
CME review article

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Innate and adaptive immunosenescence

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Objective: To review the effect of increasing age on the immune system and some of its clinical implications.

Data Sources: MEDLINE and PubMed searches were performed cross-referencing the keywords *immunosenescence*, *aging*, and *immunity*. Articles were reviewed for additional citations.

Study Selection: Articles were reviewed and selected based on relevance to subject matter.

Results: The study of immunosenescence is complex and not completely understood. Aging affects both the innate and adaptive arms of the immune response. With increased age, there may be a decrease in phagocytosis, alteration of cellular migration, changes in cell populations and numbers, and a decreased ability to produce specific antibodies. Clinically, these changes potentially increase morbidity and mortality in elderly individuals through an increased rate of infections, malignancy, and autoimmunity.

Conclusions: The process of aging is accompanied by diverse changes in immunity. Several therapeutic approaches are under investigation, including cytokine therapy, hormonal replacement, antioxidant supplementation, and caloric restriction, to attenuate or potentially reverse immunosenescence.

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INTRODUCTION

Immunosenescence is defined as changes in the immune system that develop with increasing age. Aging can affect both the innate and adaptive arms of the immune response. The clinical consequences of the aging immune system include susceptibility to infection, autoimmunity, and malignancy, which may increase hospitalizations and mortality of the aging population. Its study is important because people are living longer compared with years past and seeking to live those years in good health. The mechanisms of immunosenescence are not fully understood partly because of complexities of its research. Comorbid conditions may alter immune function studies and cytokine profiles. Therefore,

several studies have used the SENIEUR protocol to screen patients to attempt to eliminate those who are unhealthy.¹ Immunosenescence research is frequently performed in aged mice models that are easily manipulated and specifically targeted. This review focuses on the innate and adaptive age-associated immune changes and some of their clinical implications.

CHANGES IN INNATE IMMUNITY

Macrophages

Blood monocytes and tissue macrophages are important cells of the innate immune system, phagocytosing microbes either through recognition of pathogen-associated molecular patterns or opsonins coating the microbe. Once engulfed in the phagosome, microbes are destroyed after fusion with a lysosome that contains enzymes and toxic substances, such as reactive oxygen intermediates and nitric oxide. Several studies suggest that macrophage/monocyte function decreases with aging through multiple mechanisms and at different points in cellular activation (Table 1).^{2,3} On the cell surface,

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Table 1. Effect of Aging on Cell Types

Cell type	Effect of aging
Hematopoietic stem cells	Decline in function Reduced ability to repopulate
Thymic precursors	Reduced numbers of precursors Reduced ability to generate double positive thymocytes Thymus involution
T cells	Decline in thymic output Reduced response and proliferation of CD4 ⁺ Reduced proliferation of CD8 ⁺ Accumulation of CD8 ⁺ CD28 ⁻ T cells Increased oligoclonal expansion to persistent latent infections Reduced TCR diversity Reduced number of mitogen-responsive cells Reduced signal transduction
B cells	Reduced activity of transcription factors Production of low affinity antibodies Increased oligoclonal expansion Reduced surface MHC class II molecule expression
Neutrophils	Reduced phagocytosis Reduced ROS production
Macrophages	Reduced phagocytosis Reduced cytokine and chemokine secretion Reduced generation of nitric oxide and superoxide Delayed wound healing Diminished TLR expression and function

Abbreviations: MHC, major histocompatibility complex; ROS, reactive oxygen species; TCR, T-cell receptor; TLR, toll-like receptor.

there may be decreased Toll-like receptors (TLRs),^{3,4} although this is controversial. Downstream TLR-mediated signaling pathways, such as mitogen activated protein kinase (MAPK) p38 and c-Jun N-terminal kinase (c-JNK), may be altered as noted in 1 study that found that lipopolysaccharide-stimulated macrophages from aged mice had less than 70% activated MAPK p38 and c-JNK compared with young controls.⁵ Furthermore, the production of reactive oxygen species (ROS), which have a biocidal effect on invading bacteria,⁶ nitric oxide, and inducible nitric oxide synthase, has been shown to be diminished in macrophages from aged rats and mice.⁷

After phagocytosis, macrophages and monocytes secrete cytokines (eg, interleukin [IL] 1, IL-6, IL-10, IL-12, IL-15, tumor necrosis factor α [TNF- α], transforming growth factor β [TGF- β], interferon [IFN] α , and IFN- β), chemokines (eg, IL-8, growth-related oncogene), coagulation factors, complement components, leukotrienes, and prostaglandin E2. The stimulus and location of the macrophage determine which proteins are secreted and subsequently amplify the innate

response and activate the adaptive arm. The effect of age on the cytokine and chemokine secretion after macrophage stimulation is not entirely clear; however, rodent studies suggest that it declines.⁸ For example, cytokine (TNF- α and IL-6) and chemokine (macrophage inflammatory protein 1 α and CCL5) production was reduced in culture supernatants from thioglycollate-elicited peritoneal and splenic macrophages from aged mice compared with younger mice after TLR stimulation.⁴ Furthermore, after addition of lipopolysaccharide to purified splenic macrophages from aged BALB/c and C57BL/6 mice, IL-1 β , IL-6, TNF- α , and IL-12 was decreased but IL-10 increased.⁹ In vitro studies from human monocytes on cytokine and chemokine secretion suggest that there is an increase in IL-6 and IL-8 and other proinflammatory cytokines.^{10,11} This increase may be secondary to underlying inflammation and poor nutrition and not part of the natural aging process.¹² However, other studies demonstrate decreased¹³ or no change in macrophage cytokine and chemokine production.¹² These potential discrepancies between the murine and human data may be due to several factors. In humans, much of the data on macrophages have been obtained from monocytes, which are easier to obtain but represent immature macrophages. In addition, many of the murine studies were performed using stimulated spleen cell cultures, whereas the human studies were obtained from peripheral blood.

Prostaglandin E2 is a potent modulator of both inflammation and immune responses and may suppress cell-mediated immune response. Production of prostaglandin E2 from aged mice and human activated macrophages has been shown to be increased.¹⁴ In another study performed in mice, prostaglandin E2 suppressed IL-12 secretion and class II major histocompatibility complex (MHC) expression on antigen-presenting cells (APCs) and increased IL-10 secretion.¹⁵ Therefore, T-cell activation may be decreased because of increased prostaglandin E2. Furthermore, class II MHC IFN- γ -induced expression is decreased in aged murine macrophages secondary to defects in transcription of the MHC class II antigen IA molecule.¹⁶

Lastly, it is not entirely clear if the number of macrophages decreases with aging. Evidence supports the theory that hematopoietic stem cells age and have a limited functional lifespan.¹⁷ Studies in aged humans demonstrated a significant decrease in bone marrow macrophage precursors, reflecting the hypocellularity observed in the bone marrow of elderly individuals.¹⁸ The lifespan of a cell may be regulated by many factors, although studies of the cell cycle have implicated telomeres in the regulation of replicative lifespan.¹⁹ Telomeres are special structures located at the end of chromosomes, consisting of an array of tandem hexamer DNA repeats. Inability of DNA polymerase to fully replicate the end of chromosomes leads to a loss of telomere repeats and "uncapping" of the telomeres, which can signal the cell to enter cell cycle arrest or senescence. Therefore, changes in telomere length in hematopoietic progenitor cells may sub-

sequently reflect the age-related changes in other derived cell lines.²⁰

Polymorphonuclear Neutrophilic Leukocytes

Neutrophil granulocytes are recruited to inflamed tissue to phagocytose opsonized particles and enzymatically destroy invading microorganisms. The production of cytokines (specifically TNF- α and IL-1) and chemokine IL-8 by activated tissue macrophages stimulates and attracts circulating polymorphonuclear neutrophilic leukocytes (PMNs) to the site of infection through increased expression of endothelial cell selectin and neutrophil integrins (CD11a/CD18 and CD11b/CD18). Whether migration of PMNs to the site of injury on the skin is impaired with aging is not clear. Migration of PMNs to the site of skin abrasion²¹ and in an experimental gingivitis model²² in both young and aged human individuals was equivalent. However, in vitro data have been conflicting, with some studies demonstrating impairment in chemotaxis and others demonstrating no significant differences in aged populations, suggesting a potential selection bias of those individuals with "healthy" PMNs in the older population.²³ On migration to the site of injury, the PMN phagocytoses the microbe into a phagosome, which fuses with an intracellular lysosome. The microbe is destroyed by lysosomal enzymes and ROS, similar to macrophages. Neutrophils also recognize microbes through pathogen-associated molecular patterns, binding to the Fc region of IgG at specific receptors (CD16, CD32, or CD64) or through complement molecules (CD35, CD11b/CD18). The ability of the aged neutrophil to phagocytose particles may or may not be decreased.²³ Levels of CD11b and serum complement are not altered with aging, but CD16 is decreased,²⁴ potentially diminishing Fc-mediated phagocytosis. Aging appears to alter the PMN's lysosomal ability to kill the microbe.^{23,25} ROS production is decreased with gram-positive bacteria, most likely secondary to reduced intracellular calcium signaling.²⁶

The numbers of PMNs in older individuals may be lowered because of increased apoptosis. In younger individuals, the production of inflammatory mediators IL-2, granulocyte-macrophage colony-stimulating factor, or granulocyte colony-stimulating factor prevents apoptosis of PMNs. However, this antiapoptotic ability is lost with aging.²⁶ Of note, the apoptotic death of *inactivated* aged PMNs is not increased, and there is no change in the expression of CD95.²⁷ Also contributing to decreased numbers of PMNs is a diminished proliferative response to growth factors.²⁴

Natural Killer Cells

Natural killer (NK) cells are a class of lymphocytes that destroy cells infected with intracellular pathogens through the production of perforin and granzyme. Furthermore, NK cells have tumoricidal activity and produce IFN- γ , activating macrophages to kill phagocytosed microbes. Although the number of NK cells increases with age,³ whether their function is altered is controversial. Some investigators have demonstrated normal, enhanced, or diminished activity.^{3,28,29} Re-

duced cytotoxic activity may be secondary to increased expression of Ly-49 receptors, which downregulates NK activation³⁰ or an intracellular decrease in calcium mobilization, necessary for NK cell proliferation and cytotoxicity.³¹ In addition, younger NK cells may require lower concentrations of IFN- α for activation compared with older NK cells.³² Therefore, if IFN- α decreases with age, NK cells may be more difficult to activate.

CHANGES IN ADAPTIVE IMMUNE RESPONSE

T Lymphocytes

There are several key changes in T-cell immunity that develop with increasing age, including decreased numbers of naive T cells, decreased antigen response and proliferation, increased memory cells, and alterations in apoptosis (Table 1). Furthermore, production of specific cytokine profiles may change with a shift from a T_H1 response to a T_H2-like response,³³ although this is controversial.³⁴ These events are most likely interconnected and result from several intrinsic processes, including involution of the thymus, decreased T-cell survival, changes in T-cell subpopulations, and impaired T-cell signaling.³⁵

Thymic Involution

Naive T cells are generated from bone marrow precursor cells that migrate to the thymus for maturation. In the thymus, T cells that weakly recognize class I and II MHCs are selected and mature in secondary lymphoid organs. The thymus consists of a thymopoietic space, containing thymocytes and supporting thymic epithelial cells, and a perivascular space with nonepithelial, nonthymopoietic cells. The thymus is most active early in life and reaches its peak size within the first year and undergoes a steady decline with aging, a process called *involution*. The mechanisms of thymic involution include a loss of T-cell progenitors, loss of self-peptide-expressing thymic epithelium, defects in rearrangement of *TCR β* genes, and reduced thymic epithelial cell production of cytokine IL-7, necessary for thymocyte maturation.³⁶ Consequences of thymic involution include a decreased production of new T cells, which in turn reduces T-cell receptor (TCR) diversity. (In 1 study, young adults had a repertoire diversity of 20 million different TCR- β chains, whereas those older than 70 years had 200,000.³⁷) By the age of 70 years, the thymopoietic space is reduced to less than 10% of the total thymus and the perivascular space expands.³⁸ Thymic atrophy can be estimated by measurement of the TCR excision circles (TRECs) (DNA circles that are byproducts of *TCR* gene rearrangement in developing thymocytes) and in vivo labeling of recent thymic emigrants.

Decreased T-Cell Survival

Apoptosis is a physiologic form of cell death that functions to remove damaged cells. There are different apoptotic pathways, including stimulation of surface CD95 (Fas), which activates caspase 8 and/or caspase 3, or via alterations of Bcl-2, which regulates cellular calcium homeostasis. Studies

in humans report that both aged naive and memory CD4⁺ and CD8⁺ cells have an increase in Fas and that the CD95-mediated activation of caspase 8 and caspase 3 is increased.³⁹ Data on whether the expression of FasL is increased or decreased in aging are conflicting.⁴⁰ Furthermore, it has been reported that Bcl-2 (potentially induced by IL-7), which is expressed on cell surfaces and acts to prevent apoptosis, is decreased in naive and memory cells of CD4⁺ and CD8⁺ cells in aged humans compared with young controls.³⁹ Telomeres also play a role in the survival of CD4⁺ and CD8⁺ cells. Sequential loss of or shortening of telomeric DNA, seen with increased aging, increases apoptosis.⁴¹ It was recently shown in peripheral blood collected from healthy adults that IL-7 also induces telomerase activity in naive CD4⁺ cells, therefore preventing cell death through another mechanism.⁴²

Increased Memory T Cells

There are several factors that lead to both increased memory CD4⁺ and CD8⁺ cells. As naive T-cell counts decrease with aging, the proportion of memory T cells increases. However, there may be peripheral factors that could increase the numbers of memory cells. Chronic viral stimulation, in particular cytomegalovirus, could increase memory CD8⁺ cells.^{43,44} Another study reconstituted young bone marrow cells into both irradiated aged and young mice of the same strain. Twelve weeks after transplantation, peripheral CD4⁺ cells collected from the mice who underwent transplantation with aged bone marrow displayed a memory CD4⁺ phenotype similar to aged, matched, nontreated controls, whereas the CD4⁺ population in the younger, reconstituted mice had a CD4⁺ naive phenotype.⁴⁵ The authors suggested that the increased memory CD4⁺ phenotype in the aged mice was due to different lymphokine production or expression of costimulatory molecules in the aged population.

Decreased T-Cell Signaling

T-cell activation requires 2 signals; signal 1 comes from binding of the TCR/CD3 complex and signal 2 from binding of costimulatory molecules, resulting in IL-2 production and proliferation. Naive CD4⁺ T cells from an aged animal produce less IL-2 compared with younger cells on antigen-APC stimulation.⁴⁶ There are several age-related changes in T cells that can affect response to both signals 1 and 2. First, murine studies reported that aged CD4⁺ TCR synapses with APCs may not be as efficient compared with younger cells.⁴⁷ Second, several activation and differentiation markers have reduced expression in aged CD4⁺ cells, including CD40L, CD25, CD28, and CD62L.^{48,49} Third, there are changes in the signaling cascade of T cells with aging due to calcium metabolism, tyrosine kinase phosphorylation, and protein kinase C translocation to the membrane,⁵⁰ as well as alterations in cell membrane lipid rafts, that function as signaling platforms, leading to decreased T-cell signaling.⁵¹

Decreased B Cells

There are several mechanisms to account for decreased B-cell numbers with increasing age. With aging, pre-B-cell counts

decrease because of reduced expression and activity of transcription factors (E12 and E47) and recombination activating genes required for the transition of pro-B cell to pre-B cell.^{52,53} Furthermore, marrow stromal cells from aged mice release less IL-7, decreasing in vitro lymphopoiesis compared with younger mice.¹² Finally, there is a progressive change in the phenotypes of B cells, with aging to fewer naive B cells to increased memory B cells with restricted diversity.⁵⁴

Antibody Diversity

There are several important changes in antibody diversity that occur with aging. Most notable is the decreased ability to produce specific antibodies. Mechanisms for decreased antibody diversity include alterations of the number and size of lymph node germinal centers with age⁵⁴ and decreased CD40L expression on aged T cells.⁴⁸ There is also increased production of autoantibodies,⁵⁴ both organ and non-organ specific.

T-Regulatory Cells

T-regulatory (Treg) cells are specialized T cells that have the ability to suppress the immune response. Treg cells are classified as natural T regulatory (nTreg) cells or induced or adaptive Treg cells. nTreg cells are CD4⁺, CD25⁺, and Foxp3⁺ cells derived directly from the thymus, and their phenotype may also be characterized by expression of CD62L, CD103, glucocorticoid-induced tumor necrosis factor receptor, and cytotoxic T-lymphocyte antigen 4. A second population of T cells whose immunosuppressive activity is induced or acquired in the periphery has been identified and include type 1 regulatory T cells, which secrete large amounts of IL-10, and T_H3 cells, which secrete TGF- β .

The functional activity of CD4⁺CD25⁺ T cells may decrease with aging,⁵⁵ secondary to decreased IL-2 production,⁵⁰ necessary for regulatory T-cell maintenance. However, Gregg et al⁵⁶ showed that the number of CD4⁺CD25^{hi} cells (enriched population of cells with highest density of CD25 molecule) was increased and functionally intact in elderly individuals. Given the increasing interest in Treg cells, we are likely to discover more information regarding their change with aging.

CONSEQUENCES OF CELLULAR CHANGES WITH AGING

The clinical implications of age-related dysregulation of the immune system include increased risk of infections, malignancy, autoimmune disorders, atherosclerosis, and neurodegenerative changes. These conditions likely result from alterations in several aspects of the immune system previously discussed rather than an isolated defect. A few of these topics will be discussed herein.

Infections

Influenza, *Streptococcus pneumoniae*, and gram-negative bacteria urinary tract infections are leading causes of morbidity and mortality in older patients. Older patients may be at increased risk for infections due to defects in phagocytosis,

lymphopenia, and decreased specific antibody production during active infection. Of particular concern is the decreased antibody response to vaccination that occurs with aging.³⁵ Less than half of older recipients of the influenza⁵⁷ and hepatitis B⁵⁸ vaccines produced protective antibody titers. Individuals older than 65 years may have diminished response to pneumococcal vaccination, producing fewer specific antibodies to pneumococcal serotypes.⁵⁹ In addition, the specific antibodies produced may be less effective at opsonization.⁶⁰ Therefore, some have suggested that patients older than 65 years should be revaccinated with pneumococcal vaccine every 5 years if they had an initial appropriate response.⁶¹

Autoimmunity

Despite the decreased capacity of B cells to produce specific antibodies with aging, there is increased autoantibody production. Elderly populations demonstrate a predominance of non-organ-specific autoantibodies over organ-specific autoantibodies. The most frequent autoantibodies described in elderly individuals include antiphospholipid, rheumatoid factor, and antinuclear antibodies. The mechanisms for autoantibody production are not clear but may be a result of failed suppressor cell function. The increase in autoantibodies in elderly individuals seems to be inversely correlated with a decreased proliferation of T cells to mitogens.⁶² Furthermore, there is evidence in aged mice of increased percentages of “autoreactive” CD8⁺ T cells with reduced apoptosis.⁶³

Maligancy

Cancer incidence and mortality in individuals older than 65 years markedly increases in both men and women, leveling off at approximately 85 to 90 years of age.⁶⁴ There are several factors that could account for this trend, including environmental exposure and age-related changes in the immune system. It is well documented that patients with primary and acquired immunodeficiency are at risk for certain tumors; therefore, it is not unexpected that immunosenescence may also increase cancer risk. Some of the mechanisms may include diminished proliferation responses and cytotoxicity of NK cells. An 11-year, prospective study of 3,500 middle-aged and elderly, Japanese individuals demonstrated increased cancer incidence in those with lower initial NK cytotoxic activity.⁶⁵ It has also been suggested that IL-6, which has been shown to increase with aging and is associated with decreased longevity, is a stimulus of metastasis by upregulating adhesion molecule and vascular endothelial growth factor expression on endothelial cells.⁶⁶

POTENTIAL THERAPEUTIC APPROACHES

Interleukin 7

IL-7 plays several key roles in the immune system, including rearrangement of the *TCR β* chain genes and lymphocyte survival at both preselection and postselection and thymic atrophy. Furthermore, memory cells express the IL-7 receptor. Several murine studies have shown that treatment with

recombinant IL-7 in aged mice reverses thymic atrophy,^{67,68} increases thymic output, and improves immune responses,⁶⁹ whereas other studies have not reported similar results.^{70,71} Administration of simian IL-7 to aged rhesus macaques increased the numbers of CD4⁺ and CD8⁺ cells and the numbers of naive (CD62L⁺CD45RA⁺) CD4⁺ and CD8⁺ cells and TRECs.⁷² Use of IL-7 has been reported in humans, but not for aging studies. In a small clinical trial of humans aged 20 to 59 years with metastatic cancer, IL-7 administration increased CD45RA⁺ and decreased CD45RO⁺ in both CD4 and CD8 lymphocytes, although not significantly.⁷³

Hormone Treatment

With aging there is a decline in growth hormone (GH) release. Rodent studies have demonstrated that its decrease induces thymic atrophy, whereas GH replacement in aged animals improved thymic size and function of peripheral T cells.⁷⁴ Although not specifically studied for age-associated immunodeficiency, GH replacement in HIV-infected patients increased thymus size and stimulated peripheral immune response.⁷⁵ However, GH replacement has many adverse effects, including arthralgia, carpal tunnel syndrome, and hyperglycemia. Manipulation of sex hormones, specifically testosterone, has also been investigated in murine studies. In aged male mice, a reversal of thymic atrophy was noted after androgen ablation.⁷⁶ This same group also demonstrated that older patients undergoing gonadal steroid ablation therapy for prostate cancer had increases in circulating naive T cells.⁷⁶

Zinc and Other Antioxidants

The use of mineral and vitamin supplements to improve immune function with aging is complex and cannot be adequately reviewed in this article. Therefore, only a few supplements will be briefly mentioned. Zinc treatment at physiologic doses for 1 month in older patients with bronchopneumonia increased NK cell cytotoxicity and rescued IFN- γ production, leading to a 50% reduction in infection relapse.⁵⁰ Zinc decreased spontaneous apoptosis in peripheral blood mononuclear cells; however, it was accompanied by an age-dependent increase in oxidative stress-induced apoptosis, potentially limiting its use as a supplement.⁷⁷ The use of vitamin E supplementation in aged mice and older adults to augment immune function has been recently reviewed.⁷⁸ Several murine studies demonstrated that its use increased lymphocyte proliferation and production of IL-2, whereas the clinical human work show mixed results on these immune function studies and antibody response to influenza virus and numbers of upper respiratory tract infections.⁷⁸ One mechanism of improved immune function with vitamin E has been to decrease the age-related increase in prostaglandin 2 release from macrophages. This in turn decreases T-cell-mediated function.⁷⁹ Vitamin C has also been proposed to improve immune function with aging. Aged mice fed a diet enriched with vitamins C and E, beta carotenes, selenium, and zinc had improvement of oxidative functions of peritoneal leuko-

cytes.⁸⁰ However, in vitro pretreatment with vitamin C did not increase human T-cell proliferation.⁸¹

Calorie Restriction

Reduced nutrient intake, referred to as caloric restriction, has been shown to delay aging and increase life span in several species, suggesting that this process may be an evolutionary adaptation. Caloric restriction, first studied in laboratory rodents, resulted in small, lean mice with impaired fertility but otherwise healthy and living up to 40% longer compared with mice fed ad libitum.⁸² Studies in animals have demonstrated that caloric restriction in young adult animals has the most striking effect on aging.⁵⁵ However, there is some evidence that caloric restriction may be beneficial when initiated in adulthood, and in some cases, the effects may be reversible such that termination of caloric restriction results in the return of the "normal state" with an associated reduction in life span compared with animals continued on caloric restriction. This suggests that the beneficial effects of caloric restriction on aging depends on the starting age and duration of dietary restriction. Rodent studies have suggested that caloric restriction protects against cellular and DNA damage⁸³ and reduces autoimmune disease.⁸²

CONCLUSIONS

The study of immunosenescence is critical as our population ages. Although not well characterized, aging most likely has several significant consequences on the immune function. Age-associated immune dysfunction in both the innate and adaptive sides may increase the risk of infections, malignancy, and autoimmune disease. Phagocytosis by PMNs and macrophages has been shown to be suppressed in both aged mouse models and humans. Furthermore, these cells may be more likely to undergo apoptosis in older individuals. Cytokine production is also altered with aging, which may in turn affect phagocytosis and proliferation responses. The numbers of several immune cells can decrease with age, including NK cells, T lymphocytes, and B lymphocytes. Furthermore, the receptor diversity of those cells may be altered, especially in the TCR. Another important consequence of immunosenescence is the decreased production of specific antibodies and an increased production of autoantibodies. The underlying mechanisms of these changes are not fully elucidated. However, increased understanding of the pathophysiology of immunosenescence may improve the quality of life as we age.

REFERENCES

1. Ligthart GJ, Corberand JX, Fournier C, et al. Admission criteria for immunogerontological studies in man: the SENIEUR protocol. *Mech Ageing Dev.* 1984;28:47–55.
2. Kovacs EJ, Palmer JL, Fortin CF, Fulop T Jr, Goldstein DR, Linton PJ. Aging and innate immunity in the mouse: impact of intrinsic and extrinsic factors. *Trends Immunol.* 2009;30:319–324.
3. Panda A, Arjona A, Sapey E, et al. Human innate immunosenescence: causes and consequences for immunity in old age. *Trends Immunol.* 2009;30:325–333.
4. Renshaw M, Rockwell J, Engleman C, Gewirtz A, Katz J, Sambhara S. Cutting edge: impaired Toll-like receptor expression and function in aging. *J Immunol.* 2002;169:4697–4701.
5. Boehmer ED, Goral J, Faunce DE, Kovacs EJ. Age-dependent decrease in Toll-like receptor 4-mediated proinflammatory cytokine production and mitogen-activated protein kinase expression. *J Leukoc Biol.* 2004;75:342–349.
6. Kohchi C, Inagawa H, Nishizawa T, Soma G. ROS and innate immunity. *Anticancer Res.* 2009;29:817–821.
7. Kissin E, Tomasi M, McCartney-Francis N, Gibbs CL, Smith PD. Age-related decline in murine macrophage production of nitric oxide. *J Infect Dis.* 1997;175:1004–1007.
8. McLachlan JA, Serkin CD, Morrey-Clark KM, Bakouche O. Immunological functions of aged human monocytes. *Pathobiology.* 1995;63:148–159.
9. Chelvarajan RL, Collins SM, Van Willigen JM, Bondada S. The unresponsiveness of aged mice to polysaccharide antigens is a result of a defect in macrophage function. *J Leukoc Biol.* 2005;77:503–512.
10. Hasegawa Y, Sawada M, Ozaki N, Inagaki T, Suzumura A. Increased soluble tumor necrosis factor receptor levels in the serum of elderly people. *Gerontology.* 2000;46:185–188.
11. Mariani E, Pulsatelli L, Neri S, et al. RANTES and MIP-1 α production by T lymphocytes, monocytes and NK cells from nonagenarian subjects. *Exp Gerontol.* 2002;37:219–226.
12. Ahluwalia N, Mastro AM, Ball R, Miles MP, Rajendra R, Handte G. Cytokine production by stimulated mononuclear cells did not change with aging in apparently healthy, well-nourished women. *Mech Ageing Dev.* 2001;122:1269–1279.
13. Bruunsgaard H, Pedersen BK. Age-related inflammatory cytokines and disease. *Immunol Allergy Clin North Am.* 2003;23:15–39.
14. Wu D, Hayek MG, Meydani S. Vitamin E and macrophage cyclooxygenase regulation in the aged. *J Nutr.* 2001;131:382S–388S.
15. Harizi H, Juzan M, Pitard V, Moreau JF, Gualde N. Cyclooxygenase-2-induced prostaglandin e(2) enhances the production of endogenous IL-10, which down-regulates dendritic cell functions. *J Immunol.* 2002;168:2255–2263.
16. Herrero C, Sebastian C, Marques L, et al. Immunosenescence of macrophages: reduced MHC class II gene expression. *Exp Gerontol.* 2002;37:389–394.
17. Geiger H, Van Zant G. The aging of lympho-hematopoietic stem cells. *Nat Immunol.* 2002;3:329–333.
18. Ogawa T, Kitagawa M, Hirokawa K. Age-related changes of human bone marrow: a histometric estimation of proliferative cells, apoptotic cells, T cells, B cells and macrophages. *Mech Ageing Dev.* 2000;117:57–68.
19. Sebastian C, Herrero C, Serra M, Lloberas J, Blasco MA, Celada A. Telomere shortening and oxidative stress in aged macrophages results in impaired STAT5a phosphorylation. *J Immunol.* 2009;183:2356–2364.
20. Lloberas J, Celada A. Effect of aging on macrophage function. *Exp Gerontol.* 2002;37:1325–1331.
21. Biasi D, Carletto A, Dell'Agnola C, et al. Neutrophil migration, oxidative metabolism, and adhesion in elderly and young subjects. *Inflammation.* 1996;20:673–681.
22. Fransson C, Mooney J, Kinane DF, Berglundh T. Differences in the inflammatory response in young and old human subjects during the course of experimental gingivitis. *J Clin Periodontol.* 1999;26:453–460.
23. Plackett TP, Boehmer ED, Faunce DE, Kovacs EJ. Aging and innate immune cells. *J Leukoc Biol.* 2004;76:291–299.
24. Lord JM, Butcher S, Killampali V, Lascelles D, Salmon M. Neutrophil ageing and immunosenescence. *Mech Ageing Dev.* 2001;122:1521–1535.
25. Peters T, Weiss JM, Sindrilaru A, et al. Reactive oxygen intermediate-induced pathomechanisms contribute to immunosenescence, chronic inflammation and autoimmunity. *Mech Ageing Dev.* 2009;130:564–587.
26. Fulop T Jr, Fouquet C, Allaire P, et al. Changes in apoptosis of human polymorphonuclear granulocytes with aging. *Mech Ageing Dev.* 1997;96:15–34.
27. Tortorella C, Piazzolla G, Spaccavento F, Jirillo E, Antonaci S. Age-related effects of oxidative metabolism and cyclic AMP signaling on neutrophil apoptosis. *Mech Ageing Dev.* 1999;110:195–205.

28. Zhang Y, Wallace DL, de Lara CM, et al. In vivo kinetics of human natural killer cells: the effects of ageing and acute and chronic viral infection. *Immunology*. 2007;121:258–265.
29. Facchini A, Mariani E, Mariani AR, Papa S, Vitale M, Manzoli FA. Increased number of circulating Leu 11+ (CD 16) large granular lymphocytes and decreased NK activity during human ageing. *Clin Exp Immunol*. 1987;68:340–347.
30. Dorfman JR, Raulet DH. Acquisition of Ly49 receptor expression by developing natural killer cells. *J Exp Med*. 1998;187:609–618.
31. Borrego F, Alonso MC, Galiani MD, et al. NK phenotypic markers and IL2 response in NK cells from elderly people. *Exp Gerontol*. 1999;34:253–265.
32. Kutza J, Murasko DM. Effects of aging on natural killer cell activity and activation by interleukin-2 and IFN- α . *Cell Immunol*. 1994;155:195–204.
33. Rink L, Cakman I, Kirchner H. Altered cytokine production in the elderly. *Mech Ageing Dev*. 1998;102:199–209.
34. Adkins B, Du RQ. Newborn mice develop balanced Th1/Th2 primary effector responses in vivo but are biased to Th2 secondary responses. *J Immunol*. 1998;160:4217–4224.
35. Maue AC, Yager EJ, Swain SL, Woodland DL, Blackman MA, Haynes L. T-cell immunosenescence: lessons learned from mouse models of aging. *Trends Immunol*. 2009;30:301–305.
36. Andrew D, Aspinall R. Age-associated thymic atrophy is linked to a decline in IL-7 production. *Exp Gerontol*. 2002;37:455–463.
37. Naylor K, Li G, Vallejo AN, et al. The influence of age on T cell generation and TCR diversity. *J Immunol*. 2005;174:7446–7452.
38. Flores KG, Li J, Sempowski GD, Haynes BF, Hale LP. Analysis of the human thymic perivascular space during aging. *J Clin Invest*. 1999;104:1031–1039.
39. Aggarwal S, Gupta S. Increased apoptosis of T cell subsets in aging humans: altered expression of Fas (CD95), Fas ligand, Bcl-2, and Bax. *J Immunol*. 1998;160:1627–1637.
40. Pinti M, Troiano L, Nasi M, et al. Development of real time PCR assays for the quantification of Fas and FasL mRNA levels in lymphocytes: studies on centenarians. *Mech Ageing Dev*. 2003;124:511–516.
41. Kaszubowska L. Telomere shortening and ageing of the immune system. *J Physiol Pharmacol*. 2008;59(suppl 9):169–86.
42. Yang Y, An J, Weng NP. Telomerase is involved in IL-7-mediated differential survival of naive and memory CD4+ T cells. *J Immunol*. 2008;180:3775–3781.
43. Khan N, Shariff N, Cobbold M, et al. Cytomegalovirus seropositivity drives the CD8 T cell repertoire toward greater clonality in healthy elderly individuals. *J Immunol*. 2002;169:1984–1992.
44. McElhaney JE, Effros RB. Immunosenescence: what does it mean to health outcomes in older adults? *Curr Opin Immunol*. 2009;21:418–424.
45. Timm JA, Thoman ML. Maturation of CD4+ lymphocytes in the aged microenvironment results in a memory-enriched population. *J Immunol*. 1999;162:711–717.
46. Haynes L, Linton PJ, Eaton SM, Tonkonogy SL, Swain SL. Interleukin 2, but not other common gamma chain-binding cytokines, can reverse the defect in generation of CD4 effector T cells from naive T cells of aged mice. *J Exp Med*. 1999;190:1013–1024.
47. Sadighi Akha AA, Miller RA. Signal transduction in the aging immune system. *Curr Opin Immunol*. 2005;17:486–491.
48. Eaton SM, Burns EM, Kusser K, Randall TD, Haynes L. Age-related defects in CD4 T cell cognate helper function lead to reductions in humoral responses. *J Exp Med*. 2004;200:1613–1622.
49. Kovaïou RD, Grubeck-Loebenstein B. Age-associated changes within CD4+ T cells. *Immunol Lett*. 2006;107:8–14.
50. Fulop T, Larbi A, Wikby A, Mocchegiani E, Hirokawa K, Pawelec G. Dysregulation of T-cell function in the elderly: scientific basis and clinical implications. *Drugs Aging*. 2005;22:589–603.
51. Larbi A, Douziech N, Dupuis G, et al. Age-associated alterations in the recruitment of signal-transduction proteins to lipid rafts in human T lymphocytes. *J Leukoc Biol*. 2004;75:373–381.
52. Frasca D, Nguyen D, Riley RL, Blomberg BB. Decreased E12 and/or E47 transcription factor activity in the bone marrow as well as in the spleen of aged mice. *J Immunol*. 2003;170:719–726.
53. Labrie JE III, Sah AP, Allman DM, Cancro MP, Gerstein RM. Bone marrow microenvironmental changes underlie reduced RAG-mediated recombination and B cell generation in aged mice. *J Exp Med*. 2004;200:411–423.
54. Siegrist CA, Aspinall R. B-cell responses to vaccination at the extremes of age. *Nat Rev Immunol*. 2009;9:185–194.
55. Zhao L, Sun L, Wang H, Ma H, Liu G, Zhao Y. Changes of CD4+CD25+Foxp3+ regulatory T cells in aged Balb/c mice. *J Leukoc Biol*. 2007;81:1386–1394.
56. Gregg R, Smith CM, Clark FJ, et al. The number of human peripheral blood CD4+ CD25high regulatory T cells increases with age. *Clin Exp Immunol*. 2005;140:540–546.
57. Hannoun C, Megas F, Piercy J. Immunogenicity and protective efficacy of influenza vaccination. *Virus Res*. 2004;103:133–138.
58. Looney RJ, Hasan MS, Coffin D, et al. Hepatitis B immunization of healthy elderly adults: relationship between naive CD4+ T cells and primary immune response and evaluation of GM-CSF as an adjuvant. *J Clin Immunol*. 2001;21:30–36.
59. Romero-Steiner S, Musher DM, Cetron MS, et al. Reduction in functional antibody activity against *Streptococcus pneumoniae* in vaccinated elderly individuals highly correlates with decreased IgG antibody avidity. *Clin Infect Dis*. 1999;29:281–288.
60. Nicoletti C, Yang X, Cerny J. Repertoire diversity of antibody response to bacterial antigens in aged mice, III: phosphorylcholine antibody from young and aged mice differ in structure and protective activity against infection with *Streptococcus pneumoniae*. *J Immunol*. 1993;150:543–549.
61. Mufson MA, Krause HE, Schiffman G. Long-term persistence of antibody following immunization with pneumococcal polysaccharide vaccine. *Proc Soc Exp Biol Med*. 1983;173:270–275.
62. Hallgren HM, Buckley CE III, Gilbertsen VA, Yunis EJ. Lymphocyte phytohemagglutinin responsiveness, immunoglobulins and autoantibodies in aging humans. *J Immunol*. 1973;111:1101–1107.
63. Hsu HC, Zhou T, Shi J, et al. Aged mice exhibit in vivo defective peripheral clonal deletion of D (b)/H-Y reactive CD8(+) T cells. *Mech Ageing Dev*. 2001;122:305–326.
64. Caruso C, Lio D, Cavallone L, Franceschi C. Aging, longevity, inflammation, and cancer. *Ann N Y Acad Sci*. 2004;1028:1–13.
65. Imai K, Matsuyama S, Miyake S, Suga K, Nakachi K. Natural cytotoxic activity of peripheral-blood lymphocytes and cancer incidence: an 11-year follow-up study of a general population. *Lancet*. 2000;356:1795–1799.
66. Cohen T, Nahari D, Cerem LW, Neufeld G, Levi BZ. Interleukin 6 induces the expression of vascular endothelial growth factor. *J Biol Chem*. 1996;271:736–741.
67. Andrew D, Aspinall R. IL-7 and not stem cell factor reverses both the increase in apoptosis and the decline in thymopoiesis seen in aged mice. *J Immunol*. 2001;166:1524–1530.
68. Aspinall R, Andrew D. Thymic atrophy in the mouse is a soluble problem of the thymic environment. *Vaccine*. 2000;18:1629–1637.
69. Henson SM, Snelgrove R, Hussell T, Wells DJ, Aspinall R. An IL-7 fusion protein that shows increased thymopoietic ability. *J Immunol*. 2005;175:4112–4118.
70. Chu YW, Memon SA, Sharrow SO, et al. Exogenous IL-7 increases recent thymic emigrants in peripheral lymphoid tissue without enhanced thymic function. *Blood*. 2004;104:1110–1119.
71. Phillips JA, Brondstetter TI, English CA, Lee HE, Virts EL, Thoman ML. IL-7 gene therapy in aging restores early thymopoiesis without reversing involution. *J Immunol*. 2004;173:4867–4874.
72. Aspinall R, Pido-Lopez J, Imami N, et al. Old rhesus macaques treated with interleukin-7 show increased TREC levels and respond well to influenza vaccination. *Rejuvenation Res*. 2007;10:5–17.
73. Rosenberg SA, Sportes C, Ahmadzadeh M, et al. IL-7 administration to humans leads to expansion of CD8+ and CD4+ cells but a relative decrease of CD4+ T-regulatory cells. *J Immunother*. 2006;29:313–319.

74. French RA, Broussard SR, Meier WA, et al. Age-associated loss of bone marrow hematopoietic cells is reversed by GH and accompanies thymic reconstitution. *Endocrinology*. 2002;143:690–699.
75. Napolitano LA, Schmidt D, Gotway MB, et al. Growth hormone enhances thymic function in HIV-1-infected adults. *J Clin Invest*. 2008; 118:1085–1098.
76. Sutherland JS, Goldberg GL, Hammett MV, et al. Activation of thymic regeneration in mice and humans following androgen blockade. *J Immunol*. 2005;175:2741–2753.
77. Ostan R, Alberti S, Bucci L, et al. Effect of zinc ions on apoptosis in PBMCs from healthy aged subjects. *Biogerontology*. 2006;7:437–447.
78. Wu D, Meydani SN. Age-associated changes in immune and inflammatory responses: impact of vitamin E intervention. *J Leukoc Biol*. 2008; 84:900–914.
79. Beharka AA, Wu D, Serafini M, Meydani SN. Mechanism of vitamin E inhibition of cyclooxygenase activity in macrophages from old mice: role of peroxynitrite. *Free Radic Biol Med*. 2002;32:503–511.
80. Alvarado C, Alvarez P, Puerto M, Gausseres N, Jimenez L, De la Fuente M. Dietary supplementation with antioxidants improves functions and

decreases oxidative stress of leukocytes from prematurely aging mice. *Nutrition*. 2006;22:767–777.

81. Douziet N, Seres I, Larbi A, et al. Modulation of human lymphocyte proliferative response with aging. *Exp Gerontol*. 2002;37:369–387.
82. Weindruch R, Walford RL, Fligiel S, Guthrie D. The retardation of aging in mice by dietary restriction: longevity, cancer, immunity and lifetime energy intake. *J Nutr*. 1986;116:641–654.
83. Haley-Zitlin V, Richardson A. Effect of dietary restriction on DNA repair and DNA damage. *Mutat Res*. 1993;295:237–245.

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Objectives: After reading this article, participants should be able to demonstrate an increased understanding of their knowledge of allergy/asthma/immunology clinical treatment and how this new information can be applied to their own practices.

Participants: This program is designed for physicians who are involved in providing patient care and who wish to advance their current knowledge in the field of allergy/asthma/immunology.

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CME Examination

1–5, Agarwal S. 2010;104:183–190.

CME Test Questions

1. Proposed therapies for immunosenescence include which of the following?
 - a. growth hormone
 - b. caloric restriction
 - c. cytokine interleukin 7
 - d. zinc
 - e. all of the above
2. Increase susceptibility to infection in the elderly population may be due to which of the following?
 - a. increased specific antibody production
 - b. increased phagocytosis
 - c. lymphopenia
 - d. decreased autoantibody production
 - e. increased apoptosis
3. Inadequate responses to antigens in elderly individuals are secondary to which of the following?
 - a. increased naive T-cell repertoire
 - b. reduced T-cell receptor diversity
 - c. increased B-cell repertoire
 - d. increased p53 expression
 - e. increased recombination activating gene expression
4. Consequences of age-related dysregulation of the immune system include which of the following?
 - a. increased autoimmunity
 - b. decreased malignancy
 - c. decreased bacterial infections
 - d. increased vaccination response
 - e. decreased viral infections
5. Age-related changes in the thymus include which of the following?
 - a. increased interleukin 7
 - b. increased thymic epithelial cell production
 - c. reduced epithelial space
 - d. reduced perivascular space
 - e. increased cells containing T-cell receptor excision circles

Answers found on page 210.