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Modulation of Immune Senescence by Menopause and Hormone Therapy

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1. Introduction

The immune system must overcome daily challenges from pathogens to protect the body from infection. The success of the immune response to infection relies on the ability to sense and evaluate microbial threats and coordinate their elimination - all the while limiting damage to host tissues. This delicate balance is achieved through coordinated action of innate and adaptive arms of the immune system. The main distinguishing characteristic of these two branches of the immune response is the way they recognize antigens. Whereas innate immunity relies on germline-encoded receptors to sense the presence of pathogens, adaptive immunity employs a highly diverse set of receptors generated through somatic mutation and recombination that are tailored to specific pathogens. The second major defining characteristic of the adaptive immune system is the development of immunological memory that manifests with increased functionality and frequency of responding cells upon re-exposure to the same antigen.

Several immune cell subsets play a critical role in mediating innate immune responses. These include neutrophils, natural killer (NK) cells, dendritic cells (DC), and macrophages. These cells are alerted to the presence of pathogens via recognition of microbial non-self, missing self, or altered self (Medzhitov and Janeway 2002). Recognition of microbial entities relies on the detection of conserved molecular patterns referred to as pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs) of the innate immune system. The three best-characterized families of PRRs are the toll-like receptors (TLR), the NOD-Like Receptors (NLR) and the retinoic acid-inducible gene (RIG-I)-like RNA helicases (RLHs). Following PAMP encounter, these receptors initiate signaling cascades that drive production of several anti-microbial molecules that ultimately limit pathogen replication and spread. Furthermore innate immune cells activate the adaptive arm of the immune system through the action of soluble mediators and antigen processing and presentation (Kabelitz and Medzhitov 2007; Medzhitov 2007).

DCs can be divided into myeloid (mDC) also known as conventional DCs and plasmacytoid DCs (pDCs) (Sallusto and Lanzavecchia 1994; Olweus, BitMansour et al.

1997). Myeloid DCs detect pathogens via TLR-3, -4, -7, and -8 and respond to infection by upregulating surface expression of CD40 and CD86 and producing IL-12 (Ketloy, Engering et al. 2008). Their main function is to process and present pathogen-derived peptides to naïve T cells (Siegal, Kadowaki et al. 1999). On the other hand, pDCs recognize viral DNA and RNA via TLR-7 and TLR-9 and produce vast amounts of type I interferons, which are potent antiviral cytokines, such as interferon α (IFNα) in response to viral infection (Cella, Jarrossay et al. 1999; Teleshova, Kenney et al. 2004; Chung, Amrute et al. 2005; Ketloy, Engering et al. 2008).

NK cells mediate the recognition of missing and altered self through the expression of inhibitory and activation receptors (Christopher E. Andoniou 2008). These receptors are member of either the immunoglobulin-like superfamily (IgSF) or the C-type lectin-like receptor (CTLR) superfamily (Radaev and Sun 2003). Recognition of MHC class I molecules is mediated by killer inhibitory receptors (KIR) such as CD94/NKG2 heterodimers/complexes, which deliver an inhibitory signal to NK cells (Biron, Nguyen et al. 1999; Biassoni 2008). Some viruses down-regulate MHC class I molecules to evade detection by CD8 T cells (discussed later). However, NK cells that do not receive a signal through inhibitory receptors receive an activation signal and can eliminate the infected cells (Biassoni 2008). Cell damage and some additional viral infections can also result in the upregulation of stress-induced molecules such as MIC-A, MIC-B, and ULBPs (Radaev and Sun 2003). These altered self-molecules function as ligands for NK cell activating receptors such as NKG2D (Radaev and Sun 2003; Biassoni 2008). NK cells can be subdivided based on the expression of CD16 (Lanier 2008). The majority of blood and spleen resident NK cells are $CD16^{pos}$ (85-90%); they are highly cytotoxic and secrete moderate amounts of inflammatory cytokines (Werner Held 2008). The $CD16^{neg}$ NK cells cannot kill target cells but they secrete large amounts of inflammatory cytokines.

Neutrophils and macrophages play a critical role in the elimination of pathogens via phagocytosis. Neutrophils are short-lived cells that are recruited by a chemotactic gradient into infected/inflamed tissues where they then phagocytose bacteria (Svanborg, Godaly et al. 1999). Neutrophils can also kill bacteria by respiratory burst, the release of reactive oxygen species (Dahlgren and Karlsson 1999), or the release of antimicrobials (Medzhitov 2003). Neutrophils are required for the clearance of bacteria from mucosal sites (Svanborg, Godaly et al. 1999). Macrophages also play a critical role in elimination of pathogens via phagocytosis, pinocytosis, or receptor-mediated endocytosis (Aderem and Underhill 1999). As described for DCs, macrophages express several PRRs, notably TLR 4 (Aderem and Underhill 1999). Activation of PRRs on macrophages activates the release of intracellular antimicrobial molecules (Linehan, Martinez-Pomares et al. 2000) as well as inflammatory cytokines such as IL-6, IL-8, and TNFα (Larsson, Larsson et al. 1999; Beutler 2000). Like DCs, macrophages can also stimulate lymphocytes and initiate the development of the adaptive immune response (Beutler 2000).

The adaptive immune branch is composed of B and T lymphocytes, which unlike cells of the innate immune system can generate a response tailored specifically to each pathogen. This specificity is acquired through the expression of diverse, clonally distributed antigen receptors on T and B cells. The initial diversity is produced in primary lymphoid organs (the thymus in the case of T cells and the bone marrow in the case of B cells) through a series of gene recombination events; further diversification occurs by somatic hypermutation of the B-cell receptor (BCR, antibody) and by functional diversification of effector T cells.

T cells are broadly divided into αβ CD4 and CD8 T cells (90%) as well as γδ T cells (10%). T cells recognize antigens in the form of small peptides bound to major histocompatibility (MHC) class I or class II molecules. CD8 T cells, commonly known as cytotoxic T cells, recognize foreign peptide bound to MHC-I molecules and have evolved to monitor for and eliminate tumor cells and cells harboring intracellular pathogens. CD4 T cells, or helper T cells, recognize foreign peptides bound to MHC-II and secrete a broad range of cytokines, which play a crucial role in the maturation of the B cell response as well as the development and establishment of the CD8 T cell response. Once activated, CD4 T cells can differentiate into four major lineages, Th1, Th2, Th17, and regulatory (Treg) cells. These subsets can be distinguished by their unique cytokine production profiles and their functions: Th1 cells predominantly produce IFNγ and mediate responses to intracellular viral and bacterial pathogens; Th2 cells produce IL-4, IL-5, IL-9, IL-13, and IL-25 and are critical for expelling extracellular parasites such as helminths; Th17 cells are responsible for controlling extracellular bacteria and fungi through their production of IL-17a, IL-17f, and IL-22; Treg cells are important in maintaining immune tolerance, as well as in regulating lymphocyte homeostasis, activation and function and produce regulatory cytokines TGFβ and IL-10 (Zhu and Paul 2010).

The maintenance of a structurally and functionally diverse T cell repertoire is a dynamic process governed by thymic output and the exposure to antigen and cytokines, which modulate T cell survival, proliferation and death. A rigorous analysis developed over several years has demonstrated that human CD4 and CD8 T cells can be subdivided into naïve, central memory (CM) and effector memory (EM) in addition to several transitional subsets (Lanzavecchia and Sallusto 2005). Studies have identified IL-7 and IL-15 as key players in T cell homeostasis (Surh and Sprent 2008). IL-7 and MHC contact are critical for the survival of naïve T cells (Jared F. Purton 2007). These signals do not induce differentiation but rather a low level of homeostatic proliferation and promote the survival of these cells. Memory T cells on the other hand, do not require MHC contact for survival (Boyman, Purton et al. 2007), but do require both IL-7 and IL-15 (Purton, Tan et al. 2007).

Upon antigen encounter, naïve antigen-specific B cells quickly differentiate into short-lived plasma cells that can immediately produce antibodies while others travel to germinal centers to undergo the longer process of becoming memory cells and long-lived plasma cells (Tangye and Tarlinton 2009). B cells within the germinal centers undergo vigorous proliferation, isotype class switching (from IgM to IgG, IgA or IgE) and somatic hypermutation thereby differentiating into memory and plasma cells that produce high affinity antibodies (Tarlinton 1998). Naïve B cells express IgM and IgD and are induced to class switch by T cell produced cytokines (Chaplin 2010). For example, IL-10 and possibly IFN-γ induces switching to IgG, while IL-4 and IL-13 induce switching to IgE, and TGF-β to IgA (Chaplin 2010). Different antibody classes target different pathogens as a result of the activation of different T_H types. IgA are produced in response to infection of mucosal surfaces (Tiwari, Agrawal et al. 2010), IgE are important for allergic responses (Johansson) and IgG are critical for the anti-viral immune response. Long lived plasma cells continue to secrete antibodies well after antigen clearance while memory B can rapidly proliferate and differentiate into plasma cells upon antigen re-exposure (Tangye and Tarlinton 2009). B cells are also capable of T cell independent activation by polymeric antigens with a repeating structure such as LPS. However somatic mutation does not usually occur in this process and immune response tends to be weak (Chaplin 2010).

2. Gender and the immune response to infection/vaccination

The incidence and severity of several viral diseases is higher in men than women (Klein 2010). For instance, coxsackie virus associated myocarditis occurs more often in men than women (Woodruff 1980). These gender differences were recapitulated by a murine infection model, where pro-inflammatory cytokines TNFα and IL-1β are induced more strongly in male mice, resulting in the increased recruitment and accumulation of macrophages in the heart and the subsequent development of myocarditis (Huber and Pfaeffle 1994; Huber, Kupperman et al. 1999; Huber 2005). Adult women also generate a more robust cell mediated response following cytomegalovirus (CMV) infection with higher IFNγ and IL-2 production (Villacres, Longmate et al. 2004), a stronger humoral response to Epstein Barr virus (EBV) (Wagner, Hornef et al. 1994), and a better immune response to herpes simplex virus (HSV)-1 and 2 than men (Han, Lundberg et al. 2001). During human immune deficiency virus (HIV) infection pre-menopausal women have higher CD4 lymphocyte counts throughout infection and lower viral loads early during infection than men (van Benthem, Vernazza et al. 2002). Moreover, HIV+ women have higher levels of CD8+ T cell activation than men with equivalent viral loads (Meier, Chang et al. 2009). Similarly, female mice generate more robust immune responses and are better protected following infection with vesicular stomatitis virus and picornavirus (Curiel, Miller et al. 1993; Barna, Komatsu et al. 1996)

It is now well recognized that men experience greater morbidity and mortality due to bacterial infection and sepsis after trauma than women (reviewed by Marriott et al. (Marriott and Huet-Hudson 2006)). Moreover, more men develop severe septic shock than women (Schroder, Kahlke et al. 1998; Schroder, Kahlke et al. 2000; Wichmann, Inthorn et al. 2000). Similarly, male gender is a risk factor for major infections after surgery (Offner, Moore et al. 1999). The notion that males are more vulnerable to bacterial infections than females is supported by animal studies. *Mycobacterium marinum* infection in male mice results in higher bacterial burden and worse disease outcome than females (Yamamoto, Saito et al. 1991). Male rats also experience higher mortality than females following intravenous injection of LPS (Merkel, Alexander et al. 2001). Similar findings were reported in mice models of sepsis (Zellweger, Wichmann et al. 1997; Diodato, Knoferl et al. 2001). This gender difference in survival is most likely mediated by a difference in cytokine production. Whereas male patients produced higher levels of the inflammatory cytokines TNFα and IL-6 during sepsis, females produced higher levels of the regulatory cytokine IL-10 (Schroder, Kahlke et al. 1998; Offner, Moore et al. 1999).

Parasitic infections also show a strong sex bias with higher prevalence of infection and disease severity in men compared to women (Klein 2004). This increased resistance seems to be mediated by a gender difference in T cell polorization. Female mice generate a Th1 response following infection with *Plasmodium brasiliensis* whereas males produce a Th2 response (Pinzan, Ruas et al. 2010). Moreover, when castrated male mice are treated with 17ß estradiol (E2), their spleen cells produced higher levels of IFNγ and lower levels of IL-10 following stimulation with *P. brasiliensis* compared to control males (Pinzan, Ruas et al. 2010). Similarly, ovariectomized (OVX) mice treated with E2 produced higher levels of IFNγ and IL-10 (associated with a protective response) as well as higher antibody responses after *Plasmodium chabaudi* infection compared to OVX mice treated with placebo (Klein, Easterbrook et al. 2008). OVX mice receiving E2 also experienced less weight and hematocrit loss, as well as less hypothermia following malaria infection than OVX mice receiving placebo (Klein, Easterbrook et al. 2008). Finally, E2 treatment induces resistance to *Toxoplasma gondii* infection in both

female and male mice (Klein 2004). These data are consistent with the hypothesis that estrogen promotes a protective Th1 response following parasitic infections.

As described for infections, women also generate a more robust response to most vaccines as evidenced by higher rates of seroconversion and lower rates of disease after vaccination than men (Cook 2008; Klein, Jedlicka et al. 2010) as well as higher plasma levels of immunoglobulins than men (Ansar Ahmed, Penhale et al. 1985). In an influenza vaccine trial, participants aged 18-49 were given either a full or half dose of vaccine. Women who received a half dose developed an equivalent antibody response as men who received the full dose of vaccine (Engler, Nelson et al. 2008). Similarly, vaccines against HSV-2 also show sex differences in immunogenicity and efficacy. Early vaccine formulations showed some protection in women (26%) and no protection in men (4%) (Corey, Langenberg et al. 1999). More recent subunit vaccines expressing glycoprotein D resulted in 73 to 74% protection in HSV negative women while protection in men remained negligible (11%) (Stanberry, Spruance et al. 2002; Bernstein, Aoki et al. 2005).

2.1 Mechanisms of action of female sex hormomes

The mechanisms by which ovarian steroids modulate the immune response are beginning to emerge. Several lines of evidence suggest that E2 enhances the immune response whereas progesterone dampens it. For instance, prolonged exposure to progesterone in the form of the contraceptive Depo-Provera (Depo) increases susceptibility of female mice to HSV-2 genital infection (Gillgrass, Ashkar et al. 2003) and of female nonhuman primates to *Chlamydia trachomatis* (Kaushic, Murdin et al. 1998), SIV (Marx, Spira et al. 1996) and SHIV (Trunova, Tsai et al. 2006). Clinical studies also found associations between Depo use and increased chlamydia, HSV-2, HIV and HPV incidence in adult women (Marx, Spira et al. 1996; Baeten, Nyange et al. 2001; Brabin 2002; Morrison, Richardson et al. 2007). In contrast to Depo treatment, E2 administration to ovariectomized (OVX) female mice protected them from HSV-2 infection (Gillgrass, Fernandez et al. 2005). Similarly, female rhesus macaques treated with estrogen were protected from SIV transmission (Smith, Baskin et al. 2000). Interestingly, vaccination studies in humans indicate that vaginal immunizations might be more effective for induction of genital tract antibodies if performed during the mid-follicular phase of the menstrual cycle when estrogen levels are highest (Kozlowski, Williams et al. 2002).

Estrogen and progesterone can directly modulate T and B cell function or indirectly impact their function by modifying the function of innate immune cells such as DCs, or a combination of both. There are two types of nuclear estrogen receptors (ER): α and β, which form homo and heterodimers (Kovats and Agrawal 2010). The expression of ERα has been reported on lymphocytes, DCs, macrophages, monocytes, NK cells, and mast cells (Suenaga, Evans et al. 1998; Komi and Lassila 2000; Curran, Berghaus et al. 2001; Grimaldi, Cleary et al. 2002; Mor, Sapi et al. 2003; Paharkova-Vatchkova, Maldonado et al. 2004; Phiel, Henderson et al. 2005; Harkonen and Vaananen 2006). The level of expression differs between immune cell types. For instance, CD4 T cells express higher amounts of ERα than ERβ while the inverse expression profile is observed in B cells (Phiel, Henderson et al. 2005). CD8 T cells and monocytes express only low amounts of both receptor types (Phiel, Henderson et al. 2005). This difference in ER expression levels is likely to result in differential modulation of the of these immune cells by estradiol.

Progesterone receptors (PR) are not as ubiquitous as ERs and no nuclear PR have been detected in peripheral blood mononuclear cells (PBMC) (Kovats and Agrawal 2010). T cells

do however express membrane bound progesterone receptors α and β (Dosiou, Hamilton et al. 2008). The expression of PRα is also upregulated on CD8+ T cells during the luteal phase of the menstrual cycle (Dosiou, Hamilton et al. 2008). Adding to the complexity of the effects of sex steroids, PR are primarily induced by estrogen via ER, thus creating an intricate interaction between these two hormones (Kovats and Agrawal 2010). NK cells and monocytes are the only other immune cell types known to express PRs (Kovats and Agrawal 2010). Both ER and PR function as transcription factors by binding to estrogen and progesterone responsive elements upon ligation or by binding to other transcription factors (Kovats and Agrawal 2010).

Estrogen treatment of B cells increases the expression of the anti-apoptotic molecule Bcl-2 thereby potentially increasing the resistance of auto-reactive B cells to apoptosis (Evans, MacLaughlin et al. 1997; Verthelyi and Ahmed 1998; Rider, Jones et al. 2001). Estrogen also enhances B cell activation (Paavonen, Andersson et al. 1981), IgG production (Kanda and Tamaki 1999), and upregulates activation-induced deaminase (AID), thereby enhancing somatic hypermutation frequency and class-switch recombination, resulting in greater antibody affinity-maturation (Karpuzoglu and Zouali 2011). In vitro studies examining the effect of E2 on T cell proliferation and cytokine production have often yielded contradictory results when using PBMC (Bouman, Heineman et al. 2005) although some observations do suggest a potential bias towards Th2, Th17 (Polanczyk, Hopke et al. 2006) and Treg polarization in E2 treated T cell cultures (Khan, Dai et al. 2010).

Several studies have demonstrated the modulation of innate immunity by estrogen. E2 regulates TLR2 expression on lipopolysaccharide (LPS) stimulated microglial cells *in vivo* after both intracerebral and systemic LPS injection (Soucy, Boivin et al. 2005). A recent study showed that presence of estrogen related receptor ERRα on macrophages was required for IFNγ production and efficient clearance of *Listeria monocytogenes* (Sonoda, Laganiere et al. 2007). Moreover, E2 administration significantly increases mRNA for the inflammatory cytokines IL-1β, IL-6, and TNFα as well as inducible NO synthase in thioglycate-elicited macrophages from OVX mice(Calippe, Douin-Echinard et al. 2010). This mechanism was ERα dependant (Calippe, Douin-Echinard et al. 2010). Human dendritic cells matured in the presence of E2 and TNFα, but not TNFα alone, promote the differentiation of naïve CD4 T cells into Th2 cells (Uemura, Liu et al. 2008). However, E2 treatment may limit the capacity of mature DC to stimulate T cell proliferation (Segerer, Muller et al. 2009). Mouse pDCs stimulated with CpG in the presence of E2 have higher expression of the co-stimulatory molecules CD40 and CD86 as well as higher IFN-α production (Li, Xu et al. 2009). When co-cultured with B cells, these E2 treated pDCs increase B cell viability, but as described for T cells above, not proliferative capacity (Li, Xu et al. 2009). Similarly, in vitro stimulation of PBMC with HIV-1 antigens which stimulate pDC via binding to TLR-7 resulted in higher IFNα production by women than by men (Meier, Chang et al. 2009). In contrast to these data, progesterone treatment reduces the ability of dendritic cells to take up antigenic peptides, stimulate T cell responses (Butts, Shukair et al. 2007), and secrete the potent antiviral cytokine IFNα (Hughes, Thomas et al. 2008).

3. Immune senescence

Increasing age results in a gradual erosion of immune function that is commonly referred as "immune senescence" (Larbi, Franceschi et al. 2008). This age-related loss of immune fitness is believed to result in greater morbidity and mortality from infection in this age group.

Immuno-senescent changes have been described for both innate and adaptive immunity. Specifically, circulating monocyte numbers are increased in the elderly, although circulating neutrophil numbers remain unaltered (Chatta, Andrews et al. 1993; Born, Uthgenannt et al. 1995; Lord, Butcher et al. 2001; Della Bella, Bierti et al. 2007). This may reflect the skewing of bone marrow hematopoietic stem cell (HSC) progenitors in the elderly towards the myeloid lineage (Beerman, Bhattacharya et al. 2010). Nonetheless, age-related decreases in circulating mDC numbers have been reported (Della Bella, Bierti et al. 2007). In addition, aged myeloid cells exhibit hyporesponsiveness to several innate stimuli, which may reflect reduced expression of PRR and their downstream signaling mediators, or increased negative regulation of these pathways (Dunston and Griffiths 2010; Shaw, Joshi et al. 2010). Furthermore, innate immune function may be compromised by diminished phagocytic activity in the elderly (Wenisch, Patruta et al. 2000; Lloberas and Celada 2002), compounded by reduced superoxide production and intracellular killing ability in the case of Gram-positive bacteria (Lord, Butcher et al. 2001). Some reports have suggested that although NK cell numbers are conserved with age (Tarazona 2009), there is a decrease in proliferation and cytokine production (Mocchegiani and Malavolta 2004; Murasko and Jiang 2005; Zhang, Wallace et al. 2007). Changes in NK cytotoxicity with age are somewhat controversial with some studies showing a decrease while others show no change (Tarazona 2009). Preserved NK cytotoxicity is associated with lower infection and mortality rates and better vaccine response in the elderly (Ogata, Yokose et al. 1997; Mysliwska, Trzonkowski et al. 2004). Moreover, aging is associated with an increase in $CD56^{dim}$ NK cells which are cytotoxic and a decrease in $CD56^{bright}$ cells which are immuno-regulatory (Borrego, Alonso et al. 1999). Age-related changes in frequency and function of innate immune cells impact the protective immune response by decreasing anti-bacterial function as well as by impacting antigen presentation and the generation of adaptive immunity in the elderly.

Although, it is clear that aging affects innate immune function, accumulating evidence indicate that the adaptive arm of the immune system, and more specifically in the T cell compartment, exhibits more profound and consistent changes than the innate arm (Pawelec, Larbi et al. 2009). The hallmarks of T cell senescence include: 1) loss of naïve T cells and accumulation of memory T cells; 2) reduced CD4:CD8 T cell ratio; 3) increased T cell production of inflammatory cytokines; and 4) reduced T cell proliferative ability. Several phenomena are believed to contribute to these changes. Decreased production of hematopoietic stem cells in the bone marrow leads to decreased migration of early T cell progenitors to the thymus, which in turn leads to thymic atrophy and a decline in naïve T cell production (Chen 2004). Other factors that contribute to naïve T cell loss include accelerated conversion of naïve T cells into memory T cells due to increased turnover (Naylor, Li et al. 2005), and a life-long exposure to chronic/persistent viruses, notably CMV (Pawelec, Derhovanessian et al. 2009). The loss of naïve T cells is accompanied by a concomitant increase in memory T cell number/frequency, especially terminally differentiated T cells. These cells preferentially accumulate within the CD8 T cell subset where they can reach significant proportions in the aged (Vallejo 2005; Sansoni, Vescovini et al. 2008) and can often be oligoclonal (expressing a single T cell receptor) (Schwab, Szabo et al. 1997). These T cell clonal expansions (TCE) are often CMV-specific and may play a role in controlling CMV viral burden (Derhovanessian, Larbi et al. 2009), but high frequencies of terminally differentiated T cells have also been associated with the poor responses to influenza vaccines (Saurwein-Teissl, Lung et al. 2002; Trzonkowski, Mysliwska et al. 2003) and increased inflammation (Vallejo, Weyand et al. 2004).

Both quantitative and qualitative changes in the B cell compartment have been reported with age. The frequency of B cells decreases with age (Huppert, Solomou et al. 1998; Colonna-Romano, Bulati et al. 2003). More importantly, there is a consistent reduction in the antibody response to infection and vaccination. For instance, 25% of persons over the age of 65 fail to develop a neutralizing antibody response following influenza vaccination, whereas 90% of adults aged 25 to 45 successfully do so (Beyer, Palache et al. 1989). This decline was also reported in response to other vaccines such as hepatitis B (Cook, Gualde et al. 1987) and A (D'Acremont, Herzog et al. 2006; Genton, D'Acremont et al. 2006). It was initially proposed that reduced B cell function is due to diminished CD4 T cell help. However, accumulating evidence points to the fact that there are intrinsic defects within the B cell compartment independent of the CD4 helper function. One of the possible intrinsic B cell deficiencies is that isotype class switching and/affinity maturation is compromised in the elderly (Aydar, Balogh et al. 2004; Frasca, Riley et al. 2004; Cancro, Hao et al. 2009). Another contributing factor to the decreased B cell response in the elderly is the reduction in the B cell repertoire. As described for T cells, B cell clonal expansions are detected with greater frequency in the elderly and could potentially interfere in the development of a protective immune response by constricting the proliferative burst, establishment of new memory B cell population or reducing naïve B cell output (LeMaoult, Delassus et al. 1997; LeMaoult, Szabo et al. 1997; LeMaoult, Manavalan et al. 1999; Weksler and Szabo 2000; Szabo, Li et al. 2004).

Last but not least, immune senescence is associated with the upregulation of circulating pro-inflammatory cytokines, notably IL-6 and TNFα and to a lesser extent IL-1β (De Martinis, Franceschi et al. 2005; Wikby, Nilsson et al. 2006). Increased production of chemokines such as RANTES, MIP-1a,α IL-8 and MCP-1 was also reported (Gerli, Monti et al. 2000; Pulsatelli, Meliconi et al. 2000; Mariani, Pulsatelli et al. 2002). This chronic inflammatory state has been correlated with overall mortality rate and is believed to significantly contribute to the development of age-related diseases such as Alzheimer's, atherosclerosis, sarcopenia, diabetes, rheumatoid arthritis and certain types of cancer (Vasto, Candore et al. 2007).

4. Menopause and hormone therapy regimens

In women, aging is accompanied by a dramatic loss in ovarian function and subsequent menopause around the age of 51. Thus, with the average life span of ~80 years, women can expect to spend a significant portion of their lives in a post-menopausal state (Hall 2004). The endocrine changes associated with entry into menopause appear to be driven by the age-related depletion of follicular reserve, which leads to a failure to produce the hormonal support necessary to maintain levels of inhibin B. The decrease in inhibin B production results in deregulated production of follicular stimulating hormone (FSH), which in turn results in altered estrogen production and eventually a decrease in the levels of circulating estrogen (Wu, Zelinski et al. 2005; Burger, Hale et al. 2008). This diminished responsiveness results in a cycle that culminates in menopause.

Menopause not only affects women's fertility, but also exacerbates several age-related diseases such as osteoporosis, cardiovascular disease, loss of cognitive abilities and the incidence of some cancers (Prior 1998; Grady 2006). Interestingly, some of these diseases, notably osteoporosis and atherosclerosis correlate with increased inflammatory cytokine production (Ginaldi, Di Benedetto et al. 2005), thereby establishing a complex interaction between immune senescence and menopause. However, few studies have investigated the impact of menopause and hormone therapy on immune senescence.

There are three basic forms of hormone replacement therapy (HRT): 1) unopposed estrogen therapy; 2) sequentially combined HRT (scHRT) where estrogens are taken daily and; 3) progesterone or progestins are taken intermittently, and continuous combined HRT (ccHRT) where both hormones are taken daily. Estrogen administration can be accomplished orally via tablets, or transdermally through a variety of vehicles including patches, creams, and vaginal inserts. Estrogen is most commonly prescribed as conjugated equine estrogens (CEE) in the U.S. (Nelson HD 2007), but other forms such as synthetic conjugated estrogens, estradiol estropipate, esterified estrogen, and ethinylestradiol are gaining in popularity. The method of delivery is often determined by the target symptoms and patient preference. Progesterones can be prescribed as progesterone or as a wide array of synthetic congeners or progestins.

Treatment of postmenopausal symptoms with estrogen began in the 1940's (Nelson HD 2007). In the 1970's progesterone was added to regimens when a link was made between unopposed estrogen treatment and endometrial cancer (Smith, Prentice et al. 1975; Ziel and Finkle 1975). In the 1980's estrogen began to be prescribed as a prophylactic against osteoporosis when it was shown to reduce fractures (Weiss, Ure et al. 1980; Kiel, Felson et al. 1987) and was thought to be potentially beneficial against other chronic illnesses such as heart disease and dementia (Bluming and Tavris 2009). A sharp decline in prescription of HRT occurred after the termination of the combination estrogen-progestin therapy arm of the Women's Health Initiative (WHI) in 2002 (Hing and Brett 2006). Since 2002 the WHI has made a number of updated reports warning of the dangers of HRT, however careful review of the data reveals these dangers are largely unfounded in most women (Bluming and Tavris 2009). The only conclusive danger is that of an increased cardiac risk in women over the age 60 taking HRT for the first time, and only for the first year (Bluming and Tavris 2009). There is no conclusive evidence that exogenous estrogens increase the risk of breast cancer (Bluming and Tavris 2009).

5. Impact of menopause on immune cell function

In contrast to the plethora of studies examining the effect of hormone therapy on cardiovascular disease, bone metabolism and breast cancer, very few studies have examined the effects of menopause and HRT on immunological parameters. Given that female sex hormones modulate immune response to infection in young women and animal models, it has been hypothesized that that the loss of ovarian steroids during menopause could exacerbate immune senescence (Gameiro and Romao 2010; Gameiro, Romao et al. 2010; Rehman and Masson 2005). This hypothesis is supported by the observation that rhinovirus infection induces a higher IFNγ and IL-13 response in women than men, however this sex difference is no longer detected after the age of 50 (Carroll, Yerkovich et al. 2010). Similarly, hepatitis vaccines induce higher antibody titers and seroconversion rates in adult women, but this gender difference is no longer evident in vaccinees over the age of 60 (Klein, Jedlicka et al. 2010). The incidence of herpes zoster is also higher in women 50 years of age and older compared to males (Chapman, Cross et al. 2003; Fleming, Cross et al. 2004).

The mechanisms underlying these observations are being examined in rodent and nonhuman primate models where menopause was induced surgically via bilateral removal of the ovaries (ovariectomy). This approach allows the investigation of the impact of menopause without the confounding factor of age. In adult female rats, ovariectomy resulted in decreased chemotaxis (migration in response to chemokine gradients) and LPS-induced proliferation by leukocytes

as well as decreased NK cell lysis, suggestive of premature immunosenescence (Baeza, De Castro et al. 2011). More recently, studies from the same group showed that ovariectomy results in increased oxidative damage and inflammatory cytokine production by peritoneal macrophages (Baeza, De Castro et al. 2011).

Similarly, in a mouse model of HSV-2 challenge, ovariectomy resulted in a reduced response to HSV vaccine and ovariectomized female mice experienced the same rate of vaginal infection as unvaccinated controls following challenge (Pennock, Stegall et al. 2009). E2 treatment of control or OVX mice enhanced protection and decreased disease severity (Pennock, Stegall et al. 2009). Interestingly, antibody titers in E2 treated mice were not significantly higher than those observed in untreated mice, but the neutralization potential was significantly improved (Pennock, Stegall et al. 2009).

We have also recently shown that ovariectomy results in several changes in T cell homeostasis in the female rhesus macaque and that these changes were in part modulated by the age at which ovariectomy was perfomed (Engelmann, Barron et al. 2010). Young adult OVX rhesus macaques had a higher frequency of CD4 naïve T cells, whereas OVX aged female rhesus macaques had an increased frequency of terminally differentiated CD4 memory T cells. Moreover, in contrast to young adult females, OVX aged female rhesus macaques showed increased inflammatory cytokine production by T cells compared to intact aged animals. These data suggest that ovariectomy may accelerate some aspects of immune senescence in aged but not young female rhesus macaques. More importantly, both adult and aged OVX animals generated a reduced T and B cell response to vaccination compared to ovary-intact females. Specifically, T and B cell proliferative bursts were delayed and reduced in magnitude in OVX animals. Consequently IgG titers and frequency of IFNγ+ T cells were significantly reduced in OVX animals (Engelmann, Barron et al. 2010). Thus, as described in rodent models, loss of ovarian steroids results in diminished T cell responses to vaccination/infection in nonhuman primates but the mechanisms underlying this reduced immune response remain unclear. The exacerbation of immune senescence by menopause is likely mediated by changes in immune cell frequencies as well as functions discussed in the sections below.

6. Impact of menopause and hormone therapy on immune cell frequency

As reviewed earlier, aging leads to several perturbations in the frequency of several immune cell subsets. However, the contribution of menopause to those changes is not entirely clear. Some studies have reported a significant decline in total lymphocyte numbers (Giglio, Imro et al. 1994), while others report no change (Kamada, Irahara et al. 2000). Women receiving HRT were reported to have higher lymphocyte numbers than post-menopausal women not using HRT within one to six months following treatment (Kamada, Irahara et al. 2000). Peripheral blood monocytes increase after menopause (Ben-Hur, Mor et al. 1995) but the number of tissue specific macrophages in the ovary diminish (Best, Pudney et al. 1996; Katabuchi, Suenaga et al. 1997). HRT can restore the levels of circulating monocytes to levels seen in cycling women (Ben-Hur, Mor et al. 1995).

One of the most conserved age-related changes is the decrease in the percentage of naïve T cells and the accumulation of memory T cells. There is a significant decrease in naïve T cells and an increase in memory and activated T cells between early and late menopause and the use of HRT has no effect on these changes (Fahlman, Boardley et al. 2000; Kamada, Irahara et al. 2000; Yang, Chen et al. 2000), suggesting that chronological age has a more significant

impact on the loss of naïve T cells than menopause. Another hallmark of T cell senescence is a reduced CD4/CD8 ratio (Larbi, Franceschi et al. 2008). Data from a few studies suggest that menopause decreases the CD4/CD8 ratio by reducing the frequency of CD4 T cells (Gameiro and Romao 2010; Giglio, Imro et al. 1994). Since women of reproductive age have more CD4 T cells and respond more vigorously to infection/vaccination than men (Tollerud, Clark et al. 1989; Maini, Gilson et al. 1996), menopause-associated loss of CD4 T cells could be one of the mechanisms by which ovarian senescence contributes to immune senescence.

Total B cell numbers also decline with age and with menopause (Giglio, Imro et al. 1994). B cells can be broadly divided into B1 and B2 cells and their frequency is altered with increasing age (Weksler and Szabo 2000). B1 cells produce predominantly non-specific binding IgM whereas B2 cells, or conventional B cells are involved in the adaptive humoral immune response. The reduction in B cell numbers through menopause appears to be isolated to the B2 cells, which are significantly lower in late menopause compared to early and perimenopause (Kamada, Irahara et al. 2001). Furthermore, B2 cells are significantly higher in HT users than non-users (Kamada, Irahara et al. 2001). These studies suggest that menopause leads to a reduced humoral response and this change can potentially explain the disappearance of sex differences in antibody responses following infection and vaccination (Carroll, Yerkovich et al. 2010; Engler, Nelson et al. 2008; Klein, Jedlicka et al. 2010).

Similarly, oopherectomy results in a decrease in circulating B cells, CD4/CD8 ratio, and an increase in the percentage of NK cells in adult women (Kumru, Godekmerdan et al. 2004). Similarly, surgical menopause leads to increased NK cell frequencies (Giglio, Imro et al. 1994). All these changes are hallmarks of immune senescence and suggest that loss of ovarian steroids exacerbates aging of the immune system. Estrogen therapy reverses the decrease in CD4 and B cells and the increase in NK cells that is seen in patients who have undergone a hysterectomy (Giglio, Imro et al. 1994; Kumru, Godekmerdan et al. 2004). Similarly, combined hormone therapy reverses the age-related decrease in number of circulating B cells and T cell proliferative potential in post-menopausal women (Porter, Greendale et al. 2001) and leads to an increase in B2 B cells (Kamada, Irahara et al. 2001). Furthermore, estrogen has been shown to decrease the number of CD8 T cells in post-menopausal women thereby increasing the CD4/CD8 ratio (Holl, Donat et al. 2001).

7. Inflammation and menopause

It is well accepted that aging is accompanied by the establishment of a chronic proinflammatory state, notably via increased levels of IL-6 and TNFα (Krabbe, Pedersen et al. 2004; Vasto, Candore et al. 2007; Vasto, Carruba et al. 2009). This process is often referred to as inflamm-aging (Franceschi, Bonafe et al. 2000), and is associated with the development of several chronic diseases such as sarcopenia, Alzheimer's, osteoporosis and certain types of cancer (Kim, Chae et al. 2011; Giuliani, Sansoni et al. 2001; Yasui, Maegawa et al. 2007). The age related increase in IL-6 levels could in part be explained by the decline in sex hormones. Both IL-6 and soluble IL-6 receptor are significantly higher in postmenopausal than premenopausal women (Giuliani, Sansoni et al. 2001). Similarly, IL-6 production after *in vitro* stimulation also increases with age. More specifically, in vitro stimulation of PBMC with LPS results in higher production of IL-6 ,TNFα and IL-1β in women aged 52 to 63 compared to young adult women (Kim, Chae et al. 2011). Interestingly, IL-6 production by LPS stimulated PBMC is higher in women taking combined hormone therapy compared to nonusers, but not in post-menopausal

women receiving unopposed estrogen (Brooks-Asplund, Tupper et al. 2002). Similarly, women receiving transdermal estrogen experienced a significant decrease in IL-6 serum levels three months after treatment compared to post-menopausal women who did not receive estradiol (Saucedo, Rico et al. 2002). Indeed, serum IL-6 levels show a negative correlation with serum estrogen levels in users (Saucedo, Rico et al. 2002) and in women spanning the transitional stages of menopause aged 40 to 65 years (Yasui, Maegawa et al. 2007).

A trend toward an increase in serum IFNγ levels is seen during early menopause (< 5 years post menopause) followed by a slight decrease in late menopause (Yasui, Maegawa et al. 2007). Similarly, IFNγ production in whole blood or PBMC in response to either PHA or LPS stimulation *in vitro*, begins to increase at around the age of 40 and peaks during early to mid menopause before again decreasing during late menopause (Deguchi, Kamada et al. 2001; Kamada, Irahara et al. 2001; Stopinska-Gluszak, Waligora et al. 2006). Previous *in vitro* studies have shown that estrogen has a biphasic effect on IFNγ production by LPS stimulated whole blood samples, with low estrogen levels stimulating and high levels inhibiting IFNγ production (Matalka 2003). Therefore, it is possible that the initial decrease in estrogen levels during early menopause stimulates an increase in IFNγ production, but during late menopause, estrogen levels become too low to have an effect (Goetzl, Huang et al. 2010). In support of this hypothesis, IFNγ serum levels decreased in women who have had a bilateral oopherectomy and increase once estrogen treatment is initiated (Kumru, Godekmerdan et al. 2004). On the other hand, combined hormone therapy is associated with lower IFNγ production possibly due to the opposing effect of progesterone (Deguchi, Kamada et al. 2001; Stopinska-Gluszak, Waligora et al. 2006)

A transient increase in serum IL-2 was described in women within the first five years of menopause and the data suggest a weak negative correlation with serum estrogen levels (Yasui, Maegawa et al. 2007). Similarly, IL-2 production following LPS stimulation of whole blood cultures increases with age, peaking during early menopause before declining (Deguchi, Kamada et al. 2001). HRT reduces plasma IL-2 levels as well as IL-2 production by T cells following stimulation of purified PBMC with PHA (Stopinska-Gluszak, Waligora et al. 2006). In contrast, transdermal administration of estrogen does not change IL-2 levels, probably because plasma levels achieved via this delivery route are too low to modulate T cell functions (Saucedo, Rico et al. 2002). IL-4 plasma levels were reported to increase after menopause and HT reverses this increase (Vural, Canbaz et al. 2006; Yasui, Maegawa et al. 2007). In PHA stimulated whole blood, IL-4 production increases in mid menopause and then becomes significantly lower in late menopause (Deguchi, Kamada et al. 2001). In contrast, oopherectomy decreases IL-4 levels and unopposed estrogen therapy does not affect this decrease (Kumru, Godekmerdan et al. 2004).

Menopause-induced changes in circulating levels of additional cytokines are controversial. Some studies reported an increase in TNFα and IL-1β after menopause that is reversed by HRT (Kamada, Irahara et al. 2001; Vural, Canbaz et al. 2006), while other studies reported no changes (Yasui, Maegawa et al. 2007). The impact of menopause on IL-10 and IL-12 is equally controversial with some studies reporting an increase (Deguchi, Kamada et al. 2001; Vural, Canbaz et al. 2006), while others report no change (Yasui, Maegawa et al. 2007) or a decrease in these cytokines (Kamada, Irahara et al. 2001). HRT and transdermal estrogen do not seem to have an impact on IL-10 levels (Saucedo, Rico et al. 2002; Vural, Canbaz et al. 2006). A negative correlation of IL-8 with estrogen level was reported in both humans and mice (Yasui, Maegawa et al. 2007; Abu-Taha, Rius et al. 2009).

8. Alternative approaches and their effect on immunity in post menopausal women

Alternative approaches for dealing with menopausal symptoms have gained significant interest in recent years. One of the most popular interventions is nutritional supplementation with estrogen-like substances that might not have the undesirable side effects of hormones. Dietary phyto-estrogens are organic compounds found in soy products, fruits and legumes (Huntley and Ernst 2004). It has been proposed that the beneficial effects of soybean compounds are mediated by isoflavones such as genistein since they show structural similarities to estradiol (Bingham, Atkinson et al. 1998).

Some rodent studies support a beneficial effect of isoflavones on immune function in post-menopausal animals. In mature ovariectomized female rats, nutritional supplementation with soybean or soybean and green tea improved chemotaxis, phagocytic index as well as the production of reactive oxygen species by peritoneal macrophages (Baeza, De Castro et al. 2010). This nutritional supplementation also improved T and B cell proliferative potential and NK cell killing (Baeza, De Castro et al. 2010). Similar results were reported for human (Zhang, Song et al. 1999) and murine (Guo, McCay et al. 2001) NK cells after exposure to another isoflavone, genistein. Genistein treatment of murine splenocytes in vitro increased IL-10 production thereby tilting the cytokine balance towards a Th2 response (Rachon, Rimoldi et al. 2006).

Post-menopausal women receiving a daily dose of 70mg of isoflavones either in the form of soy milk (700ml) or oral supplements for 16 weeks experienced an increase in the frequency of circulating B cells as well as a reduction in plasma concentrations of 8-hydroxy-2-deoxy-guanosine (8-OHdg), an oxidative damage marker (Ryan-Borchers, Park et al. 2006). No changes in the plasma levels of IL-2, IFNγ or TNFα were observed in this and a second study where women consumed comparable amount of soymilk (Beavers, Serra et al. 2009). However in an earlier study where women consumed 1064 ml of soymilk for 16 weeks, a decrease in plasma levels of TNFα and IL-1, but not IL-6, were detected (Huang, Cao et al. 2005). These data suggest that additional studies with a bigger range of doses in different populations of post-menopausal women need to be conducted in order to define dynamic ranges and individuals who stand to benefit the most from such nutritional interventions (Genazzani and Pluchino 2011).

Dehydroepiandrosterone (DHEA) is produced by the adrenal cortex and is the most abundant steroid in humans. Serum levels of DHEA and its sulfated conjugation product, DHEA sulfate (DHEAS), peak in men and women in the third decade and decrease progressively and profoundly with age. In the longitudinal Baltimore study, plasma levels of DHEAS emerged at the most consistent aging biomarker and correlated with longevity. In addition to its role as a precursor for androgens and estrogens, DHEA can exert a direct, physiologically relevant, agonistic effect on ERβ, a lesser antagonistic effect on androgen receptor, and a modest effect on ERα (Chen, Knecht et al. 2005). Therefore, DHEA supplementation has been explored as an alternative to classical hormone therapy. Early studies in aged mice, showed that age-related upregulation of IL-6 production could be effectively prevented and/or reversed by supplementing aging animals with DHEA (Daynes, Araneo et al. 1993). More importantly, either DHEA or DHEA sulfate supplementation promoted enhanced antibody responses against recombinant hepatitis B surface antigen by aged mice when incorporated directly into the vaccine (Araneo, Woods et al. 1993). In contrast to the rodent data, the effect of DHEA on the immune response to

influenza vaccine in older humans is controversial. Earlier studies showed one oral dose of DHEAS before influenza vaccination was associated with a demonstrable increase in the number of individuals with a fourfold increase in hemagglutinin inhibition (HI) titers following vaccination (Araneo, Dowell et al. 1995). Similarly, one dose of DHEAS administered at the time of influenza vaccination appeared to enhance the HI titer in a small group of older adults with lower prevaccination titers and lower DHEAS concentrations (Degelau, Guay et al. 1997). In contrast, a 6-day course of DHEA treatment that began 2 days before vaccination did not improve the age-related declined response to immunization against influenza in human subjects (Danenberg, Ben-Yehuda et al. 1997). These results suggest additional detailed immunologic investigations on the role of DHEAS in the aging human immune response are warranted.

9. Conclusions and perspectives

A considerable body of data strongly suggests that sex hormones modulate immune function with estrogen having an immune stimulatory effect whereas progesterone an immune inhibitory effect. Aging results in several changes in both the immune and the endocrine systems. However the interplay between these two organ systems remains poorly understood. While it is clear that some changes (such as increased IL-6 levels) can be strongly attributed to loss of ovarian steroids, other changes such as lymphocyte function are not easily attributable to menopause. Moreover, the effects of hormone therapy on the post-menopausal immune system are controversial. The discrepancies between studies are in large part due to the variety of hormone replacement regimens available (conjugated equine estrogens, 17β estradiol, progestin), but also reflect the lack of consensus over which immune parameters are analyzed. As new safer hormone replacement therapies become available such as transdermal low levels of estradiol, the immune modulatory capacities of these treatments should be characterized. Future studies should also examine how changes in additional sex hormones such as FSH, LH and increased androgen production by the senescent ovary affect the immune system.

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11. References

Abu-Taha, M., C. Rius, et al. (2009). "Menopause and ovariectomy cause a low grade of systemic inflammation that may be prevented by chronic treatment with low doses of estrogen or losartan." J Immunol 183(2): 1393-402.

Aderem, A. and D. M. Underhill (1999). "Mechanisms of phagocytosis in macrophages." Annu Rev Immunol 17: 593-623.

Ansar Ahmed, S., W. J. Penhale, et al. (1985). "Sex hormones, immune responses, and autoimmune diseases. Mechanisms of sex hormone action." Am J Pathol 121(3): 531-51.

Araneo, B., T. Dowell, et al. (1995). "DHEAS as an effective vaccine adjuvant in elderly humans. Proof-of-principle studies." Ann N Y Acad Sci 774: 232-48.

Araneo, B. A., M. L. Woods, 2nd, et al. (1993). "Reversal of the immunosenescent phenotype by dehydroepiandrosterone: hormone treatment provides an adjuvant effect on the immunization of aged mice with recombinant hepatitis B surface antigen." J Infect Dis 167(4): 830-40.

Aydar, Y., P. Balogh, et al. (2004). "Follicular dendritic cells in aging, a "bottle-neck" in the humoral immune response." Ageing Res Rev 3(1): 15-29.

Baeten, J. M., P. M. Nyange, et al. (2001). "Hormonal contraception and risk of sexually transmitted disease acquisition: results from a prospective study." Am J Obstet Gynecol 185(2): 380-5.

Baeza, I., N. M. De Castro, et al. (2010). "Soybean and green tea polyphenols improve immune function and redox status in very old ovariectomized mice." Rejuvenation Res 13(6): 665-74.

Baeza, I., N. M. De Castro, et al. (2011). "Ovariectomy causes immunosenescence and oxi-inflamm-ageing in peritoneal leukocytes of aged female mice similar to that in aged males." Biogerontology 12(3): 227-38.

Baeza, I., N. M. De Castro, et al. (2010). "Ovariectomy, a model of menopause in rodents, causes a premature aging of the nervous and immune systems." J Neuroimmunol 219(1-2): 90-9.

Barna, M., T. Komatsu, et al. (1996). "Sex differences in susceptibility to viral infection of the central nervous system." J Neuroimmunol 67(1): 31-9.

Beavers, K. M., M. C. Serra, et al. (2009). "Soymilk supplementation does not alter plasma markers of inflammation and oxidative stress in postmenopausal women." Nutrition research (New York, N.Y.) 29(9): 616-622.

Beerman, I., D. Bhattacharya, et al. (2010). "Functionally distinct hematopoietic stem cells modulate hematopoietic lineage potential during aging by a mechanism of clonal expansion." Proc Natl Acad Sci U S A 107(12): 5465-70.

Ben-Hur, H., G. Mor, et al. (1995). "Menopause is associated with a significant increase in blood monocyte number and a relative decrease in the expression of estrogen receptors in human peripheral monocytes." Am J Reprod Immunol 34(6): 363-9.

Bernstein, D. I., F. Y. Aoki, et al. (2005). "Safety and immunogenicity of glycoprotein D-adjuvant genital herpes vaccine." Clin Infect Dis 40(9): 1271-81.

Best, C. L., J. Pudney, et al. (1996). "Localization and characterization of white blood cell populations within the human ovary throughout the menstrual cycle and menopause." Hum Reprod 11(4): 790-7.

Beutler, B. (2000). "Endotoxin, toll-like receptor 4, and the afferent limb of innate immunity." Curr Opin Microbiol 3(1): 23-8.

Beyer, W. E., A. M. Palache, et al. (1989). "Antibody induction by influenza vaccines in the elderly: a review of the literature." Vaccine 7(5): 385-94.

Biassoni, R. (2008). "Natural killer cell receptors." Adv Exp Med Biol 640: 35-52.

Bingham, S. A., C. Atkinson, et al. (1998). "Phyto-oestrogens: where are we now?" Br J Nutr 79(5): 393-406.

Biron, C. A., K. B. Nguyen, et al. (1999). "Natural killer cells in antiviral defense: function and regulation by innate cytokines." Annu Rev Immunol 17: 189-220.

Bluming, A. Z. and C. Tavris (2009). "Hormone replacement therapy: real concerns and false alarms." Cancer J 15(2): 93-104.

Born, J., D. Uthgenannt, et al. (1995). "Cytokine production and lymphocyte subpopulations in aged humans. An assessment during nocturnal sleep." Mech Ageing Dev 84(2): 113-26.

Borrego, F., M. C. Alonso, et al. (1999). "NK phenotypic markers and IL2 response in NK cells from elderly people." Exp Gerontol 34(2): 253-65.

Bouman, A., M. J. Heineman, et al. (2005). "Sex hormones and the immune response in humans." Hum Reprod Update 11(4): 411-23.

Boyman, O., J. F. Purton, et al. (2007). "Cytokines and T-cell homeostasis." Current Opinion in Immunology 19(3): 320-326.

Brabin, L. (2002). "Interactions of the female hormonal environment, susceptibility to viral infections, and disease progression." AIDS Patient Care STDS 16(5): 211-21.

Brooks-Asplund, E. M., C. E. Tupper, et al. (2002). "Hormonal modulation of interleukin-6, tumor necrosis factor and associated receptor secretion in postmenopausal women." Cytokine 19(4): 193-200.

Burger, H. G., G. E. Hale, et al. (2008). "Cycle and hormone changes during perimenopause: the key role of ovarian function." Menopause 15(4 Pt 1): 603-12.

Butts, C. L., S. A. Shukair, et al. (2007). "Progesterone inhibits mature rat dendritic cells in a receptor-mediated fashion." Int. Immunol. 19(3): 287-296.

Calippe, B., V. Douin-Echinard, et al. (2010). "17{beta}-Estradiol Promotes TLR4-Triggered Proinflammatory Mediator Production through Direct Estrogen Receptor {alpha} Signaling in Macrophages In Vivo." J Immunol 185(2): 1169-1176.

Cancro, M. P., Y. Hao, et al. (2009). "B cells and aging: molecules and mechanisms." Trends Immunol 30(7): 313-8.

Carroll, M. L., S. T. Yerkovich, et al. (2010). "Adaptive immunity to rhinoviruses: sex and age matter." Respir Res 11: 184.

Cella, M., D. Jarrossay, et al. (1999). "Plasmacytoid monocytes migrate to inflamed lymph nodes and produce large amounts of type I interferon [see comments]." Nat Med 5(8): 919-23.

Chaplin, D. D. (2010). "Overview of the immune response." J Allergy Clin Immunol 125(2 Suppl 2): S3-23.

Chapman, R. S., K. W. Cross, et al. (2003). "The incidence of shingles and its implications for vaccination policy." Vaccine 21(19-20): 2541-2547.

Chatta, G. S., R. G. Andrews, et al. (1993). "Hematopoietic progenitors and aging: alterations in granulocytic precursors and responsiveness to recombinant human G-CSF, GM-CSF, and IL-3." J Gerontol 48(5): M207-12.

Chen, F., K. Knecht, et al. (2005). "Direct agonist/antagonist functions of dehydroepiandrosterone." Endocrinology 146(11): 4568-76.

Chen, J. (2004). "Senescence and functional failure in hematopoietic stem cells." Exp Hematol 32(11): 1025-32.

Christopher E. Andoniou, J. D. C., Mariapia A. Degli-Esposti, (2008). "Killers and beyond: NK-cell-mediated control of immune responses." European Journal of Immunology 38(11): 2938-2942.

Chung, E., S. B. Amrute, et al. (2005). "Characterization of virus-responsive plasmacytoid dendritic cells in the rhesus macaque." Clin Diagn Lab Immunol 12(3): 426-35.

Colonna-Romano, G., M. Bulati, et al. (2003). "B cells in the aged: CD27, CD5, and CD40 expression." Mech Ageing Dev 124(4): 389-93.

Cook, I. F. (2008). "Sexual dimorphism of humoral immunity with human vaccines." Vaccine 26(29-30): 3551-5.

Cook, J. M., N. Gualde, et al. (1987). "Alterations in the human immune response to the hepatitis B vaccine among the elderly." Cell Immunol 109(1): 89-96.

Corey, L., A. G. Langenberg, et al. (1999). "Recombinant glycoprotein vaccine for the prevention of genital HSV-2 infection: two randomized controlled trials. Chiron HSV Vaccine Study Group." JAMA 282(4): 331-40.

Curiel, R. E., M. H. Miller, et al. (1993). "Does the gender difference in interferon production seen in picornavirus-infected spleen cell cultures from ICR Swiss mice have any in vivo significance?" J Interferon Res 13(6): 387-95.

Curran, E. M., L. J. Berghaus, et al. (2001). "Natural killer cells express estrogen receptor-alpha and estrogen receptor-beta and can respond to estrogen via a non-estrogen receptor-alpha-mediated pathway." Cell Immunol 214(1): 12-20.

D'Acremont, V., C. Herzog, et al. (2006). "Immunogenicity and safety of a virosomal hepatitis A vaccine (Epaxal) in the elderly." J Travel Med 13(2): 78-83.

Dahlgren, C. and A. Karlsson (1999). "Respiratory burst in human neutrophils." J Immunol Methods 232(1-2): 3-14.

Danenberg, H. D., A. Ben-Yehuda, et al. (1997). "Dehydroepiandrosterone treatment is not beneficial to the immune response to influenza in elderly subjects." J Clin Endocrinol Metab 82(9): 2911-4.

Daynes, R. A., B. A. Araneo, et al. (1993). "Altered regulation of IL-6 production with normal aging. Possible linkage to the age-associated decline in dehydroepiandrosterone and its sulfated derivative." J Immunol 150(12): 5219-30.

De Martinis, M., C. Franceschi, et al. (2005). "Inflamm-ageing and lifelong antigenic load as major determinants of ageing rate and longevity." FEBS Lett 579(10): 2035-9.

Degelau, J., D. Guay, et al. (1997). "The effect of DHEAS on influenza vaccination in aging adults." J Am Geriatr Soc 45(6): 747-51.

Deguchi, K., M. Kamada, et al. (2001). "Postmenopausal changes in production of type 1 and type 2 cytokines and the effects of hormone replacement therapy." Menopause 8(4): 266-73.

Della Bella, S., L. Bierti, et al. (2007). "Peripheral blood dendritic cells and monocytes are differently regulated in the elderly." Clin Immunol 122(2): 220-8.

Delpy, L., V. Douin-Echinard, et al. (2005). "Estrogen enhances susceptibility to experimental autoimmune myasthenia gravis by promoting type 1-polarized immune responses." J Immunol 175(8): 5050-7.

Derhovanessian, E., A. Larbi, et al. (2009). "Biomarkers of human immunosenescence: impact of Cytomegalovirus infection." Curr Opin Immunol 21(4): 440-5.

Diodato, M. D., M. W. Knoferl, et al. (2001). "Gender differences in the inflammatory response and survival following haemorrhage and subsequent sepsis." Cytokine 14(3): 162-9.

Dosiou, C., A. E. Hamilton, et al. (2008). "Expression of membrane progesterone receptors on human T lymphocytes and Jurkat cells and activation of G-proteins by progesterone." J Endocrinol 196(1): 67-77.

Dunston, C. R. and H. R. Griffiths (2010). "The effect of ageing on macrophage Toll-like receptor-mediated responses in the fight against pathogens." Clin Exp Immunol 161(3): 407-16.

Engelmann, F., A. Barron, et al. (2010). "Accelerated immune senescence and reduced response to vaccination in ovariectomized female rhesus macaques." Age (Dordr).

Engler, R. J., M. R. Nelson, et al. (2008). "Half- vs full-dose trivalent inactivated influenza vaccine (2004-2005): age, dose, and sex effects on immune responses." Arch Intern Med 168(22): 2405-14.

Evans, M. J., S. MacLaughlin, et al. (1997). "Estrogen decreases in vitro apoptosis of peripheral blood mononuclear cells from women with normal menstrual cycles and decreases TNF-alpha production in SLE but not in normal cultures." Clin Immunol Immunopathol 82(3): 258-62.

Fahlman, M. M., D. Boardley, et al. (2000). "Effects of hormone replacement therapy on selected indices of immune function in postmenopausal women." Gynecol Obstet Invest 50(3): 189-93.

Fleming, D. M., K. W. Cross, et al. (2004). "Gender difference in the incidence of shingles." Epidemiol Infect 132(1): 1-5.

Franceschi, C., M. Bonafe, et al. (2000). "Inflamm-aging. An evolutionary perspective on immunosenescence." Ann N Y Acad Sci 908: 244-54.

Frasca, D., R. L. Riley, et al. (2004). "Effect of age on the immunoglobulin class switch." Crit Rev Immunol 24(5): 297-320.

Gameiro, C. and F. Romao (2010). "Changes in the immune system during menopause and aging." Front Biosci (Elite Ed) 2: 1299-303.

Gameiro, C. M., F. Romao, et al. (2010). "Menopause and aging: changes in the immune system--a review." Maturitas 67(4): 316-20.

Genazzani, A. R. and N. Pluchino (2010). "DHEA therapy in postmenopausal women: the need to move forward beyond the lack of evidence." Climacteric 13(4): 314-6.

Genton, B., V. D'Acremont, et al. (2006). "Hepatitis A vaccines and the elderly." Travel Med Infect Dis 4(6): 303-12.

Gerli, R., D. Monti, et al. (2000). "Chemokines, sTNF-Rs and sCD30 serum levels in healthy aged people and centenarians." Mech Ageing Dev 121(1-3): 37-46.

Giglio, T., M. A. Imro, et al. (1994). "Immune cell circulating subsets are affected by gonadal function." Life Sci 54(18): 1305-12.

Gillgrass, A. E., A. A. Ashkar, et al. (2003). "Prolonged exposure to progesterone prevents induction of protective mucosal responses following intravaginal immunization with attenuated herpes simplex virus type 2." J Virol 77(18): 9845-51.

Gillgrass, A. E., S. A. Fernandez, et al. (2005). "Estradiol regulates susceptibility following primary exposure to genital herpes simplex virus type 2, while progesterone induces inflammation." J Virol 79(5): 3107-16.

Ginaldi, L., M. C. Di Benedetto, et al. (2005). "Osteoporosis, inflammation and ageing." Immun Ageing 2: 14.

Giuliani, N., P. Sansoni, et al. (2001). "Serum interleukin-6, soluble interleukin-6 receptor and soluble gp130 exhibit different patterns of age- and menopause-related changes." Exp Gerontol 36(3): 547-57.

Goetzl, E. J., M. C. Huang, et al. (2010). "Gender specificity of altered human immune cytokine profiles in aging." FASEB J 24(9): 3580-9.

Grady, D. (2006). "Clinical practice. Management of menopausal symptoms." N Engl J Med 355(22): 2338-47.

Grimaldi, C. M., J. Cleary, et al. (2002). "Estrogen alters thresholds for B cell apoptosis and activation." J Clin Invest 109(12): 1625-33.

Guo, T. L., J. A. McCay, et al. (2001). "Genistein modulates immune responses and increases host resistance to B16F10 tumor in adult female B6C3F1 mice." J Nutr 131(12): 3251-8.

Hall, J. E. (2004). "Neuroendocrine physiology of the early and late menopause." Endocrinol Metab Clin North Am 33(4): 637-59.

Han, X., P. Lundberg, et al. (2001). "Gender influences herpes simplex virus type 1 infection in normal and gamma interferon-mutant mice." J Virol 75(6): 3048-52.

Harkonen, P. L. and H. K. Vaananen (2006). "Monocyte-macrophage system as a target for estrogen and selective estrogen receptor modulators." Ann N Y Acad Sci 1089: 218-27.

Hing, E. and K. M. Brett (2006). "Changes in U.S. prescribing patterns of menopausal hormone therapy, 2001-2003." Obstet Gynecol 108(1): 33-40.

Holl, M., H. Donat, et al. (2001). "[Peripheral blood lymphocyte subpopulations of postmenopausal women with hormone replacement therapy]." Zentralbl Gynakol 123(9): 543-5.

Huang, Y., S. Cao, et al. (2005). "Decreased Circulating Levels of Tumor Necrosis Factor-Œ± in Postmenopausal Women during Consumption of Soy-Containing Isoflavones." Journal of Clinical Endocrinology & Metabolism 90(7): 3956-3962.

Huber, S. A. (2005). "Increased susceptibility of male BALB/c mice to coxsackievirus B3-induced myocarditis: role for CD1d." Med Microbiol Immunol 194(3): 121-7.

Huber, S. A., J. Kupperman, et al. (1999). "Hormonal regulation of CD4(+) T-cell responses in coxsackievirus B3-induced myocarditis in mice." J Virol 73(6): 4689-95.

Huber, S. A. and B. Pfaeffle (1994). "Differential Th1 and Th2 cell responses in male and female BALB/c mice infected with coxsackievirus group B type 3." J Virol 68(8): 5126-32.

Hughes, G. C., S. Thomas, et al. (2008). "Cutting Edge: Progesterone Regulates IFN-{alpha} Production by Plasmacytoid Dendritic Cells." J Immunol 180(4): 2029-2033.

Huntley, A. L. and E. Ernst (2004). "Soy for the treatment of perimenopausal symptoms--a systematic review." Maturitas 47(1): 1-9.

Huppert, F. A., W. Solomou, et al. (1998). "Aging and lymphocyte subpopulations: whole-blood analysis of immune markers in a large population sample of healthy elderly individuals." Exp Gerontol 33(6): 593-600.

Jared F. Purton, J. S., Charles D. Surh, (2007). "Staying alive – naïve CD4(+) T cell homeostasis." European Journal of Immunology 37(9): 2367-2369.

Johansson, S. G. "The History of IgE: From discovery to 2010." Curr Allergy Asthma Rep 11(2): 173-7.

Kabelitz, D. and R. Medzhitov (2007). "Innate immunity--cross-talk with adaptive immunity through pattern recognition receptors and cytokines." Curr Opin Immunol 19(1): 1-3.

Kamada, M., M. Irahara, et al. (2001). "Transient increase in the levels of T-helper 1 cytokines in postmenopausal women and the effects of hormone replacement therapy." Gynecol Obstet Invest 52(2): 82-8.

Kamada, M., M. Irahara, et al. (2001). "Postmenopausal changes in serum cytokine levels and hormone replacement therapy." American Journal of Obstetrics and Gynecology 184(3): 309-314.

Kamada, M., M. Irahara, et al. (2000). "Effect of hormone replacement therapy on post-menopausal changes of lymphocytes and T cell subsets." J Endocrinol Invest 23(6): 376-82.

Kamada, M., M. Irahara, et al. (2001). "B cell subsets in postmenopausal women and the effect of hormone replacement therapy." Maturitas 37(3): 173-179.

Kanda, N. and K. Tamaki (1999). "Estrogen enhances immunoglobulin production by human PBMCs." J Allergy Clin Immunol 103(2 Pt 1): 282-8.

Karpuzoglu, E. and M. Zouali (2011). "The multi-faceted influences of estrogen on lymphocytes: toward novel immuno-interventions strategies for autoimmunity management." Clin Rev Allergy Immunol 40(1): 16-26.

Katabuchi, H., Y. Suenaga, et al. (1997). "Distribution and fine structure of macrophages in the human ovary during the menstrual cycle, pregnancy and menopause." Endocr J 44(6): 785-95.

Kaushic, C., A. D. Murdin, et al. (1998). "Chlamydia trachomatis infection in the female reproductive tract of the rat: influence of progesterone on infectivity and immune response." Infect Immun 66(3): 893-8.

Ketloy, C., A. Engering, et al. (2008). "Expression and function of Toll-like receptors on dendritic cells and other antigen presenting cells from non-human primates." Vet Immunol Immunopathol 125(1-2): 18-30.

Khan, D., R. Dai, et al. (2010). "Estrogen increases, whereas IL-27 and IFN-gamma decrease, splenocyte IL-17 production in WT mice." Eur J Immunol 40(9): 2549-56.

Kiel, D. P., D. T. Felson, et al. (1987). "Hip fracture and the use of estrogens in postmenopausal women. The Framingham Study." N Engl J Med 317(19): 1169-74.

Kim, O. Y., J. S. Chae, et al. (2011). "Effects of aging and menopause on serum interleukin-6 levels and peripheral blood mononuclear cell cytokine production in healthy nonobese women." Age (Dordr).

Klein, P. W., J. D. Easterbrook, et al. (2008). "Estrogen and progesterone affect responses to malaria infection in female C57BL/6 mice." Gend Med 5(4): 423-33.

Klein, S. H., S. (2010). Sex Differences in Susceptibility to Viral Infection. Sex Hormones and Immmunity to Infection. S. R. Klein, C. Berlin/Heidelberg, Springer.

Klein, S. L. (2004). "Hormonal and immunological mechanisms mediating sex differences in parasite infection." Parasite Immunology 26(6-7): 247-264.

Klein, S. L., A. Jedlicka, et al. (2010). "The Xs and Y of immune responses to viral vaccines." Lancet Infect Dis 10(5): 338-49.

Komi, J. and O. Lassila (2000). "Nonsteroidal anti-estrogens inhibit the functional differentiation of human monocyte-derived dendritic cells." Blood 95(9): 2875-82.

Kovats S, E. C., and Hemant Agrawal (2010). Sex Steroid Receptors in Immune Cells. Sex Hormones and Immunity to Infection. R. C. Klein S. Berlin/Heidelberg, Springer.

Kozlowski, P. A., S. B. Williams, et al. (2002). "Differential induction of mucosal and systemic antibody responses in women after nasal, rectal, or vaginal immunization: influence of the menstrual cycle." J Immunol 169(1): 566-74.

Krabbe, K. S., M. Pedersen, et al. (2004). "Inflammatory mediators in the elderly." Exp Gerontol 39(5): 687-99.

Kumru, S., A. Godekmerdan, et al. (2004). "Immune effects of surgical menopause and estrogen replacement therapy in peri-menopausal women." J Reprod Immunol 63(1): 31-8.

Lanier, L. L. (2008). "Up on the tightrope: natural killer cell activation and inhibition." Nat Immunol 9(5): 495-502.

Lanzavecchia, A. and F. Sallusto (2005). "Understanding the generation and function of memory T cell subsets." Curr Opin Immunol 17(3): 326-32.

Larbi, A., C. Franceschi, et al. (2008). "Aging of the Immune System as a Prognostic Factor for Human Longevity." Physiology 23(2): 64-74.

Larsson, B. M., K. Larsson, et al. (1999). "Gram positive bacteria induce IL-6 and IL-8 production in human alveolar macrophages and epithelial cells." Inflammation 23(3): 217-30.

LeMaoult, J., S. Delassus, et al. (1997). "Clonal expansions of B lymphocytes in old mice." J Immunol 159(8): 3866-74.

LeMaoult, J., J. S. Manavalan, et al. (1999). "Cellular basis of B cell clonal populations in old mice." J Immunol 162(11): 6384-91.

LeMaoult, J., P. Szabo, et al. (1997). "Effect of age on humoral immunity, selection of the B-cell repertoire and B-cell development." Immunol Rev 160: 115-26.

Li, X., Y. Xu, et al. (2009). "17beta-estradiol enhances the response of plasmacytoid dendritic cell to CpG." PLoS One 4(12): e8412.

Linehan, S. A., L. Martinez-Pomares, et al. (2000). "Macrophage lectins in host defence." Microbes Infect 2(3): 279-88.

Lloberas, J. and A. Celada (2002). "Effect of aging on macrophage function." Exp Gerontol 37(12): 1325-31.

Lord, J. M., S. Butcher, et al. (2001). "Neutrophil ageing and immunesenescence." Mech Ageing Dev 122(14): 1521-35.

Maini, M. K., R. J. Gilson, et al. (1996). "Reference ranges and sources of variability of CD4 counts in HIV-seronegative women and men." Genitourin Med 72(1): 27-31.

Mariani, E., L. Pulsatelli, et al. (2002). "RANTES and MIP-1alpha production by T lymphocytes, monocytes and NK cells from nonagenarian subjects." Exp Gerontol 37(2-3): 219-26.

Marriott, I. and Y. M. Huet-Hudson (2006). "Sexual dimorphism in innate immune responses to infectious organisms." Immunol Res 34(3): 177-92.

Marx, P. A., A. I. Spira, et al. (1996). "Progesterone implants enhance SIV vaginal transmission and early virus load." Nat Med 2(10): 1084-9.

Matalka, K. Z. (2003). "The effect of estradiol, but not progesterone, on the production of cytokines in stimulated whole blood, is concentration-dependent." Neuro Endocrinol Lett 24(3-4): 185-91.

Medzhitov, R. (2003). The Innate Immune System. Fundamental Immunology. W. Paul, Lippincott Williams & Wilkins: 509.

Medzhitov, R. (2007). "Recognition of microorganisms and activation of the immune response." Nature 449(7164): 819-26.

Medzhitov, R. and C. A. Janeway, Jr. (2002). "Decoding the patterns of self and nonself by the innate immune system." Science 296(5566): 298-300.

Meier, A., J. J. Chang, et al. (2009). "Sex differences in the Toll-like receptor-mediated response of plasmacytoid dendritic cells to HIV-1." Nat Med 15(8): 955-9.

Merkel, S. M., S. Alexander, et al. (2001). "Essential role for estrogen in protection against Vibrio vulnificus-induced endotoxic shock." Infect Immun 69(10): 6119-22.

Mocchegiani, E. and M. Malavolta (2004). "NK and NKT cell functions in immunosenescence." Aging Cell 3(4): 177-84.

Mor, G., E. Sapi, et al. (2003). "Interaction of the estrogen receptors with the Fas ligand promoter in human monocytes." J Immunol 170(1): 114-22.

Morrison, C. S., B. A. Richardson, et al. (2007). "Hormonal contraception and the risk of HIV acquisition." Aids 21(1): 85-95.

Murasko, D. M. and J. Jiang (2005). "Response of aged mice to primary virus infections." Immunol Rev 205: 285-96.

Mysliwska, J., P. Trzonkowski, et al. (2004). "Immunomodulating effect of influenza vaccination in the elderly differing in health status." Exp Gerontol 39(10): 1447-58.

Naylor, K., G. Li, et al. (2005). "The Influence of Age on T Cell Generation and TCR Diversity." J Immunol 174(11): 7446-52.

Nelson HD, N. P., Freeman M, Chan BKS. (2007). "Drug Class Review on Hormone Therapy." from http://www.ohsu.edu/drugeffectiveness/reports/final.cfm.

Offner, P. J., E. E. Moore, et al. (1999). "Male gender is a risk factor for major infections after surgery." Arch Surg 134(9): 935-8; discussion 938-40.

Ogata, K., N. Yokose, et al. (1997). "Natural killer cells in the late decades of human life." Clin Immunol Immunopathol 84(3): 269-75.

Olweus, J., A. BitMansour, et al. (1997). "Dendritic cell ontogeny: a human dendritic cell lineage of myeloid origin." Proc Natl Acad Sci U S A 94(23): 12551-6.

Paavonen, T., L. C. Andersson, et al. (1981). "Sex hormone regulation of in vitro immune response. Estradiol enhances human B cell maturation via inhibition of suppressor T cells in pokeweed mitogen-stimulated cultures." J Exp Med 154(6): 1935-45.

Paharkova-Vatchkova, V., R. Maldonado, et al. (2004). "Estrogen preferentially promotes the differentiation of CD11c+ CD11b(intermediate) dendritic cells from bone marrow precursors." J Immunol 172(3): 1426-36.

Pawelec, G., E. Derhovanessian, et al. (2009). "Cytomegalovirus and human immunosenescence." Rev Med Virol 19(1): 47-56.

Pawelec, G., A. Larbi, et al. (2009). "Senescence of the Human Immune System." J Comp Pathol.

Pennock, J. W., R. Stegall, et al. (2009). "Estradiol improves genital herpes vaccine efficacy in mice." Vaccine 27(42): 5830-6.

Phiel, K. L., R. A. Henderson, et al. (2005). "Differential estrogen receptor gene expression in human peripheral blood mononuclear cell populations." Immunol Lett 97(1): 107-13.

Pinzan, C. F., L. P. Ruas, et al. (2010). "Immunological basis for the gender differences in murine Paracoccidioides brasiliensis infection." PLoS ONE 5(5): e10757.

Polanczyk, M. J., C. Hopke, et al. (2006). "Estrogen-mediated immunomodulation involves reduced activation of effector T cells, potentiation of Treg cells, and enhanced expression of the PD-1 costimulatory pathway." J Neurosci Res 84(2): 370-8.

Porter, V. R., G. A. Greendale, et al. (2001). "Immune effects of hormone replacement therapy in post-menopausal women." Exp Gerontol 36(2): 311-26.

Prior, J. C. (1998). "Perimenopause: the complex endocrinology of the menopausal transition." Endocr Rev 19(4): 397-428.

Pulsatelli, L., R. Meliconi, et al. (2000). "Chemokine production by peripheral blood mononuclear cells in elderly subjects." Mech Ageing Dev 121(1-3): 89-100.

Purton, J. F., J. T. Tan, et al. (2007). "Antiviral CD4+ memory T cells are IL-15 dependent." J. Exp. Med. 204(4): 951-961.

Rachon, D., G. Rimoldi, et al. (2006). "In vitro effects of genistein and resveratrol on the production of interferon-gamma (IFNgamma) and interleukin-10 (IL-10) by stimulated murine splenocytes." Phytomedicine 13(6): 419-24.

Radaev, S. and P. D. Sun (2003). "Structure and function of natural killer cell surface receptors." Annu Rev Biophys Biomol Struct 32: 93-114.

Rehman, H. U. and E. A. Masson (2005). "Neuroendocrinology of female aging." Gender Medicine 2(1): 41-56.

Rider, V., S. Jones, et al. (2001). "Estrogen increases CD40 ligand expression in T cells from women with systemic lupus erythematosus." J Rheumatol 28(12): 2644-9.

Ryan-Borchers, T. A., J. S. Park, et al. (2006). "Soy isoflavones modulate immune function in healthy postmenopausal women." The American Journal of Clinical Nutrition 83(5): 1118-1125.

Sallusto, F. and A. Lanzavecchia (1994). "Efficient presentation of soluble antigen by cultured human dendritic cells is maintained by granulocyte/macrophage colony-stimulating factor plus interleukin 4 and downregulated by tumor necrosis factor alpha." J Exp Med 179(4): 1109-18.

Sansoni, P., R. Vescovini, et al. (2008). "The immune system in extreme longevity." Exp Gerontol 43(2): 61-5.

Saucedo, R., G. Rico, et al. (2002). "Transdermal estradiol in menopausal women depresses interleukin-6 without affecting other markers of immune response." Gynecol Obstet Invest 53(2): 114-7.

Saurwein-Teissl, M., T. L. Lung, et al. (2002). "Lack of antibody production following immunization in old age: association with CD8(+)CD28(-) T cell clonal expansions and an imbalance in the production of Th1 and Th2 cytokines." J Immunol 168(11): 5893-9.

Schroder, J., V. Kahlke, et al. (2000). "Gender differences in sepsis: genetically determined?" Shock 14(3): 307-10; discussion 310-3.

Schroder, J., V. Kahlke, et al. (1998). "Gender differences in human sepsis." Arch Surg 133(11): 1200-5.

Schwab, R., P. Szabo, et al. (1997). "Expanded CD4+ and CD8+ T cell clones in elderly humans." J Immunol 158(9): 4493-9.

Segerer, S. E., N. Muller, et al. (2009). "Impact of female sex hormones on the maturation and function of human dendritic cells." Am J Reprod Immunol 62(3): 165-73.

Shaw, A. C., S. Joshi, et al. (2010). "Aging of the innate immune system." Curr Opin Immunol 22(4): 507-13.

Siegal, F. P., N. Kadowaki, et al. (1999). "The nature of the principal type 1 interferon-producing cells in human blood." Science 284(5421): 1835-7.

Smith, D. C., R. Prentice, et al. (1975). "Association of exogenous estrogen and endometrial carcinoma." N Engl J Med 293(23): 1164-7.

Smith, S. M., G. B. Baskin, et al. (2000). "Estrogen protects against vaginal transmission of simian immunodeficiency virus." J Infect Dis 182(3): 708-15.

Sonoda, J., J. Laganiere, et al. (2007). "Nuclear receptor ERR alpha and coactivator PGC-1 beta are effectors of IFN-gamma-induced host defense." Genes Dev 21(15): 1909-20.

Soucy, G., G. Boivin, et al. (2005). "Estradiol is required for a proper immune response to bacterial and viral pathogens in the female brain." J Immunol 174(10): 6391-8.

Stanberry, L. R., S. L. Spruance, et al. (2002). "Glycoprotein-D-adjuvant vaccine to prevent genital herpes." N Engl J Med 347(21): 1652-61.

Stopinska-Gluszak, U., J. Waligora, et al. (2006). "Effect of estrogen/progesterone hormone replacement therapy on natural killer cell cytotoxicity and immunoregulatory cytokine release by peripheral blood mononuclear cells of postmenopausal women." J Reprod Immunol 69(1): 65-75.

Suenaga, R., M. J. Evans, et al. (1998). "Peripheral blood T cells and monocytes and B cell lines derived from patients with lupus express estrogen receptor transcripts similar to those of normal cells." J Rheumatol 25(7): 1305-12.

Surh, C. D. and J. Sprent (2008). "Homeostasis of Naive and Memory T Cells." Immunity 29(6): 848-862.

Svanborg, C., G. Godaly, et al. (1999). "Cytokine responses during mucosal infections: role in disease pathogenesis and host defence." Curr Opin Microbiol 2(1): 99-105.

Szabo, P., F. Li, et al. (2004). "Evolution of B-cell clonal expansions with age." Cell Immunol 231(1-2): 158-67.

Tangye, S. G. and D. M. Tarlinton (2009). "Memory B cells: effectors of long-lived immune responses." Eur J Immunol 39(8): 2065-75.

Tarazona, R. (2009). NK Cells in Human Aging. Handbook on Immunosenescence, Springer.

Tarlinton, D. (1998). "Germinal centers: form and function." Curr Opin Immunol 10(3): 245-51.

Teleshova, N., J. Kenney, et al. (2004). "CpG-C immunostimulatory oligodeoxyribonucleotide activation of plasmacytoid dendritic cells in rhesus macaques to augment the activation of IFN-gamma-secreting simian immunodeficiency virus-specific T cells." J Immunol 173(3): 1647-57.

Tiwari, S., G. P. Agrawal, et al. (2010). "Molecular basis of the mucosal immune system: from fundamental concepts to advances in liposome-based vaccines." Nanomedicine (Lond) 5(10): 1617-40.

Tollerud, D. J., J. W. Clark, et al. (1989). "The influence of age, race, and gender on peripheral blood mononuclear-cell subsets in healthy nonsmokers." J Clin Immunol 9(3): 214-22.

Trunova, N., L. Tsai, et al. (2006). "Progestin-based contraceptive suppresses cellular immune responses in SHIV-infected rhesus macaques." Virology 352(1): 169-77.

Trzonkowski, P., J. Mysliwska, et al. (2003). "Association between cytomegalovirus infection, enhanced proinflammatory response and low level of anti-hemagglutinins during the anti-influenza vaccination--an impact of immunosenescence." Vaccine 21(25-26): 3826-36.

Uemura, Y., T. Y. Liu, et al. (2008). "17 Beta-estradiol (E2) plus tumor necrosis factor-alpha induces a distorted maturation of human monocyte-derived dendritic cells and promotes their capacity to initiate T-helper 2 responses." Hum Immunol 69(3): 149-57.

Vallejo, A. N. (2005). "CD28 extinction in human T cells: altered functions and the program of T-cell senescence." Immunol Rev 205: 158-69.

Vallejo, A. N., C. M. Weyand, et al. (2004). "T-cell senescence: a culprit of immune abnormalities in chronic inflammation and persistent infection." Trends Mol Med 10(3): 119-24.

van Benthem, B. H., P. Vernazza, et al. (2002). "The impact of pregnancy and menopause on CD4 lymphocyte counts in HIV-infected women." AIDS 16(6): 919-24.

Vasto, S., G. Candore, et al. (2007). "Inflammatory networks in ageing, age-related diseases and longevity." Mech Ageing Dev 128(1): 83-91.

Vasto, S., G. Carruba, et al. (2009). "Inflammation, ageing and cancer." Mech Ageing Dev 130(1-2): 40-5.

Verthelyi, D. (2001). "Sex hormones as immunomodulators in health and disease." Int Immunopharmacol 1(6): 983-93.

Verthelyi, D. I. and S. A. Ahmed (1998). "Estrogen increases the number of plasma cells and enhances their autoantibody production in nonautoimmune C57BL/6 mice." Cell Immunol 189(2): 125-34.

Villacres, M. C., J. Longmate, et al. (2004). "Predominant type 1 CMV-specific memory T-helper response in humans: evidence for gender differences in cytokine secretion." Hum Immunol 65(5): 476-85.

Vural, P., M. Canbaz, et al. (2006). "Effects of menopause and postmenopausal tibolone treatment on plasma TNFalpha, IL-4, IL-10, IL-12 cytokine pattern and some bone turnover markers." Pharmacol Res 53(4): 367-71.

Wagner, H. J., M. Hornef, et al. (1994). "Sex difference in the serostatus of adults to the Epstein-Barr virus." Immunobiology 190(4-5): 424-9.

Weiss, N. S., C. L. Ure, et al. (1980). "Decreased risk of fractures of the hip and lower forearm with postmenopausal use of estrogen." N Engl J Med 303(21): 1195-8.

Weksler, M. E. and P. Szabo (2000). "The effect of age on the B-cell repertoire." J Clin Immunol 20(4): 240-9.

Wenisch, C., S. Patruta, et al. (2000). "Effect of age on human neutrophil function." J Leukoc Biol 67(1): 40-5.

Werner Held (2008). "Tolerance and reactivity of NK cells: Two sides of the same coin?" European Journal of Immunology 38(11): 2930-2933.

Whitacre, C. C., S. C. Reingold, et al. (1999). "A gender gap in autoimmunity." Science 283(5406): 1277-8.

Wichmann, M. W., D. Inthorn, et al. (2000). "Incidence and mortality of severe sepsis in surgical intensive care patients: the influence of patient gender on disease process and outcome." Intensive Care Med 26(2): 167-72.

Wikby, A., B. O. Nilsson, et al. (2006). "The immune risk phenotype is associated with IL-6 in the terminal decline stage: findings from the Swedish NONA immune longitudinal study of very late life functioning." Mech Ageing Dev 127(8): 695-704.

Woodruff, J. F. (1980). "Viral myocarditis. A review." Am J Pathol 101(2): 425-84.

Wu, J. M., M. B. Zelinski, et al. (2005). "Ovarian aging and menopause: current theories, hypotheses, and research models." Exp Biol Med (Maywood) 230(11): 818-28.

Yamamoto, Y., H. Saito, et al. (1991). "Sex differences in host resistance to Mycobacterium marinum infection in mice." Infect Immun 59(11): 4089-96.

Yang, J. H., C. D. Chen, et al. (2000). "Hormone replacement therapy reverses the decrease in natural killer cytotoxicity but does not reverse the decreases in the T-cell subpopulation or interferon-gamma production in postmenopausal women." Fertil Steril 74(2): 261-7.

Yasui, T., M. Maegawa, et al. (2007). "Changes in serum cytokine concentrations during the menopausal transition." Maturitas 56(4): 396-403.

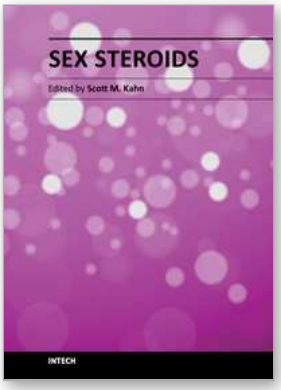
Zellweger, R., M. W. Wichmann, et al. (1997). "Females in proestrus state maintain splenic immune functions and tolerate sepsis better than males." Crit Care Med 25(1): 106-10.

Zhang, Y., T. T. Song, et al. (1999). "Daidzein and genistein glucuronides in vitro are weakly estrogenic and activate human natural killer cells at nutritionally relevant concentrations." J Nutr 129(2): 399-405.

Zhang, Y., D. L. Wallace, et al. (2007). "In vivo kinetics of human natural killer cells: the effects of ageing and acute and chronic viral infection." Immunology 121(2): 258-65.

Zhu, J. and W. E. Paul (2010). "Peripheral CD4+ T-cell differentiation regulated by networks of cytokines and transcription factors." Immunol Rev 238(1): 247-62.

Ziel, H. K. and W. D. Finkle (1975). "Increased risk of endometrial carcinoma among users of conjugated estrogens." N Engl J Med 293(23): 1167-70.



Sex Steroids

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This book, entitled "Sex Steroids", features a valuable collection of reviews and research articles written by experts in signal transduction, cellular biology, diseases and disorders. "Sex Steroids" is comprised of four sections, "The Biology of Sex Steroids", "Sex Steroids, Memory, and the Brain", "Sex Steroids and the Immune Response", and "Therapy"; individual chapters address a broad range of recognized and predicted functions and applications of sex steroids. "Sex Steroids" is intended to provide seasoned veterans as well as newcomers to this area of research with informative, resourceful, and provocative insights. Readers of "Sex Steroids" should emerge with an appreciation and understanding of the multitude and complexity of biologic processes attributed to these important hormones, and possible future directions of research in this fascinating and ever evolving field.

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