Journal of Steroid Biochemistry & Molecular Biology 142 (2014) 171–175

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Review

The immune system in menopause: Pros and cons of hormone therapy☆

Mimi Ghosh[a,*], Marta Rodriguez-Garcia[b], Charles R. Wira[b]

[a] Department of Epidemiology and Biostatistics, The George Washington University, Washington, DC 20037, USA
[b] Department of Physiology and Neurobiology, Geisel School of Medicine at Dartmouth, Lebanon, NH 03756, USA

ARTICLE INFO

Article history:
Received 5 December 2012
Received in revised form 26 August 2013
Accepted 4 September 2013
Available online 13 September 2013

Keywords:
Female reproductive tract
Menopause
Menopausal hormone therapy
Estrogen
Progesterone
HIV
Immunity

ABSTRACT

With aging, a general decline in immune function is observed leading to immune-senescence. Several of these changes are gender specific affecting postmenopausal women. Menopause is a normal part of a woman's lifecycle and consists of a series of body changes that can last from one to ten years. It is known that loss of sex hormones due to aging results in a reduction of immune functions. However, there remains a major gap in our understanding regarding the loss of immune functions particularly in the female reproductive tract (FRT) following menopause and the role of menopausal hormone therapy (MHT) in protecting against immune senescence. The current review presents an overview of changes in the immune system due to aging, focusing on genital tract immunity in menopausal women and the risks and benefits of using MHT.

This article is part of a Special Issue entitled 'Menopause'.

Contents

1. Introduction

Immunologically, aging is characterized by a general dysregulation of immune responses culminating in a gradual immune senescence of all cells. Aging is gender specific and is marked by "menopause" in women. Menopausal symptoms are variable among women and can include hot flashes, night sweats, sleeplessness, mood changes, loss of energy, loss of libido, vaginal dryness, and urinary symptoms. Usage of menopausal hormone therapy (MHT), estrogens, progestogen, or a combination of the two, relieves some of these symptoms. Although quality of life improvement has been reported for MHT users versus placebo, serious side-effects, especially upon long-term use, remain a concern [1].

Although systemic side-effects of MHT have been studied, details on its effects on the aging immune system are less clear. Particularly little is known about effects on the immune environment of the female reproductive tract (FRT). This article will focus on the effects of menopause and hormone therapy on the immune system, particularly in the FRT. Other aspects of menopause and hormone therapy are discussed elsewhere in this issue.

☆ This work was supported by NIH grants AI51877 and AI071761 (awarded to Dr. Wira) and AI102837 (awarded to Dr. Ghosh).
* Corresponding author at: The George Washington University, Ross 232D, 2300 Eye Street, Washington, DC 20037, USA. Tel.: +1 2029945740.
E-mail address: mghosh@gwu.edu (M. Ghosh).

0960-0760/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jsbmb.2013.09.003

2. Immune system and aging

The hallmarks for immune senescence include (i) immune profile, characterized by decreased CD4+:CD8+ T cell ratio, increased numbers of differentiated memory and effector T cells, depletion of naïve T cells and decreased frequency of B cells; and (ii) Inflamm-Aging, characterized by an increased inflammatory state with increased levels of pro-inflammatory cytokines. In consequence, aging of the immune system results in an increased susceptibility to infections and decreased response to vaccination [2–5]. Aging has been shown to impair responses to viral infections including Human Immunodeficiency Virus (HIV), Herpes Simplex Virus (HSV), Cytomegalovirus (CMV), and Influenza through multiple mechanisms including the functional impairment of plasmacytoid dendritic cells, the major producer of type I interferons and the main defense against viral infections [2].

The *innate* immune system, which is the first line of defense against invading pathogens, is altered with aging. Natural killer (NK) cells, which play a significant role in protection against viral pathogens and tumors, actually increase in number with age. However, they show decreased cytotoxicity and decreased ability to produce cytokines [6,7]. Chemotaxis, a hallmark of immune response, is dysregulated in neutrophils, monocytes/macrophages and dendritic cells. Phagocytosis by macrophages and dendritic cells (DC) and super-oxide production by neutrophils and monocytes/macrophages are reduced as well. DC show reduced capacity to present antigen thereby disrupting the ability of the innate immune system to activate the adaptive immune system. In addition, recognition by and signaling through the major innate pattern recognition receptor (PRR) families, toll-like receptor (TLR), NOD-like receptors (NLR), is also dysregulated in the aged [8,9].

The *adaptive* immune system is also compromised with aging. Studies with octogenarians and nonagenarians (OCTO and NONA studies respectively [10,11] have associated aging and CD4+ and CD8+ T cells with impaired function and reduced ability to respond to pathogens [3]. Persistent viral infections, especially CMV, have been consistently detected in the aged and are considered to be biomarkers of immunosenescence [3]. B-cell function is also reduced in the elderly in that the ability to produce robust high affinity antibodies is impaired [3]. Age associated immune impairments result in predisposition to infections and poor vaccination responses [7,12–15] making them a high risk population and creating a need in the field to optimize therapeutics and vaccines specifically for the elderly.

3. Aging in women

Gender-specific decline in immune functions has been described. It is well-known that women are at a higher risk of developing autoimmune diseases, which indicates that certain disease conditions are mediated by sex hormones [16]. As multiple immune parameters are estrogen responsive, several patho-physiological conditions are altered by natural or induced changes in estrogen levels that vary with adolescence, menstrual cycle, pregnancy, menopause, as well as the use of corticosteroids, oral contraceptives (OC) and MHT. While this review, focuses primarily on the effects of estrogens on the immune system, it is important to recognize that progesterone, testosterone, and prolactin have all been implicated in affecting immunity in women [16].

An inflammatory state devoid of protective immune factors characterizes the immune microenvironment in menopausal women. Postmenopausal women show higher chronic levels of pro-inflammatory cytokines MCP-1, TNF-α, and IL-6 as well as a reduced ability to respond to pathogens or stimuli [16,17]. In addition to its role as a pro-inflammatory cytokine, IL-6 is also a key factor in bone reabsorption by osteoclast activation and also seems to be correlative with other diseases that have been associated with menopausal women such as diabetes, atherosclerosis and cardiovascular diseases [16]. CD4T and B lymphocytes and cytotoxic activity of NK cells are typically decreased in postmenopausal women [16]. As a result, attenuated immune response and higher susceptibility to pathogenic invasion and infection are more common in this group.

Kumru et al. [18] analyzed immune profile in blood from perimenopausal women who underwent total abdominal hysterectomy and bilateral salpingo-oopherectomy for uterine myoma (fibroids). One month after the surgery, an increase in CD8T cells and decrease in B cells, CD4:CD8T cell ratio and serum levels of IL-4 and IFN-γ were observed and, importantly, these effects were reversed by MHT. In a different study [19], blood analysis from postmenopausal women, relative to premenopausal women, showed decreased number of B cells and CD4T cells, increased CD8T cells and NK cells and generalized activation of the immune system. These immune alterations were also present in women with premature menopause included in the study, which showed reduction in total lymphocyte numbers and general immune activation compared to fertile women of the same age.

4. Effects of sex hormones on the immune system in the female reproductive tract

Sex hormones, estrogen (E_2) and progesterone are the master regulators of the immune system of the FRT. Estrogen exerts its biological effects via receptors estrogen receptor alpha (ER-α) and estrogen receptor beta (ER-β) which are differentially expressed in tissues and functionally distinct, often showing opposing effects [20]. Binding of estrogen to its receptors can regulate over 200 genes with distinct subsets affected by each receptor [21]. Most immune cells as well as epithelial cells and stromal cells throughout the FRT express estrogen and progesterone receptors and are responsive to sex hormones [22]. In addition to direct effects mediated through hormone receptors in immune cells, sex hormones act indirectly on immune cells through their actions on epithelial cells and stromal fibroblast secretion of growth factors [23]. For example, uterine epithelial cell proliferation and endometrial development is dependent on estradiol stimulation of underlying ERα-positive stromal cells to produce growth factors such as HGF and KGF [24,25]. Ochiel et al. demonstrated that conditioned media, containing TGF-β from uterine epithelial cells suppressed differentiation and responses to TLR agonists in immature dendritic cells and also inhibited HIV trans-infection by immature dendritic cells [26,27]. Recently, potentially protective effects of 17β-estradiol have been demonstrated when treatment of CD4+ T cells and macrophages with E_2 prior to HIV challenge reduced their susceptibility to HIV infection in a dose-dependent manner [28].

5. Effects of hormone deprivation on the innate immune system in the female reproductive tract

In contrast to age-related changes in systemic immune responses, age-related immune responses in FRT of postmenopausal women remain mostly unknown. Considering that several reports demonstrate a lack of correlation between peripheral blood and the mucosal tissue [29,30], characterization of local responses becomes necessary [30].

Studies have demonstrated that innate immune factors are compromised in the reproductive tract of postmenopausal women [31]. As multiple immune factors of the FRT are estrogen responsive, the absence of estrogen with aging results in loss of TLR function, secretory antimicrobial components, commensal lactobacilli,