversified and effective immune responses. However, women are at a higher risk of contracting autoimmune disorders and this is attributed to gene dosage from X chromosome [6].

Immunomodulatory functions of sex steroid hormones

Sex hormones significantly affect the functions of immune cells. This is evident from transcriptome analysis of peripheral blood monocytes (PBMCs) of men and women of all ages. Data reveal that age and sex potently alter the transcriptional responses in immune cells. Like other hormones, sex steroids exert their function by binding to specific receptors. Immune cells such as lymphocytes and myeloid cells have been shown to express estrogens receptors (ER), androgen receptors (AR), and progesterone receptors (PR). The sex steroid receptors act as nuclear transcription factors through different ligand-dependent or ligand-independent mechanisms [12]. The expression of the hormone receptors on immune cells clearly signifies that they have key immunoregulatory functions. The majority of the scientific work has focused on the ER. Two subtypes of ER, ERα, and ERβ are known so far and their roles in the immune regulation are subject of current research. Most immune cells such as B- and T-lymphocytes, dendritic cells, macrophages, monocytes, natural killer cells, and mast cells express ERα, while ERβ is infrequently expressed. The expression of ERs is autoregulated [13]. ERα and ERβ deficient mice develop fully established immune system. However, their immune system becomes disoriented by age. Thus aged ERα knockout ($ER\alpha^{-/-}$) mice develop autoimmune disorders [14] and aged $ER\beta^{-/-}$ mice develop chronic myeloid leukemia [15]. Moreover, estradiol has been shown to increase both the humoral and cell-mediated immune responses. Interestingly, estrogen positively regulates TLR-mediated pro-inflammatory pathways in murine macrophages and plasmacytoid dendritic cells (pDCs). It enhances the cytotoxic activity of natural killer cells (NK-cells) and also upregulates pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1. Estradiol has also been reported to affect the function of invariant natural killer T cells (iNKT). ERα deficiency, ovariectomy, or continuous administration of estradiol leads to altered production of interferon gamma (IFNγ) and IL-4 production [16]. In vivo administration of alpha-galactosylceramide (iNKT ligand) induces higher cytokine production in female than in the male mice. However, the effect was not observed in ovariectomized female mice, suggesting that the increase in cytokine expression is an effect of estradiol [17].

Androgen Receptors and cognate receptors for progesterone have also been detected in immune cells, implicating a direct effect of androgens on the development and function of immune system [18–20]. However, the underlying mechanisms are not well understood. Contrary to estrogens, androgen and progesterone are known to be anti-inflammatory. Testosterone reduces NK-cell activity and the secretion of pro-inflammatory cytokines by downregulating NF-κB signaling, but increases the production of anti-inflammatory cytokines. It is also known to suppress the expression of TLRs upon infection. Similar to testosterone, progesterone also inhibits NF-κB-mediated pro-inflammatory cytokines and increases anti-inflammatory signatures. During pregnancy, progesterone has been reported to skew the T cell responses toward Th2 response [6]. This could partly explain why pregnant women are more susceptible to infections such as *Listeria monocytogenes*, *Rubella virus,* and *Toxoplasma gondii*. Considering the differential immunoregulatory properties of sex steroid hormones, it is perceivable that hormonal changes during menstrual cycle, menopause, and pregnancy could greatly influence the immune responses.

Viral infections

Human immunodeficiency virus

In the context of Human immunodeficiency virus (HIV) infection, sex-based differences in the course of disease progression have been reported: women have lower plasma

viral loads, higher CD4+ T cell counts, and higher risk of progressing to AIDS than men [21–23]. Moreover, women are more prone to anti-retroviral drug-induced adverse effects. Therefore, it has been suggested to revise treatment recommendations for women and men [24, 25].

Persistent chronic inflammation in women contributes to immune pathology and impairment of the immune system. This could explain the faster disease progression observed in chronically infected women despite similar pace of viral replication compared to men. Meier et al. could demonstrate that women have higher TLR-7-mediated response of pDCs. This leads to elevated expression of interferon alpha (IFN-α) and IFN-Stimulated Genes (ISGs) resulting in stronger secondary activation of CD8+ T cells [26]. IFN-alpha is known for its antiviral and immunomodulatory function but it also can cause immunopathologies [27]. Therefore, in HIV-infected women, IFN-α could be beneficial through its antiviral activity, but in it might also have deleterious contributions to chronic immune activation associated with HIV disease progression.

Moreover, studies in rhesus macaques have also shown differential susceptibility to intravaginal SIV infection during luteal phase (high progesterone levels) compared to that of the follicular phase (high estrogen levels) [28]. However, understanding the underlying mechanisms involved in the regulation of immune responses by sex hormones during long-term HIV disease is crucial in order to develop individualized treatment concepts that take sex-specific host factors into account.

Hepatitis C

Numerous studies have demonstrated that women are more likely to spontaneously clear Hepatitis C Virus (HCV) during acute infection than males [29]. Moreover, the risk of cirrhosis is higher for men than women during chronical stage of HCV infection [30]. However, after menopause the sex differences in chronic HCV disease are attenuated. Di Martino et al. [31] observed that the accelerated rates of cirrhosis and fibrotic progression in postmenopausal female can be prevented through hormone substitution therapy. These differences in clinical outcomes during the acute and chronic phase of infection could in part be explained by the increased response of the TLR7/8 signaling pathway which in the context of HCV infection proves to be beneficial. However, further research is required to better understand the mechanisms behind the potential effect of female sex on HCV viral control [29].

Bacterial infections

In General, men are more susceptible to bacterial infections than women. Thus, sex determinants are considered to play a key role in immune response against bacterial infections such as *Mycobacterium* spp., *Listeria monocytogenes*, *Treponema pallidum*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Vibrio vulnificus*, *Borrelia burgdorferi,* and *Escherichia coli* [32, 33].

In 2012, the analysis of the tuberculosis notification data revealed a male-to-female ratio of 1.9:1 [34], which has been consistent with the data from earlier years [35, 36]. Behavioral and physiological reasons are being discussed as explanations. With regard to behavioral factors, smoking, alcohol consumption, and mine-related silicosis, especially in countries with high bacterial burden are correlated with male sex. To study the physiological sex differences, animal models have been used. One study demonstrated that fertile male mice were more susceptible to infection with *Mycobacterium marinum* and *Mycobacterium intracellulare*. Male mice exhibited severe disease pathology compared to castrated male mice [37]. Few studies have examined sex differences in humans. A study in patients of an American institution for mentally ill patients showed that only 8.1 % of castrated men died from tuberculosis compared to 20.6 % of intact males. Another study in young Swedish women who underwent oophorectomy due to salpingitis found that the tuberculosis mortality rate increased to 7 % compared to 0.7 % [38]. These differences are thought to be X-linked immune responses. In mouse models of *Mycobacterium* spp infections, the resistance offered by female mice has been attributed to better anti-bacterial activity of macrophages [39]. The susceptibility of male mice has been linked to decreased production of antibodies against lipoarabinomannan (lipid present in mycobacterial cell wall) [40].

Syphilis caused by *Treponema pallidum* also has been reported to show sexual dimorphism. The resistance shown by females has been correlated with increased CD4+ and CD8+ T-cells [41]. Similarly, it has been observed that females are more resistant to other bacterial infections such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Vibrio vulnificus*, *Borrelia burgdorferi*. Conversely, females are susceptible to *E. coli* bacteremia. This bias is perhaps due to *E. coli* associated urinary tract infection prevalent in women. Women are prone to Listeria infection. It has been reported that the susceptibility of mice to *Listeria* is linked to increased IL-10 secretion by female mice. Female non-obese diabetic mice have a higher incidence of developing type I diabetes. This increased incidence is linked to the difference in beneficial microbes colonizing the gut of male and female mice. This trend was reversed by male castration, meaning androgens influence gut microbiota [42]. Thus sexual dimorphism plays a key role in the resistance mechanisms against pathogens and maintaining a healthy microbiota in the gut. However, to date there are no studies which define a complete explanatory mechanism for the sexual dimorphism exhibited during infection.

Parasitic infections

Parasites are phylogenetically diverse and they target different tissues. The influence of female and male sex hormones on the immune responses toward different parasitic infections is pathogen specific [43]. In studies which analyzed the sex-based differences in immunity toward different parasitic infections, males were found to be more resistant to *Trichomonas vaginalis* [44] and *Toxoplasma gondii* [45], while females were more resistant to infections with *Leishmaniasis* [46, 47], *Trypanosoma cruzi* and *Trypanosoma brucei* [48], *Giardia lamblia*, and *Schistosoma mansoni* [49]. Animal models have been conducted to analyze the sex-related differences in parasitic infection. For instance, it was shown that testosterone influences the disease outcome of *Leishmania* infection by affecting antigen-presenting cells and T cells as well as rising an anti-inflammatory T-helper 2 (Th2) response. In comparison to females, male rodents present more lesions and higher parasite burdens. This observation was explained by an increased Th2 response including an augmented mRNA expression of interleukin 4 (IL-4), interleukin 10 (IL-10), transforming growth factor (TNF) β, and TNF-α [50, 51]. Moreover, the resistance of female hamsters toward *Leishmania mexicana* correlated with an increased expression of IFNγ [50]. Overall, using *Leishmania* as a parasitic model provides insights into how sex hormones can influence immunological mechanisms.

Conclusions

Males have a higher susceptibility to many infectious pathogens compared to women. This can in part be explained by stronger Th1 immune responses in women. However, in some infections, females are at a risk of developing intensified immunopathology due to higher levels of pro-inflammatory immune responses (e.g., HIV infection). Nevertheless, this simplification does not apply to all infectious conditions. Thus, as recognized by the National Institute of Health (NIH), the significance of including sex as a criteria in studies conducted with human subjects or on material of human origin is mandatory to improve a better understanding of the sex-related differences in immunity to infections (NIH Policy and guideline on the inclusion and minorities as subjects in Clinical Research, amended October, accessed January 2015, [52].

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