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Review

Probing the impact of sex steroids and menopause-related sex steroid deprivation on modulation of immune senescence

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ABSTRACT

Immune senescence denotes the general decline in immune system function, characterized by a reduced immune response and an increased inflammatory state. Menopause is a natural change in a women's life, the menopause-related low estrogen levels affecting many body functions, among them the immune system. Numerous human studies with menopausal women and animal models with surgically induced menopause show a clear impact of sex steroids in immune responses. Female superiority in vaccination response and predisposition to infections are eliminated after menopause, while during menopause inflammatory cytokines such as Tumor Necrosis Factor-α (TNF-α), Interleukins-1β, 6, 8 and 13 (IL-1β, IL-6, IL-8, IL-13) and Monocyte Chemoattractant Protein-1 (MCP-1) are increased, implying a molecular connection of sex steroid loss with immune senescence. Moreover, immune cells modify their number and function after the menopausal transition, this offering another explanation for immune senescence. Until now most of the existing studies have concluded that menopause plays an additional role to aging in immune senescence. While it is clear that we are as yet far from thoroughly understanding the molecular pathways connecting sex steroids and menopause with immune senescence, such knowledge is highly likely to enable future targeted interventions in treatment and prevention of age-related diseases in women.

Contents

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1. Introduction

Immunosenescence denotes the general decline with aging in immune system function, which comes about through changes in cellular and humoral immune response. It is characterized by a reduced immune response and an increased inflammatory state that results in the triggering or exacerbation of many disorders, such as Alzheimer's disease and atherosclerosis as well as cancer. Increased susceptibility to infectious diseases and decreased efficacy of vaccination are also common in the elderly, all these conditions inevitably resulting in greater morbidity and mortality.

Menopause is a natural change in a woman's life. It is characterized by the loss of reproductive ability due to the cessation of ovarian function, this last leading to termination of the ovarian production of estrogen and progesterone. Menopausal symptoms subsequently appear as well as numerous changes in body systems, among these the immune system, which is radically affected as it interacts intimately with sex steroids.

Over the past decade, there have been several studies demonstrating the significant beneficial impact of female sex hormones on the immune system in the setting of autoimmune diseases and infections [1,2], along with the fact that low estrogen levels mitigate the immune response and predispose to disease and infection [3]. Several studies suggest a contribution of ovarian sex steroid loss to immune senescence [4,5], since menopausal hormone therapy (MHT) is found to delay some of these changes [6,7]. What however remains unclear is the exact pathophysiological and molecular pathways accounting for the interaction between immune senescence due to aging on the one hand and sex steroids and sex steroid loss due to menopause on the other.

We have previously reported that inflammation is clearly associated with increased morbidity and mortality in mature and premature infants [8,9]. In addition, we have shown that markers of vascular inflammation, such as sCD40L and sP-selectin, are increased in early menopausal women compared with age-matched premenopausal women, thus demonstrating that increased vascular inflammation is due to menopause and not aging [10]. We therefore conclude that molecular pathways of the inflammatory cascade comprise highly promising targets for future therapies [11].

In this review we present some of the most recent data concerning the impact of sex steroids and menopause on the immune system, given that elucidation of their exact interaction holds promise of revealing possible targets for future treatment interventions.

2. The immune system

The role of the human immune system is to cope with challenges from outside pathogens and provide defense against infections. Moreover, it provides recognition of self and non-self antigens, evaluating microbial threats and coordinating their elimination. It is also vital in maximizing elimination of the damage to host tissues, which impedes the development of (auto-immune) diseases. This delicate balance, which is of great importance for human beings, is achieved via the two branches of the immune system: innate and adaptive immunity.

Innate immunity, which is a natural defense against diseases that are not specific for any pathogen, consists of anatomical, physiological, phagocytic and inflammatory barriers. The function of the innate immune response is mediated through neutrophils, Natural Killer cells (NK), macrophages and dentritic cells, which recognize microbial non-self pathogens through pattern recognition repeaters (PRRS), the best characterized family being the toll-like receptors (TLR). NK mediate the recognition of missing and altered self by expressing activation and inhibitory receptors. Macrophages and neutrophils mediate the elimination of pathogens through phagocytosis, their activation resulting in an inflammatory response via the production of Interleukin-6 (IL-6), interleukin-8 (IL-8) and interferon-α (IFN-α).

The second branch of the immune system is adaptive immunity, which is characterized by very high specificity and memory competence. It is composed of T and B lymphocytes that respond specifically to each pathogen. The contact of an antigen with the lymphoid system stimulates B lymphocytes that produce very large amounts of antibodies specific to that antigen. T lymphocytes are divided into CD4 and CD8 cells and recognize small peptides as antigens. Inflammatory molecules, such as IL-7 and IL-5, play a very important role in T-cell homeostasis.

3. Gender and the immune system

Over the last few years, a large number of studies have revealed that females are more prone to autoimmune diseases and infections. The reasons for this are as yet not fully understood, but it seems that sex steroids play a major role by affecting the immune response. More specifically, it was found that adult women respond to cytomegalovirus (CMV) infections with a higher production of IFN-γ and IL-2 production than men [12]. The same stronger humoral response was also found in Epstein Barr virus (EBV) infection [13] and the herpes simplex virus (HSV)-1 and 2 as compared with men [14].

In cases of infection with the human immune deficiency virus (HIV), women had statistically significant viral loads and higher CD4 lymphocyte counts compared with men [15], although another study on HIV infected women showed viral loads to be equivalent [16].

Other studies have shown that men suffer higher morbidity and mortality, compared to women, from bacterial infections [17]. The frequency and severity of septic shock is always lower in women [18], while male gender is regarded as a major risk factor for surgical trauma infections [19]. The same higher prevalence in men was also found for parasitic infection [20].

Apart from human studies, a large number of animal studies have demonstrated the same advantage among females. In a murine infection model, levels of pro-inflammatory cytokines TNF-α and IL-1β were significantly lower in females, causing a decreased recruitment and accumulation of macrophages [21]. In addition, female mice were seen to be better protected through the immune response from infection with picornavirus and vesicular stomatitis virus [22]. Male rats also experienced worse disease outcomes and higher mortality after LPS intravenous infection

[23] and mycobacterium infection [24], while the prevalence of sepsis was likewise found lower in females [25]. The above data all point to reduced levels of inflammatory cytokines being the primary cause. IL-6 and TNF-α in females are decreased during sepsis, whereas, by contrast, expression of IL-10 regulatory cytokine is increased [19]. Moreover, T-cell polarization seems to be different between the two genders, as female rats produce more Th1 cells and males more Th2 cell after parasitic infection [26].

The better immune response of females is also evidenced after vaccinations. Women reveal higher levels of immunoglobulins and seroconversion and lower rates of disease [27]. Of particular interest was a study on the influenza vaccine, where women received a half dose and developed equivalent antibodies with men who received the full dose [28].

4. Sex steroids and the immune system

The abovementioned differences between the two genders appear to stem from the actions of sex steroids, mainly estrogen and progesterone, with estrogen enhancing humoral immunity and progesterone functioning as an immunosuppressor.

It is of importance to note that the menstrual cycle is characterized by fluctuations in the levels of estrogen and progesterone. During the follicular phase, there is an increase in the production of 17-beta estradiol by the dominant follicle, whereas during the luteal phase there is an increase in progesterone production by the corpus luteum. A recent study revealed that these fluctuations in estrogen and progesterone levels influence IFN-γ production, proliferation of T lymphocytes, p-NF-κB expression in the PBMCs, SOD and catalase activity and NO production in the plasma.

Estrogen has two types of nuclear receptors, α and β, that are expressed at entirely different levels in immune cells. This significantly dissimilar expression seems to offer a very plausible explanation for the different modulation of immune cells by estrogen. ER-α is expressed on lymphocytes, macrophages, NK cells, monocytes and DC cells, among which the highest expression is found in CD4 T-cells, while B-cells express higher ER-β receptors. On the other hard, CD8 T-cells and monocytes express very low levels of both ER.

Progesterone, the other important sex steroid, does not have nuclear receptors, expressing only membrane bound receptors in CD8 T-cells and monocytes. Meanwhile, CD8 T-cells reveal increased expression of PR-α in the luteal phase.

The function of sex steroids has also been investigated in animal studies. Estrogens stimulate microglial cells after intravenous as well as intracerebral LPs injection [29]. Another study noted the need for estrogens for IFN-γ production and clearance of listeria infection [30]. In mouse, the presence of E2 involves a higher expression of CD40 and CD86 in DCs molecules and higher production of IFN-α [31].

In an another animal model, infection with the influenza A virus resulted in higher levels of IL-6, TNF-α and IFN-γ in females, while administration of high doses of estrogens reduced TNF-α levels and subsequently morbidity and mortality [32].

These interactions between estrogen and progesterone and the immune system account for the modification of the immune response during the menstrual cycle. In the follicular phase, a domain in the cellular phase, and especially the mid-follicular phase, has been detected which is characterized by the highest estrogen levels, this making it the best period for vaginal immunization. In the pre-ovuralatory period, there is reduced cytolitic activity of NK cells and in the luteal phase an increased humoral response. Finally, in the menstrual phase activity of NK is significantly suppressed [33].

5. Menopause and the immune system

Menopause is the permanent cessation of menses following the loss of ovarian follicular activity and subsequent hormonal deficiency. Women demonstrate a higher expression of IL-13 and IFN-γ after rhinovirus infections, compared to men of the same age. This difference ceases rapidly after the age of 50, implying that menopausal transition modifies immune function [34]. The same gender difference is found in antibody titers and seroconversion rates after vaccination for hepatitis and it is also no longer detected after the age of 60. Another study has demonstrated that after the age of 50 years, the incidence of herpes zoster is higher among females than in men [35].

Other human studies examining total lymphocyte number remain controversial, showing either a decreased number of lymphocytes [36] or no change [37]. On the other hand, advanced age is clearly related to a decreased percentage of naïve T-cells and accumulation of memory T-cells. This becomes even greater after the menopausal transition, when the naïve T-cells are still further reduced and, at the same time, activated and memory T-cells are elevated [37,38]. It is also reported that during menopause the ratio of CD4/CD8 T-cells is significantly decreased, probably due to CD4 reduction [5]. The loss of CD4 T-cells in menopause seems a very possible explanation for the loss of the better response to vaccination among women after menopause, as compared to men.

Similarly, there is a reduction in the total number of B-cells [36], this reduction having been attributed to decrease of B2 cells that are involved in the adaptive humoral immune response [39]. The latter could also be an explanation for the previously reported sex difference in antibody response after vaccination that is no longer evident after menopause. Another study in women with ovariectomy also confirmed the decreased levels of B-cells, and CD4/CD8 ratio along with a parallel increase in NK cells [40].

In a mouse model, a reduced response to the HSV vaccine after ovariectomy was observed [41]. The previously reported data on naïve CD4 T-cells have additionally been confirmed in animal models, along with increased terminally differentiated CD4 memory cells [42]. The same study also reported a reduced T and B response to vaccination and a reduction in T-cells and IFN-γ. Moreover, it was recently found that surgically induced menopause results in an increased production of inflammatory cytokines and oxidative damage [43].

Menopause is generally regarded as an inflammatory state characterized by increased expression of interleukins and other inflammatory cytokines. Aging is associated with increased levels of IL-6, but when comparing premenopausal with postmenopausal women, an even greater increase of IL-6 and IL-6 soluble receptor after menopause is found [44]. The same increase in IL-6, IL-1β and TNF-α was also noted in another study of menopausal women [45].

We have shown that increased indices of vascular inflammation in early menopausal women compared with age-matched premenopausal women may indicate a higher atherosclerotic risk [10]. Of note, increased severity of hot flushes, the most common menopausal symptom, was associated with adverse changes in vascular inflammation [10], this supporting the emerging role of estrogen loss in cardiovascular disease.

However, the effect of MHT remains controversial, as there are studies that report either decrease of cytokines after treatment [4] or no changes [46]. Possibly the route of administration of MHT (i.e. oral or parenteral) is an important factor accounting for the discrepancy in the reported effects of MHT on markers of inflammation.

Concerning IL-2, it was found increased in postmenopausal women [46], while IL-2 production was also elevated after LPS stimulation [47]. Similarly, increases in IL-4 were also observed after menopause [4,46].

Table 1
Inflammatory molecules after the menopause.

Interleukins: IL-1β, IL-6, IL-8, IL-13	Increased
Interleukins: IL-2, IL-4	Controversial data
Tumor Necrosis Factor-α (TNF-α)	Increased
Interferon-γ (IFN-γ)	Increased
Monocyte Chemoattractant Protein 1 (MCP-1)	Increased

IFN-γ is another factor that is significantly increased in menopause [46]. It seems, however, that estrogens have a dual impact on IFN-γ, as high levels inhibit and low levels stimulate IFN-γ production [48].

A recent study with detailed classification of the study group [49] showed that IL-8 levels were significantly higher in postmenopausal women. Moreover, MCP-1 (monocyte chemoattractant protein-1) was also higher, showing at the same time a positive correlation with FSH levels.

In another animal model with ovariectomized rats, LPS induction resulted in elevated IL-1β and TNF-α and IL-6 were elevated in the hypothalamus, while in serum the only increase was in IL-6 [50]. These data reveal a different inflammatory response at the central and peripheral levels, implying a possibly enhanced inflammatory cascade in the central nervous system as compared to peripheral blood and adipose tissue.

In Table 1 we summarize the data on the changes in inflammatory mediators during menopause. It should be mentioned that while there are abundant data on many molecules, the findings are still controversial as regards IL-2 and IL-4.

6. Conclusion

Menopause is a physiologic event in a woman's life, characterized by the loss of ovarian estrogen and progesterone production with subsequent pathophysiologic changes which affect, among other systems, the immune system. Until now, the exact mechanisms and molecular pathways connecting sex steroids levels and menopause with the function of the immune system have remained unclear. It is nevertheless certain that a fuller understanding of the pathophysiology of immune senescence will enable the pinpointing of targets for potential future therapies for autoimmune diseases, cancer and cardiovascular disease as well as for prevention of infection in menopausal women.

Contributors

Vrachnis N: conceived the idea, wrote the paper and revised the paper. Zygouris D: wrote the paper, literature search. Iliodromiti Z: wrote the paper, literature search. Daniilidis A: wrote the paper, literature search. Valsamakis G: conceived the idea, literature search. Kalantaridou S: literature search, revised the paper.

Competing interest

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