http://www.medscape.com/viewarticle/775536_1

Effects of Menopause on Autoimmune Diseases

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November 2012
(doi:10.1586/eog.12.63)

Abstract

Despite the fact that women living in industrialized countries are likely to spend a third of their lives in menopause, the influence of the estrogen withdrawal associated with menopause on many body systems is not fully understood.

This is particularly true of the immune system. Autoimmune diseases show a clear predominance in women, implying a central role for estrogen in their development. A thorough elucidation of that role, however, has been challenged by the observation of undeniable contributions to autoimmune disease by genetics, immunosenescence and environmental triggers as well. The global incidence of autoimmune disease has risen steadily in recent years, worldwide and in all ages, in parallel with steadily increasing global lifespans. Given the prevalence of autoimmunity in women, and the significant increase in the number of women in their postmenopausal years, the effect of menopause on autoimmunity is an area well deserving of further research effort.

Introduction

Life expectancy in human beings has increased dramatically in the last century[1] and is expected to continue to increase, reaching 100 years in the USA and other industrialized countries by approximately 2040.[2] In the USA, life expectancy has increased 10% since 1970 from an average of 70.8 years to an average of 78.3 years.[3] Women, on average, currently live nearly 3 years longer than men.[2]

The dramatic gains in life expectancy achieved have allowed for concomitant gains in an understanding of immune system aging, termed immunosenescence. Recent analyses of immune system aging have revealed that individual longevity is closely tied to the preservation of healthy immune function.[4]

The immunosenescence that occurs as humans age is therefore of increasing interest in medicine and deserving of research effort as life expectancy, particularly in developed countries, is increasing at a more rapid rate than concomitant improvements in meeting the medical needs of the elderly.[5] This is particularly true in women, who at current life expectancies will spend more than a third of their lifetimes in menopause.

Menopause, a period of time defined by the cessation of menstruation, is an experience common to all aging females. Cessation of menses results from a gradual deterioration in ovarian function, with declining production of follicles and falling levels of numerous endogenous hormones. Estrogen produced in postmenopausal females, furthermore, is of a different form than the one that is predominant during the reproductive years. Levels of the ovarian-derived 17b estradiol (E2), as ovarian follicles cease production, plunge as menopause nears, and estrogen in the form of estrone (E1) becomes the predominant form. E1 is produced by secretion of androstenedione by the ovarian stroma and the adrenal gland and is aromatized to E1 in the peripheral circulation. Conversion to E1 occurs primarily in adipose tissue, but also in muscle, liver, bone, bone marrow, fibroblasts and hair roots.[201] Postmenopausal deficits in estrogen and progesterone, and the replacement of E2, the primary estrogen of the reproductive years, to E1 carry impact far beyond the immune system.

Estrogen, with receptors in nearly every tissue of the body, is a principal regulator of homeostasis in the female body, with the hormonal tides characteristic of a woman's reproductive years having demonstrable effects on nearly every body system. The sudden and dramatic removal of estrogen from the female body, particularly in the form of estradiol, is a veritable tsunami with

significant and largely negative effects on many body tissues, including a loss of skin integrity and tone, poorer muscle tone (affecting heart, vasculature, eye and bladder function; declining brain function; and deterioration in bone strength). Estrogen levels, and particularly the estrogen withdrawal of menopause, undeniably impact autoimmunity in women as well.

Autoimmune disease as a category affects an estimated 50 million Americans[6] and is the top cause of morbidity in women in the USA.[6] The annual cost of only seven of the 100+ known autoimmune diseases (Crohn's disease, ulcerative colitis, systemic lupus erythematosus [SLE], multiple sclerosis [MS], rheumatoid arthritis [RA], psoriasis and scleroderma) are estimated, through epidemiological studies, to total as much as US$70 billion annually.[6]

The development of autoimmunity clearly involves genetic and environmental contributions to existing levels of endogenous estrogen and the precise contributions of each are not fully understood. Additional research, to focus on how autoimmune disease is impacted by the plummeting estrogen levels associated with menopause, is needed.

Immunosenescence: How the Immune System Ages

The immune system undergoes constant physiological changes over the human lifespan.[7] The infant has no immunity of its own at birth; immune function develops quickly over the first few years and then builds to a complete maturation by puberty.[8] In fertile women, immunity fluctuates cyclically in sync with the menstrual cycle; dramatic changes occur during pregnancy as well as the postpartum period.[8]

Throughout life, homeostasis is preserved in all systems through tightly regulated interactions between numerous interdependent body tissues (Figure 1).[7] Driven by inalterable genetic factors, environmental insults, such as UV light, and lifestyle factors like nutrition and nicotine use,[9] body tissues, with age, experience a progressive deterioration of cellular and tissue functions, largely due to genetic decay and the byproducts of metabolism.[9] The study of aging in the immune system has revealed that immunosenescence represents a substantial remodeling of major immune functions.[7]

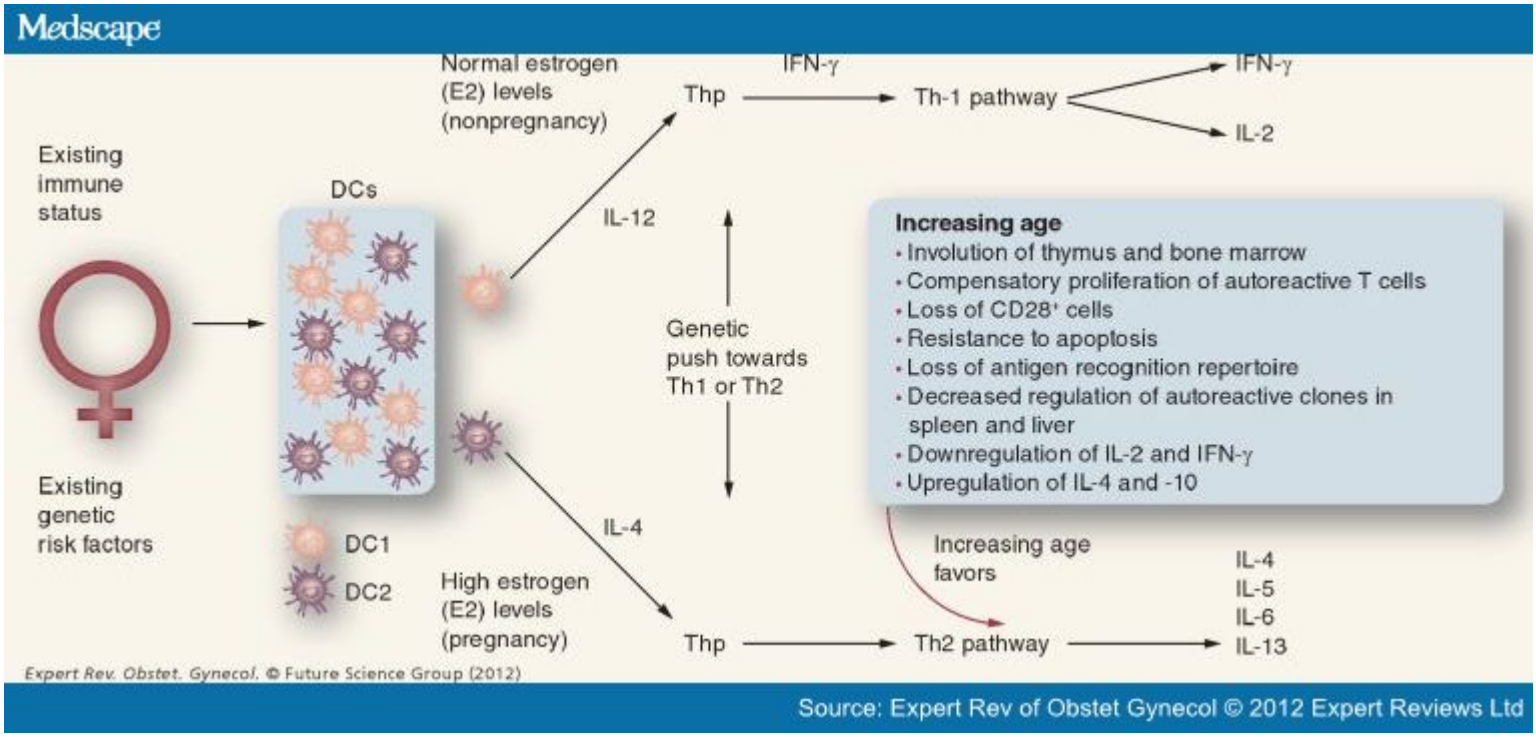

Figure 1.

Interaction between genetic factors, estrogen and aging in the development of Th1/TH2 differentiation and subsequent autoimmune diseases in aging women.
DC: Dendritic cell; Th: T-helper cell.

Immunosenescence in both genders impacts cellular, humoral and innate immunity.[10] Significant consequences of aging include atrophy of the thymus, changes in both the total numbers and subsets of lymphocytes, changes in the function of both B and T cells, changes in the patterns of secretion of cytokines and growth factors, disruption of intracellular signaling, changes in the patterns of antibody production, loss of antibody repertoire, loss of response to antigens and mitogens and disruption of immunological tolerance (Table 1). Gender-specific increases in some aspects of immunosenescence have been observed and will be discussed below.

Although aging affects many immune cell types, the cumulative effects of aging on T-cell function are the most consistently observed and most extensive.[11] The human thymus decreases in both size and cellularity in a process called thymic involution; thymus tissue is replaced with fat.[12] By 60 years, thymus-derived hormones are absent from the circulation.

Involution of the thymus in humans occurs in concert with a depletion of naive T cells and a shift in the T-cell population toward memory CD4+ cells.[13] In young adulthood, the CD4+ subset is characterized by roughly equivalent numbers of memory and naive CD4+ cells but in older adults becomes predominantly memory CD4+,[14] a shift that reduces the potential antigenic repertoire.[15] The shift toward memory T cells with age is largely a consequence of the imbalance in T-cell maturation produced by thymus involution[16] paired with an age-related impairment of T-cell proliferation[17] in concert with clonal expansion of T cells activated by specific antigens.[15] The shift toward memory cells in the T-cell compartment affects cytokine production as well, with less IL-2 produced (primarily a product of naive T cells) but more IL-4 (primarily a product of memory T cells).[18]

The cumulative loss of T helper (Th) cells with age plays a profound role in immunosenescence, ultimately affecting both cellular and humoral immunity. Disruption of Th cells and alterations of cytokine levels that control B-cell functions compromise humoral immunity substantially, with decreased production of long-term immunoglobulin (Ig)-producing B cells as well as a reduction of Ig diversity.[5] Although B-cell numbers do not change significantly, there is a significant impairment of B-cell response to primary antigenic stimulation;[15] specific immunoglobulins produced become more random, and those produced have decreased affinity for their specific antigen.[15] With age, therefore, the B-cell repertoire poised to respond to new antigenic challenge is limited, and the predominance of memory T cells seen with thymic involution is mirrored in the B-cell compartment.[19] IL-15, particularly, stimulates proliferation of memory T cells; IL-15 levels are nearly double in healthy adults 95 years or older (3.05 pg/ml compared with both older adults [60–89 years] 1.94 pg/ml and midlife adults [30–59 years] 1.73 pg/ml).[20]

Immunosenescence is compounded by the presence in the aged of a chronic low-grade inflammation characterized by increased proinflammatory cytokines, such as IL-6 and TNF-a, compounds that create oxidative stress and decrease cellular antioxidant capacity.[10] These proinflammatory cytokines are positively associated with stress as well as salivary cortisol levels and may play a significant role in creating the degenerative changes associated with aging.[17] Other body processes, most notably innate immunity[21] and interactions of immunity with the neuroendocrine system,[22] also contribute to immune system aging.

Antigen-presenting cells such as dendritic cells (DCs) and macrophages serve as a bridge between the innate and the adaptive immune systems. Antigen-presenting cells interact with foreign molecules and release pathogen-specific cytokines that drive the activation of naive CD4 helper cells into either Th1 or Th2 effector cells.[23]

Production of IL-12 and IFN-g drive commitment of naive T cells to the Th1 lineage. Th1 cells produce cytokines that favor a cell-mediated response (IL-2, lymphotoxin, IFN-γ and TNF-β), warding off intracellular pathogens, mounting delayed-type hypersensitivity responses to viral and bacterial antigens and eliminating tumor cells.[15]

Production of IL-4 and IL-10 drive commitment to the Th2 subtypes.[23] Th2 cells release cytokines which produce an environment favoring humoral immunity (IL-4, -5, -6, -10, and -13) by stimulating Th2 cell proliferation, differentiation, and participation in humoral immunity.[15]

In the aged, however, naive cells are less likely to become effectors. In those that do, there is a documented shift towards a Th2 cytokine response.[15]

The molecular and cellular changes associated with aging have substantial clinical ramifications. The elderly have impaired ability to achieve immunization but much higher levels of circulating autoantibodies, (due to the lack of naive effectors) impaired response to viral infections, increased risk of bacterial infections, and increased risk of both neoplastic and autoimmune disease.[7]

Gender & Immunity

Immunosenescence does not affect men and women equally.[11] The dysregulation in T-cell function, for example, that is associated with aging, occurs much more dramatically in women than in men.[24,25]

Gender-specific differences in immunosenescence are at least partly attributable to sex hormones, evidenced by the fact that men and postmenopausal women have reduced T-cell immunity compared with premenopausal women.[26] The fact that men live shorter lives, on average, than women is also partially attributed to the thymic involution produced by higher circulating levels of androgens in men.[27]

Much is known about the influence of sex hormones on immunity in general. Androgens, estrogen, and progesterone all influence immune functions; estrogen in the form of 17b estradiol has been particularly associated with profound influences on the immune system (Table 2).

Females, in general, have superior immune vigilance compared with males, with both humoral and cell-mediated arms mounting more vigorous responses to immune stimulation.[28] Women maintain higher antibody levels than men, as well as higher levels of circulating IL-1, IL-4 and IFN-g[29] and females reject grafts faster.[30] A general pattern is observed in which estrogen enhances humoral immunity while androgens as well as progesterone tend to suppress it.[31] Women respond to antigenic stimulation with a predominantly Th2 response, with increased antibody production.[32] Estrogen stimulates the Th2 response by stimulating Th lymphocytes to secrete type 2 cytokines, which promote the synthesis of antibodies.[33] High estrogen levels associated with pregnancy also produce a shift towards Th2 response.[34]

Conversely, men respond to antigenic stimulation with primarily a Th1 response.[32] Androgens stimulate Th cells to produce type 1 cytokines, which suppress Th2 activity and stimulate CD8 cells,[35] a process that produces inflammation as the predominant immune response.[32]

The fact that estrogen favors a stronger overall immune response, particularly with regard to antibody response in women, is a mixed blessing. Although it produces a superior resistance to infection compared with men it also increases the risk in women of autoimmune disease.[36]

Aging & the Development of Autoimmunity

There are at least 70 documented autoimmune diseases[36] and the prevalence of autoimmune disease is rapidly rising worldwide, for reasons not completely understood.[37] Although the disorders share a pathogenic immunity against the body's own tissues that is the product of a progressive disorganization of immune function, the precise etiology is unknown. Autoimmunity appears to be a multifactorial process in which genetic, environmental, and biochemical processes all participate.

A genetic or familial predisposition to autoimmunity clearly plays a role. Pairwise analyses examined discordant familiar risks for seven common autoimmune diseases using a large national databank that included the records of 172,242 patients. Records examined demonstrated a genetic pattern of inheritance for RA, SLE, Type I diabetes, ankylosing spondylitis, Crohn's disease,

celiac disease and ulcerative colitis. Incidence of each of the seven autoimmune diseases analyzed were associated additionally with at least three of the others.[38]

Environmental factors, such as pollution or occupational exposures, or contact with viral, bacterial or parasitic pathogens may trigger autoimmunity. Lifestyle differences like nutritional choices, sleep patterns, medications, and stress may also trigger illness.[36]

Endogenous factors also play a role; for example, sex hormones are a major influence.[29] The most striking gender-based difference in immune system function is the remarkable female predominance of autoimmune diseases.[39] An estimated 78% of those affected by autoimmune disease are women.[32]

Gender-specific patterns in the development of autoimmune diseases suggest a strong role of sex hormones, as predominance in the female sex changes with age at disease diagnosis, lending strong support.[40] Autoimmunity in males show less age-dependent variation. Autoimmune diseases prevalent in males typically present before the sixth decade with the appearance of autoantibodies, acute inflammation and an increase in the proinflammatory cytokines characteristic of a Th1 response.

Those that manifest primarily in females are more complicated. Autoimmune diseases that manifest early in life in females generally have a clear antibody-mediated pathology. Those with increased incidence in females that appear after the age of 50 year (in menopause) tend to be characterized by a more chronic disease course and fibrotic Th-mediated pathology.

A central role for sex hormones in autoimmune disease in women is also evidenced by the dramatic differences in prevalence during the different reproductive periods of a woman's life, which are themselves driven by profound modulation of circulating levels of sex steroids, particularly estrogen.[29] Many autoimmune diseases in which women predominate are exacerbated by the higher levels of female sex steroids in pregnancy (a period that is also characterized by a shift towards Th2 response), primarily estrogen, which worsens disease while androgens produce beneficial effects.

Strict correlation of autoimmunity with estrogen levels, however, is not observed. Other female-predominant autoimmune diseases, such as MS and RA, worsen during pregnancy[41] and improve in the postmenopausal period (Table 3).[42]

The influence on autoimmune disease of the decreasing levels of estrogen associated with aging in women is essentially unascertained. The declining efficacy of the immune system with age, in both genders is accompanied by a characteristic increase in both the variety and level of circulating autoantibodies.[7] Anti-nuclear antibodies levels remain constant until approximately 60 years, and then rise. Approximately 5% of healthy individuals of that age have high anti-nuclear antibody titers (1:160), compared with 37% of those over 70 years of age.[43]

Although autoantibodies, found in the blood of all healthy humans, serve a useful function in a healthy adult, acting to clear away cellular debris produced by routine injury and inflammation,[44] the number of different circulating autoantibodies has proven to be a good predictor of autoimmune disease. The risk of developing childhood diabetes within 5 years, for example, is only 10% with the presence of one autoantibody specificity, but increases to as much as 80% if there are three.[32] Autoantibody levels are normally kept in check by immune tolerance processes, but can (through age or overt disease) reach clinically significant levels, at which point the binding of self-antigens activates the complement cascade and results in cytotoxicity or other immune pathology.[32] Rising levels of antibodies, apart from the number of different specificities, are also associated with a generally increased risk of autoimmunity in old age.[7]

What specifically causes the documented increase in both autoantibodies and autoimmunity in older adults is a matter of debate. With age, the normally tight orchestration of interdependent immune functions begins to decay, with progressive perturbation of immune function that can eventually lead to autoimmune disease.[7] Increased autoimmunity appears to be primarily the result of the combined effects of the reduction in naive T cells (produced by thymus involution) in concert with an activation of self-reactive memory B cells.

B-cell activation may result from a variety of antigenic stimuli.[45] Exposure to an infectious agent with molecular mimicry of a self-antigen may prompt a memory response.[15] Cumulative exposure to a variety of antibody specificities, in the presence of chronic infections, for example, may also produce hyperstimulation of B cells. In a study of the elderly in Cameroon (where multiple chronic infections are not uncommon) the pattern of autoantibodies observed in the elderly subjects was markedly different from that in industrialized countries, suggesting a role for long-term multiple antigen exposures.[46] Normal aging can also reduce the efficiency of normal physical immune barriers, resulting in increased pathogen intrusion.[47] Innate immunity

also deteriorates with age, which can contribute to chronic immune stimulation. The persistence of high antigen levels can also make costimulatory T cells less susceptible to downregulation.[47]

Another source of B-cell memory activation are neoantigens, which are revealed by a progressive loss of tissue integrity and increased inflammation as individuals age.[48] Inappropriate activation of lymphocytes can also result from defective clearance of cellular debris, resulting in prolonged exposure to autoantigens.[47] Self-antigens may also acquire alterations that increase immunogenicity. For example, post-translational modification of proteins increases in immunosenescence; particular modifications, such as isoaspartyl formation, can trigger an autoimmune response.[47]

Improper self-antigen recognition by DCs and T-cell initiates, through release of specific cytokines (as described above), destructive Th1 or Th2 responses. RA, for example, is characterized by an exaggerated Th1 self-reactive immunity; SLE by an excessive Th2 response.[23] Estrogens are known to drive physiological selection of Th1 or Th2 pathways.

A perturbation in immune receptor signaling may underlie the increase in autoimmune phenomena in the elderly, particularly those that contribute to the regulation of immune tolerance. Optimal immune function necessitates a tight balance of the signaling pathways in both T- and B-cell compartments; these pathways are altered in both compartments in SLE and other autoimmune diseases.[49]

Other aspects of aging can increase immune dysfunction as well: stress, with associated increased cortisol levels; sleep dysregulation and associated effects on immunity; decrease in physical activity and negative effects on immunocompetence; and the nutritional deficiencies common in old age with a negative impact on immunocompetence.[4]

Specific Effects of Estrogen on Autoimmunity

In women, the cumulative physiological degeneration associated with normal aging is augmented by a dramatic and systemic estrogen deprivation. Estrogens generally favor immune processes involving CD4+ Th2 cells and B cells, thereby promoting B-cell-mediated autoimmune diseases.[50] Physiologic levels of estrogen, however, also stimulate the expansion of CD4+ CD25+ Tregs, which help maintain tolerance to self-antigens and therefore ameliorate autoimmune disease, as well as the expression of the Foxp3 gene, a marker for Treg function.[51] Follicular Th cells by contrast, appear to drive autoantibody production in the germinal center and are associated with the development of systemic autoimmunity.[52]

Androgens, on the other hand, encourage processes involving CD4+ Th1 cells and CD8+ cells, acting to suppress or ameliorate B-cell-mediated autoimmune diseases.[29] The influence of these hormones on the immune system, therefore, produce more autoimmune pathology in women in autoimmune disease mediated by Th2 dominant processes, and more in men when Th1 processes are involved (Table 3).

Hormonal manipulations can alter immune reactivity and modulate disease expression.[39] Estrogens provoke involution of the thymus;[36] treatment of castrated animals with exogenous sex hormones causes massive atrophy of the thymus.[53] Thymus regeneration occurs following ovariectomy,[5] and thymus involution occurs during pregnancy, which reverts after lactation ceases.[54]

Estrogen-induced involution of the thymus is associated with a reduction in numbers of immature T lymphocytes.[36] Estrogen affects T-cell subset composition, as well as T-cell function and activation.[11] Oral estrogen-replacement therapy has been shown to restore T-cell function.[55]

Estrogen drastically reduces not only the size of the thymus, but also the bone marrow cavity as well, the sites where most deletion of autoreactive cells occur. B cells developing at alternative sites (liver and spleen), where less stringent selection occurs, may escape normal controls.[29]

Estrogens, in fact, stimulate lymphopoiesis outside of the bone marrow.[56] Mice treated with exogenous estrogen develop impressive hemopoietic centers in the liver and spleens filled with antibody-producing cells.[29]

Estrogen depletion in women, characteristic of postmenopausal women, has been specifically associated with reductions in B

and T cells[57] and Th-derived cytokines[58] as well as an impaired immune response to viral infections.[59] In vitro, estrogen stimulates Th1 cytokine production by T cells.[45]

Estrogens diminish the number of monocytes, through apoptosis, as well as through a modulation of the cell cycle which delays mitosis.[60] Autoreactive B-cell apoptosis, particularly, is inhibited.[61] Estrogen, however, simultaneously induces a rapid maturation of B lymphocytes[36] and stimulates Th lymphocytes to secrete type 2 cytokines that promote antibody production.[33, 35]

What is Known About the Estrogen Deficiency of Menopause & Specific Autoimmune Diseases

It is known that many natural, pathological and therapeutic conditions can change serum estrogen levels, including the menstrual cycle, pregnancy, menopause, use of oral contraceptives, use of hormonal replacement treatment and disease. The estrogen withdrawal of menopause, however, is a significant hormonal transition, and one with numerous physiologic ramifications. The normal immunosenescence evidenced in both sexes may be modulated in some degree by changing levels and forms of endogenous estrogen.

The production of cytokines IL-6, IL-1, and TNF-a increase after menopause, as does the physiological response to those cytokines.[10] There is a postmenopausal decrease in CD4 T and B lymphocytes, as well as decrease in the cytotoxic activity of natural killer cells.[31]

In vitro analysis of three different T-cell signaling proteins (Janus kinase 2 [JAK2], Janus kinase 3 [JAK3], and CD3-z) found that postmenopausal levels were substantially reduced compared with premenopausal levels.[11] In addition, Jurkat T cells exposed to premenopausal levels of E2 also formed significantly more IL-2 producing colonies compared with those exposed to premenopausal levels (75.3 ± 2.2 vs 55.7 ± 2.1 [$p < 0.0001$]).[11] Studies suggest a normalization of cellular response after hormone-replacement therapy (HRT).[10]
Systemic Lupus Erythematosus

SLE is an autoimmune disorder characterized by the production of pathogenic autoantibodies, primarily to nuclear antigens, as well as dysregulation of both T and B cells.[62] B cells display accelerated maturity.[63] SLE patients exhibit monocyte-derived DCs, which display an activated, proinflammatory phenotype.[63]

SLE has a female preponderance of 9:1. Although there are X-chromosome abnormalities associated with SLE,[64] estrogen itself is strongly implicated in SLE autoimmunity.[10] SLE is associated with a disrupted sex hormone balance characterized by lower amounts of androgens and dramatically higher levels of the estrogen metabolite, 16-hydroxyestrone.[65] Pregnancy worsens the disease;[23] incidence of SLE diminishes after menopause.[36, 42, 66] Administration of an estrogen receptor (ER) blocker (fulvestrant) to human female SLE patients produces clinical improvement[67] as does treatment with testosterone.[68]

Increased risk has been associated with higher lifetime levels of estrogen exposure. In a cohort of 238,308 adult women evaluated prospectively over 27 years, the 262 women diagnosed with SLE over the course of the study were analyzed for relative risk factors. Increased risk was associated with early menarche (aged less than 10 years; relative risk: 2.1; 95% CI: 1.4–3.2) and oral contraceptive use (relative risk: 1.5; 95% CI: 1.1–2.1).[69] Menstrual irregularity increased risk of SLE diagnosis in a Japanese case–control study.[70] Menstrual cycles of abnormal length (either long and short) increased risk as well.[71] Estradiol treatment of mouse lupus-prone strains produces disease onset, increases autoantibody production, and increases risk of mortality.[23]

Hormonal fluctuations also appear to influence the course of SLE. Dual studies evaluated the course of disease in early-onset SLE patients versus late-onset patients; later-onset patients (after the age of 50 years) had lower incidences of renal disease, arthritis, malar rash and photosensitivity compared with patients who were younger at diagnosis.[72] Younger patients had a more aggressive disease course as well, with time from symptom onset to diagnosis being 3 years compared with 5 years in older patients.[72] Similar results were observed in a study of 125 Chinese SLE patients.[73] A pooled analysis that compared 714 late-onset patients with 4700 early-onset patients confirmed earlier results, finding also a lower incidence of purpura,

alopecia and Raynaud's phenomenon in the late-onset group. The late-onset group, however, had a higher prevalence of rheumatoid factor, with antibodies to ribonucleoprotein and sphingomyelin less frequently.[74]

SLE patients have also been evaluated for effect of previous hysterectomy (with and without concomitant oophorectomy). SLE patients (n = 3389) who had undergone hysterectomy were less likely to develop nephritis or positive anti-double-strand DNA antibodies than age-matched SLE patients who had not (odds ratio: 6.66 [95% CI: 3.09–14.38] in European patients and 2.74 [95% CI: 1.43–5.25] in African–American patients). SLE patients with hysterectomy before disease onset had later onset of disease (p = 0.0001).[62]

The role of estrogen, rather than age alone, was investigated by studies which utilized younger SLE patients who underwent ovarian failure produced by cyclophosphamide. Significantly fewer flares were observed in the group with ovarian failure compared with normally menstruating SLE women.[75] The cyclophosphamide group, however, was significantly older than the control group (37.9 years compared with 25.5 years). Other research, however, followed two groups of SLE patients: one early onset and one late onset and concluded that the decrease in disease activity after menopause could not conclusively be determined to be related to hormonal status.[76]

HRT has documented benefits for women with regard to some aspects of aging; and in some cases may be medically necessary.[77] Postmenopausal osteoporosis, for example, directly tied to estrogen deficiency, may require hormonal intervention, shown to reduce the risk of hip fractures by as much as 30%.[78] HRT, however in patients with SLE, which is induced or exacerbated by oral contraceptives has the potential to produce disease flares.

Examination of the effects of HRT in postmenopausal women found that in 351 postmenopausal SLE patients, combined estrogen/progesterone hormone replacement (0.625 mg conjugated estrogen daily, plus 5 mg medroxyprogesterone for 12 days/month) given for 12 months produced only a small increase in the risk of disease flares (0.64 probability in HRT patients vs 0.51 in placebo controls, with most flares mild or moderate [p = 0.01]). HRT use did not significantly increase the risk of severe flares.[77]

An overall assessment of the consequences of SLE in postmenopausal patients looked at damage accrual in SLE as part of the LUMINA (Lupus in Minorities: Nature vs Nurture) study and found that despite the drop in disease activity in the postmenopausal period (with a reduction in the risk of renal disease), overall damage scores were higher due to an increase in cardiovascular disease. Whether higher damage accrual is related to the changing hormones of menopause or due simply to longer disease duration is as yet undetermined.[79] It is known that estrogen promotes SLE through ER-a by inducing IFN-g.[80] Testosterone is most likely protective in SLE patients by driving the Th1 immune pathway.[10]

Although no differences are observed in SLE patients as compared with normal controls with regard to circulating estrogen levels (17b-estradiol), number of ERs or binding affinities of ER to estrogen, blocking of the ERs using fulvestrant in patients with moderately active SLE produced a significant decrease in disease activity (as measured by the SLE disease activity index score).[67]

Female SLE patients have abnormal metabolism of sex hormones, with an increase in the production of 16-hydroxyestrone and metabolites that may produce a chronic state of excessive estrogen.[81] Elevated aromatase activity (an enzyme found in all organ systems and integral to sexual reproduction, that converts androgens into estrogens) is also observed in SLE patients.[36]

The molecular mechanism leading to a gender preponderance in SLE appears to be demethylation of CD40 ligand on CD40+ T cells,[82] which, appearing on an inactive X-chromosome, results in overexpression of CD40 ligand on CD4+ cells.[83] SLE patients are typically characterized by high titers of autoantibodies directed against nuclear antigens, antibodies which have been demonstrated to potentially arise from germline-coded polyreactive antibodies induced to class-switch to IgG by a proinflammatory milieu.[84]

Rheumatoid Arthritis

RA is an autoimmune disease in which multiple components of the immune system produce tissue damage and contribute to systemic inflammation. T cells, B cells and macrophages infiltrate into the inflamed synovial membrane whose resident cells proliferate and differentiate; macrophages and other activated tissue-resident cells begin to produce cytokines which induce B- and T-cell responses that act in concert to erode bone and cause destruction of cartilage. RA is associated with an altered sex hormone balance characterized by lower amounts of androgens and higher estrogens.[65] RA incidence increases with

postmenopause, suggesting that decreased E2 levels are involved in disease onset. The incidence of RA incidence peaks in the seventh decade.[85] Pregnancy ameliorates disease activity,[86] however, the postpartum period is a time of high risk for new-onset RA.[87] Aromatase inhibitors, compounds that interfere with estrogen production, trigger onset of RA or produce arthritis flares in both premenopausal and postmenopausal women.[88]

RA is characterized by a profile of generalized immunosenescence typical with age. Early-onset RA may represent premature immunosenescence,[89] a loss of T-cell diversity and T-cell reactivity, a slide towards proliferative arrest, and significant production of inflammatory cytokines. Levels of autoantibodies increase as well.[85] In addition, RA patients carry large, clonally expanded populations of CD4+ and CD8+ cells; CD4+ clones are consistently autoreactive.[85]

Menopause is associated with an increased risk of disease onset. In a cohort of nearly 32,000 women in Iowa (USA), those who reached menopause before 45 years of age had a higher risk of RA than women who reached menopause after 51 years of age.[90] Similar results were obtained in a study that evaluated 18,326 Swedish women and compared those who entered menopause before 45 to those who reached menopause after 45 years of age.[91]

Another author followed RA patients over a 6-year period; the 209 female patients evaluated were divided into premenopausal and postmenopausal groups. Postmenopausal subjects had greater joint damage as measured radiographically as well as by health assessment questionnaires. In addition, comparison with both premenopausal women and men determined that estrogen deprivation of menopause was a significant factor in the disparity of damage between men and women.[92] Although the use of HRT does not appear to influence the risk of developing RA,[93] HRT improves both symptoms and progression of disease.[94]
Scleroderma

Scleroderma is an autoimmune disease of the connective tissues characterized by a buildup of collagen in body tissues. Typically involving primarily the skin on the hands and face, scleroderma can affect many organ systems, including the heart, lungs, and kidneys. Scleroderma affects mostly women, with onset typically around the same time as menopause; early menopause increases risk.[95] Scleroderma involves significant vasculopathy, which is accentuated by menopause-related loss of estrogen. A prospective Italian study found that the estrogen removal of the postmenopausal period was a risk factor for the development of pulmonary arterial hypertension in scleroderma patients, with relative risk due to postmenopausal state of 5.2 ($p = 0.000$).[96] Twenty-three postmenopausal scleroderma patients were subsequently treated with HRT for a mean follow-up of 7.5 years. None of the HRT scleroderma patients developed pulmonary arterial hypertension as compared with 19.5% of those not on HRT.[97]
Sjögren's Syndrome

Sjögren's syndrome (SS) is an autoimmune disorder that affects mucous membranes as well as tear ducts and salivary glands but may also impact other organs such as the kidneys, stomach, intestines, vasculature, lungs, liver, pancreas and the CNS. The large majority of SS patients are women, with onset after the age of 40 years. SS is associated with a T-cell infiltration of the exocrine glands with associated autoantibodies.[98] Estrogen suppresses disease development while ovariectomy leads to an SS-like condition with increased epithelial cell apoptosis.[23] Estrogen-deficient mice develop an autoimmune exocrinopathy resembling SS.[99] It is believed that estrogen deficiency may influence autoantigen cleavage in such a way that it results in autoimmune exocrinopathy in postmenopausal women.[99]
Multiple Sclerosis

MS is an episodic autoimmune disease in which autoantibodies attack the CNS, particularly the myelin sheath; symptoms vary with the location of the attack. MS is typically diagnosed in young adulthood. As the target tissue of MS is the CNS, MS has debilitating and systemic effects. More women than men suffer from MS; estrogen influence is also suggested by the fact that MS symptoms improve during pregnancy but worsen postpartum. MS pathogenesis is largely driven by antigen-specific CD4+ Th1 cells, specific for the CNS, which secrete proinflammatory cytokines such as IFN-g, TNF-a and IL-12. Active disease is well-correlated with T-cell production of proinflammatory cytokines.[23] Most (54%) MS patients reported a worsening of symptoms after menopause; 75% of those who had used HRT (at all stages of menopause) reported improvement.[100]
Autoimmune Hepatitis

Autoimmune hepatitis (AIH) is an autoantibody-induced inflammation of the liver, although a variety of autoantibodies (directed against specific liver antigens as well as nuclear DNA, mitochondrial antigens, and smooth muscle antigens) are involved. AIH also affects predominantly females, most often with onset in childhood but also postmenopause,[45] although men may be affected more often than women in old age. Autoantibodies are directed against hepatocytes, the putative result of an insidious progressive destruction of the hepatic parenchyma.[45] AIH often ameliorates during pregnancy; many cases, however, are

diagnosed in the postpartum period.[101,102]

Conclusion

Immunosenescence is a complex phenomenon, involving cellular, humoral and innate immunity in a downward spiral of dysregulation of the tightly interdependent responses characteristic of young adulthood, with multiple effects on hematopoiesis, immune cell proliferation and differentiation, and immune cell function. The eventual result is an immune system that is hyperactivated but defective, which sets the stage for a rise in autoantibodies and thus autoimmunity.

Unraveling the respective roles of genes, hormones, lifestyle factors and environment in autoimmunity in general and in postmenopausal women in particular has yet to be accomplished. Although the general understanding that estrogen skews immune responses toward Th2 pathways, while androgens drive the Th1 pathway explains many of the gender discrepancies and age-related peaks of disease observed, it does not explain all. There are discrepancies and it proves difficult to attach hormones to specific mechanisms.

Obviously other factors are at play. Genetic and epigenetic components need further investigation. The major autoimmune diseases of the connective tissue all have a strong predominance in women, tissue specificity for Th1 or Th2 responses may be a factor as well.

The specificity of Ig subclass may influence autoimmunity as autoimmunity is characterized by a marked increase of IgM levels produced by B cells. The role of sex hormones in autoimmunity and in the menopausal period is unmistakable but not easily understood. Estrogen, progesterone and testosterone share the same precursor: cholesterol, as well as common intermediate metabolites that are known to interact with the immune system. Levels of both estrogen and progesterone decline rapidly as menopause nears; progesterone levels drop more steeply than estrogen. Progesterone may substantially impact autoimmune development, as progesterone receptors are ubiquitous in immune organs tissues and cells. Progesterone has different immunomodulatory effects from estrogen but shares interdependent signaling pathways.

The profound female predisposition to autoimmunity as well as the fact that significant immune derangement occurs during the estrogen-infused months of pregnancy suggest the likelihood that, in general, lower physiological amounts of estrogen stimulate Th1 effects whereas higher doses stimulate Th2.

The presence of at least two different types of ERs also allows for multiple levels of control, as does the fact that at menopause, the predominant circulating form of estrogen changes. In addition, the X-chromosome, apart from female hormones, may contribute to the female predominance in autoimmune diseases. Racial differences have yet to be seriously explored; other factors implicated in autoimmunity have lacked significant research effort as well. For example, geographical differences in autoimmune disease prevalence have been note, as has level of industrialization. Increased parity has also been associated with an increased risk in autoimmunity.

With steadily expanding life expectancy, immunosenescence in general, and autoimmunity in old age in particular should be given increased medical focus. The role of menopause, with its attendant depletion of estrogen, in autoimmune disease should be an important part of that research effort, given the drastic dichotomy in incidence of autoimmune disease in women and men and the longer expected female lifespan. A better understanding of the interplay between genetic, hormonal and environmental factors that lead to autoimmunity in menopause is necessary to provide appropriate prevention and/or treatment options for older patients, preserving health into old age and providing an increased quality of life throughout those additional years.

Expert Commentary

Estrogen rules a women's body. With ERs in every organ system and nearly every tissue and organ, estrogen's actions continue to be catalogued but a comprehensive understanding of its dominion over the physiology of the female has yet to be attained.

Estrogen maintains female health, protecting a women's cardiovascular system, maintaining bone health, and preserving neural health and brain function. It ferries her from childhood to motherhood yet eventually brings the curtain down on her fertility. Estrogen can also betray her, promoting cancers in the reproductive organs (breast, ovary and uterus) and causing both mood swings and migraines. It also plays a role in autoimmune disease.

The dramatic preponderance of autoimmune disease in females makes a leading role for estrogen in autoimmune disease nearly certain. The specific contributions that estrogen makes to autoimmunity, however, have been difficult to tease out, due largely to the magnitude of estrogen's influence in female physiology, with seemingly infinite possible actions in multiple biochemical processes. The fact that estrogen, over the lifespan of the human female, shapeshifts also complicates the picture. E2, the predominant form during the reproductive years, is complemented by estriol (E3) during pregnancy and replaced as the dominant form by E1 after menopause. Another complicating factor is existence of dual forms of receptors which act to modulate how estrogen is expressed. Variations in the circulating level of the different forms of estrogen also modulate immune processes, particularly with regard to whether immune response is driven towards cellular (Th1 pathway) or humoral (Th2 pathway) immune responses. A better understanding of the role of estrogen in immune processes is critical for elucidating the role that aging (and its associated estrogen withdrawal in women) plays in both the development and the course of autoimmune disease.

Five-year View

This review revealed a disturbing absence of data on the influence of menopause on autoimmune disease given its predominance in women and the fact that autoimmunity increases with age, an absence possibly related to an existing deficit in the understanding of the physiological basis for autoimmune disease in general. A meaningful understanding of the physiology is a challenging goal because autoimmunity clearly has multifactorial origins: a genetic component clearly provides a foundation, estrogen plays a documented role and prevalence shows a clear correlation with age. The influence of heredity on autoimmunity is being rapidly unveiled now and will no doubt contribute greatly to the elucidation of the relative additional contributions of epigenetic processes, changes in hormone levels and immunosenescence on immune function. A better understanding of the processes by which molecular events, hormonal shifts and immunosenescence impact a healthy immune system will provide a physiological basis for better ways to treat both immunosenescence and autoimmunity, a critical goal as the world population, particularly in the developed world, continues to age.

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Papers of special note have been highlighted as:
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