Cellular Immunology 294 (2015) 102–110

Contents lists available at ScienceDirect

Cellular Immunology

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

Review

Sex, the aging immune system, and chronic disease

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ARTICLE INFO

Article history:
Received 2 January 2015
Accepted 3 February 2015
Available online 10 February 2015

Keywords:
Aging
Immune system
Sex hormones
Chronic inflammatory diseases
Type 2 diabetes
Atherosclerosis
Autoimmunity

ABSTRACT

The immune systems of men and women differ in significant ways, especially after puberty. In particular, females are generally more prone to autoimmunity, but experience lower rates of infections and chronic inflammatory disease. Sex hormones, genes encoded on the sex chromosomes, and gender-specific behaviors likely contribute to these differences. The aging process is associated with changes in the composition and function of the immune system and these changes may occur at an accelerated rate in men as compared to women. Moreover, after the age of menopause, the incidence of chronic inflammatory disease in women approaches or exceeds that observed in males. At the same time, the incidence of autoimmunity in post-menopausal women is decreased or equivalent to the rates observed in similarly-aged men. Additional studies addressing the influence of sex on the pathogenesis of chronic and autoimmune diseases in the aged are warranted.

1. Introduction

In general, prior to menopause, females are more prone to autoimmunity and adverse reactions to vaccines, while higher incidences of infections, type 2 diabetes and atherosclerosis are associated with the male gender. Sex hormones certainly influence the development and function of the immune system and some of the observed gender differences in disease risk are likely, to some extent, the result of these effects. In addition, genes encoded on the sex chromosomes and gender-specific behaviors and exposures likely also contribute. Advanced age is a risk factor for many of these sex-influenced diseases and aging-related changes in the immune system may partially account for this risk. Men and women experience the same types of aging-related changes to the immune system, but males experience them earlier or more dramatically than women. In addition, the relative risks that men and women experience for each type of disease changes throughout the aging process in interesting, and potentially informative ways. It is important that future studies specifically address sex-effects on the pathogenesis of chronic and autoimmune diseases in the aged so that potential differences can be identified and properly addressed therapeutically.

2. Immunologic differences between males and females prior to menopause

Males and females exhibit a number of immunologic differences prior to menopause that encompass both the innate and adaptive arms of the immune response. The number, differentiation state, and function of innate cells differ dramatically between the sexes in both rodents and humans; with innate cells isolated from females generally demonstrating a more intense response than cells isolated from males. For example, a larger number of macrophages are observed in the pleural and peritoneal cavities of female mice as compared to male mice, and female resident macrophages undergo phagocytosis more efficiently and express higher levels of Toll-like receptors-2, -3, and -4 [1]. In addition, female antigen presenting cells (APCs) appear generally more efficient at presenting antigen by expressing higher concentrations of MHC Class II and co-stimulatory molecules in some contexts [2,3]. Female-derived APCs secrete IL-12, but not IL-10, during non-specific T cell activation while male-derived APCs exhibit the opposite behavior [4]. IL-12 drives naïve T cells to differentiate into T helper type 1 effector cells, which secrete IFN-γ and enhance the functions of macrophages, CD8+ T cells, and B cells that secrete opsonizing antibodies [5]. IL-10 opposes Th1-associated cytokines, diminishes the antigen-presentation functions of macrophages, and enhances B cell survival and function [6]. Excitingly, a gene expression analysis study conducted after immunization with the yellow fever virus vaccine strain 17D demonstrated that women, but not men, up-regulate over 600 Toll-like receptor (TLR)-associ-

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http://dx.doi.org/10.1016/j.cellimm.2015.02.002
0008-8749/

ated genes that activate the interferon pathway, strengthening the hypothesis that female innate immune cells drive a more robust inflammatory response than male cells, at least in response to this viral vaccine [7].

In keeping with this idea, the female adaptive response is also generally more robust than that observed in males. This may be in part due to the stronger activation signals female APCs may provide in some environments, but studies have also demonstrated that the numbers and functions of lymphocytes differ between males and females. Females exhibit higher basal immunoglobulin levels, increased numbers of circulating and resident CD4+ T cells, and an increased CD4/CD8 T cell ratio as compared to males [1,8–11]. As observed in the innate immune response, gender-specific adaptive immunity is not simply a numbers game. Female lymphocytes also react more strongly to a variety of immune challenges than male lymphocytes. Antigen-specific antibody responses, cytotoxic T cell responses, and the levels of cytokines produced by differentiated CD4+ T cells isolated from females are often higher or are different than those produced in cells isolated from males [12–16].

3. Mechanisms potentially responsible for gender differences in the immune system

The mechanisms responsible for sex-specific differences in the immune response are complex and likely involve effects of the sex hormones on the immune system, genetic factors, and gender-specific behaviors and exposures. In addition, although this review focuses on the effects of estrogen and testosterone on the immune system, it is important to recognize that progesterone and prolactin have been implicated in affecting immunity as well [17].

3.1. Estrogens

Women are exposed to higher levels of estrogen until menopause, at which time estrogen concentrations in men can actually be greater than in women due to the age-associated increased aromatization of testosterone in men and the loss of gonadal estrogen in women (Fig. 1) [18]. During the childbearing years, between puberty and perimenopause, women experience cyclical elevations of estrogen during the follicular phase of the menstrual cycle. In the years prior to menopause, women experience perimenopause, which lasts on average for 4 years and involves erratic and at times dramatically increased levels of estrogen as compared to the levels of estrogen experienced during the childbearing years [19]. Menopause begins 1 year after the last menstrual cycle and is characterized by low levels of estrogen, which decline further after the 7th decade of life. The average age of menopause in the United States is 51 [20].

Estrogens bind three functionally-distinct receptors, comprised of either homo- or hetro-dimers of ERα and ERβ [21]. ERs can be found in T cells, B cells, dendritic cells, neutrophils, macrophages, NK cells, thymic stomal cells, and bone marrow [9,12,22,23]. Estrogen-bound ERs translocate to the nucleus to regulate the expression of genes with estrogen responsive elements (EREs) in their promoters or they may interact with other transcription factors, like NF-kB, to modulate the transcription of genes without ERE's [24]. In some cases, non-classical, membrane-associated ERs work to amplify signal transduction cascades after estrogen binding, as occurs in T cells during antigen-specific activation [22]. It is important to note that the effect of estrogens on target cells is biphasic, with enhancement of inflammation occurring at cyclical/low doses and inhibition at chronic/high concentrations as experienced during pregnancy [25–27]. A thorough review of the effect of estrogens on the innate immune response is available elsewhere in this issue, so this review will focus on the effects of estrogens on the adaptive response.

Estrogens influence the development of both T and B cells. In particular, exposure to estrogens results in IL-7 down-regulation by bone marrow stromal cells and diminishes the numbers of double-positive (CD4+CD8+) thymic T cells [21,28]. High estrogen levels (either administered exogenously or experienced during pregnancy) induce transient thymic atrophy in female mice [29,30]. At the same time, estrogens appear to promote extra-medullary hematopoiesis and T cell lymphopoiesis in the liver; both of which may contribute to increased escape from negative selection in B cells and T cells, respectively, thus increasing the risk of autoimmunity [21,31]. Estrogen exposure may further increase the risk of autoimmunity by positively affecting the survival of auto-reactive B and T cells [21,32]. On the other hand, exposure to estrogens may promote enhanced T cell receptor diversity [33]. Thus, estrogen alters lymphocyte development in ways that may enhance the repertoire, but also increases the risk of autoimmunity.

Beyond developmental impacts, estrogens also influence T and B cell function during antigen-specific activation events. Estrogens increase B cell production of antigen-specific antibodies in response to infection, vaccines, and autoantigens [34,35]. In addition, long-term exposure to high doses of exogenous estradiol enhances polyclonal B cell activation in mice and can enhance non-specific differentiation of human immunoglobulin-secreting cells (ISCs) *in vitro*, perhaps by stimulating CD8+ T cells to secrete IFN-γ [36–40]. Estrogens also appear to upregulate CD8+ T cell-derived help to B cells via reverse signaling through FasL on activated CD8+ T cells [37]. Low concentrations of estrogen tend to promote Th1 cell proliferation and IFN-γ production; while high concentrations increase Th2 cell production of IL-4 and enhance regulatory T cell function [21]. Thus a pattern emerges in which low concentrations of estrogens appear to strengthen antibody secretion and are relatively inflammatory, while higher concentrations may have more anti-inflammatory effects.

3.2. Androgens

Most men do not clinically experience effects related to low androgen concentrations the same way that women experience the dramatic, menopause-associated reduction in estrogens. Instead, aging-related reductions of androgens are much more gradual, diminishing at rate of 1% per year after the age of 30 years [41,42]. Aging-related increases in sex hormone binding globulin (SHBG) and body mass index (BMI) further reduce the bioavailability of testosterone in older men [42]. In fact, increasing BMI has a much more dramatic effect on testosterone levels than aging [42]. Still, most aged men maintain testosterone concentrations within the normal range and many men do not experience clinical symptoms associated with low testosterone levels [42]. Women experience relatively lower concentrations of testosterone after puberty than men and testosterone concentrations further decline after menopause. However in women, testosterone levels gradually return to pre-menopausal levels 20–30 years after menopause [43] (Fig. 1). Thus, as men and women approach the end of the lifespan, differences in testosterone concentrations between the two sexes are less dramatic, but still present.

The effects of androgens are mediated through classical intracellular androgen receptors (AR) and more recently discovered membrane-bound ARs [44]. Peripheral T and B cells, thymocytes, bone marrow stromal cells, thymic epithelial cells, macrophages, monocytes, dendritic cells, and mast cells express intracellular androgen receptors and peripheral T cells and circulating monocytes also express membrane-bound ARs [45–48]. In general,