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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

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