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Age-related Changes in Immune Function: Impact on Airway Inflammation

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Abstract

Immunosenescence is defined as changes in the innate and adaptive immune response associated with increased age. The clinical consequences of immunosenescence include increased susceptibility to infection, malignancy, and autoimmunity, decreased response to vaccination and impaired wound healing. However, there are several immune alterations which may facilitate persistence of asthma into late adulthood, or development of asthma after the age of 50-60 years. Asthma in older patients is not uncommon and is a growing population as the average lifespan increases. Specific innate changes which may affect severity of asthma in older patients, or be involved in the development of late onset asthma include impaired mucociliary clearance, and changes in airway neutrophil, eosinophil and mast cell numbers and function. Additionally, age-related altered antigen presentation and decreased in specific antibody responses may increase the risk of respiratory infections. Respiratory infections exacerbate asthma in older patients, and possibly play a role in the pathogenesis of late onset asthma. Furthermore, cytokine profiles may be modified with aging; some investigators suggesting a trend towards Th2 cytokine expression. This review examines specific innate and adaptive immune responses affected by aging that may impact the inflammatory response in older adults with asthma.

Keywords

Asthma; atopy; aging; elderly; immune function; immunosenescence

INTRODUCTION

Research from animal models and human subjects suggests that with increasing age, there are several important changes in the innate and adaptive immune responses, a phenomenon termed “immunosenescence”. Immunosenescence most likely plays a role in the increased susceptibility to infections and increased rates of malignancies and autoimmune diseases in the elderly. Older individuals with fewer features of immunosenescence may have a prolonged lifespan.⁽¹⁾ Conversely, specific features of immunosenescence including impaired T-cell proliferation, increased CD8⁺ cytotoxic/suppressor cell numbers, and decreased CD4⁺ T-cell and CD19⁺ B-cell numbers are associated with increased morbidity and mortality.⁽²⁾ Another finding of immunosenescence is the presence of chronic systemic inflammation, referred to as “inflamm-aging”, characterized by increased serum IL-6 and TNF- α and clinically with more “frail” individuals.⁽³⁾

Altered immune response with aging may affect the pathophysiology of asthma in older patients. Although asthma is typically considered a disease of early childhood, asthma in older patients is not uncommon; reported that between 4-13% of the population over 65 years of age has a diagnosis of current asthma. ⁽⁴⁻⁸⁾ However, this number is likely to be an underestimate, as asthma in the elderly is underdiagnosed. ^(5;9;10) Asthma in older adults can be classified as long-standing/childhood-onset, childhood-onset which became quiescent and returned later in life, or late-onset. There is no strict age definition which classifies late-onset asthma. Older patients with asthma have a high rate of morbidity and mortality, ^(11;12) possibly due to undertreatment ^(5;9) and co-morbid conditions. ^(13;14) However, it may also be due to immunosenescence.

This review will focus upon changes in the immune system with age, specifically targeting those which may influence asthma (Table 1). There are several features that are well characterized, whereas, for others there are conflicting reports. This may be due to differences in experimental protocols or to inclusion of individuals with co-morbidities which could affect the immunological function. As a result, , much of the research on immunosenescence has been performed using aged murine models.

AGE-RELATED CHANGES IN INNATE IMMUNITY

Epithelial cells

The respiratory epithelium is composed of ciliated and secretory cells, and is an important component of the innate immune system. Ciliated cells propel inhaled antigens and irritants trapped in mucus produced by goblet cells, proximally up the tracheobronchial tree via mucociliary clearance. Additionally, the airway epithelial cells produce nitric oxide, secrete several cytokines, in particular type I and III IFNs, growth factors such as granulocyte/macrophage colony-stimulating factor, IgA and several antimicrobial proteins. There are notable changes in the airway epithelium in patients with asthma which including disruptions of the epithelial cell tight junctions, increased susceptibility to apoptotic effects of oxidants, and impaired production of IFN- β and IFN- α , which promote epithelial damage and increase the susceptibility to viral infections. ⁽¹⁵⁾

Lung epithelial cell senescence may contribute to the pathogenesis of late-onset asthma or to persistence of asthma into later years. Nasal epithelial tissue collected from non-smoking healthy individuals (ages 11 to 90 years) without respiratory disease demonstrated a significantly decreased ciliary beat frequency and clearance with age accompanied by microtubular disarrangements. ⁽¹⁶⁾ Svartengren *et al* reported a decreased clearance of labeled Teflon particles deposited in smaller airways in older (range 19-81 years) healthy subjects. ⁽¹⁷⁾ The effect of age on mucosal cell hyperplasia and mucus hypersecretion is not well studied. In a study of 51 patients undergoing endoscopy, the mean number of *fundic* mucus cells peaked in the 41-50 year old group, remained elevated in the 51-60 age group (compared to <40 years old) and was lowest >60 years old. ⁽¹⁸⁾ In aged (18-month) BALB/c mice sensitized and challenged intratracheally to ovalbumin (OVA), *airway* mucus metaplasia measured by periodicacid-Schiff (PAS) staining and mRNA expression for the mucin-producing MUC-5AC gene were increased compared to younger (6-week) antigen treated mice. ⁽¹⁹⁾ The effect of increased age on VCAM and ICAM expression on airway epithelial cells has not been investigated. This is an important question, as these markers are involved in cell trafficking and ICAM-1 is a receptor for rhinovirus. In aged mice, these adhesion markers are increased in the endothelium and in hepatic macrophages. ^(20;21) Viral respiratory infections may be an initiating event in the pathogenesis of late-onset asthma. ⁽²²⁾

Neutrophils

Although the neutrophil number in the peripheral circulation does not vary with age, there is evidence that its chemotaxis and phagocytotic properties, and generation of superoxide may change. Both impaired and normal chemotaxis has been reported to occur with aging.^(23;24) Although *in vitro* peripheral neutrophil production of superoxide in response to fMLP was not reduced in healthy older subjects (mean age 68.2 years) compared to healthy young adults (mean age 25.9 years), phagocytosis of FITC-labeled *E. Coli* was decreased. The authors concluded that the decreased phagocytic index in the older subjects was secondary to an age-related decline in surface CD16 expression, necessary for Fc-mediated phagocytosis.⁽²⁵⁾ However, other groups have reported a diminished respiratory burst and protection from apoptosis from PMNs collected in older healthy subjects upon engagement of the surface TREM-1 receptor⁽²⁶⁾ or fMLP⁽²⁷⁾, but a similar production of reactive oxygen species (ROS) with PMA stimulation.⁽²⁸⁾ Thus, the capacity to produce ROS may be intact, but specific signaling pathways to evoke ROS production may be deficient in the elderly. In addition, it has been observed that GM-CSF, IL-2 or LPS treatment of neutrophils from the elderly were less protected from apoptosis than neutrophils from younger subjects.⁽²⁹⁾ Collectively, these observations suggest neutrophils may be less abundant in acute inflammatory responses due to greater apoptosis, and those present may have diminished anti-pathogen activity resulting in more frequent and more severe respiratory infections.

The effect of aging on the airway neutrophil, specifically in asthma, is not as well characterized. The aging process has been shown to be associated with increased lung inflammation without concomitant lung disease. Bronchoalveolar lavage (BAL) fluid from subjects ages 19 to 83 year lacking a history of allergies, pulmonary disease or gastroesophageal reflux, showed an increase in BAL neutrophils and CD4+ T-cells with age^(30;31), which may differ from peripheral blood changes, i.e. CD4+ T-cell count may decrease with age. Patients older than 55 years of age with asthma, demonstrating reversibility on spirometry, with less than 5 year pack-year history of tobacco use had greater sputum neutrophils than younger patients with asthma.⁽³²⁾ Furthermore, the increased airway neutrophilia corresponds to increased levels of sputum neutrophil mediators including MMP-9, neutrophil elastase and IL-8, in older asthma subjects, resembling changes seen neutrophil-predominant severe asthma.⁽³³⁾ Thus, it is possible the increased airspace neutrophils contribute to greater severity of asthma in the elderly.

NK cells

Natural killer (NK) cells are cytotoxic cells that play an important role in anti-viral host defense. In a study of 82 subjects (30-99 years of age), the numbers of NK cells (CD3-CD16+CD56+) increased with aging; however, the cytotoxicity of these cells, measured by ⁵¹Cr release, diminished on a per cell basis with aging.⁽³⁴⁾ In contrast to NK cells, NKT cell (CD3+CD16+CD56+) numbers have been shown to decrease in elderly subjects.^(35;36) Furthermore, proliferation in response to IL-2 and α -GalCer, a specific ligand for CD1d on iNKT cells, is diminished in older subjects.⁽³⁷⁾ There is emerging interest in the involvement of NK and NKT cells in the pathophysiology of asthma.⁽³⁸⁻⁴⁰⁾ The clinical impact of a decline in the function and/or numbers of these cells with aging has not been established in asthma. However, given their role in pathogen clearance, especially viruses, it is possible that virus-induced exacerbations of asthma may be more severe in the elderly.

Macrophages and Monocytes

Macrophage and monocytes are phagocytic cells that express toll-like receptors (TLR) which recognize pathogen associated molecular patterns. With aging, there may be decreased surface expression and altered down-stream TLR-mediated signaling, increasing

the risk of respiratory infections. Macrophages derived from *in vitro* differentiation of monocytes had decreased expression of TLR3 mRNA and intracellular protein in older subjects.⁽⁴¹⁾ Monocytes stimulated via the TLR1/2 heterodimeric receptor generated fewer IL-6 and TNF- α producing cells in older subjects.⁽⁴²⁾ Additionally, the production of ROS, important for killing of invading bacteria, may be altered. In alveolar macrophages isolated from rats, fewer cells produced ROS upon LPS stimulation in senescent animals, though there was also a suggestion of more ROS per cell.⁽⁴³⁾ The total *in vitro* LPS-induced production of nitric oxide was also significantly diminished in the macrophages from senescent animals.

The ability of the aged airway macrophage (AM) to release arachidonic acid (AA) and secrete leukotrienes has been evaluated in the context of respiratory infections. In aged rats, there was no significant difference between release of these factors after AM culture with *Klebsiella pneumoniae* in aged and young rats.⁽⁴⁴⁾ However, decreased urinary levels of the anti-inflammatory AA byproduct, lipoxin (LX)A₄, which antagonizes the pro-inflammatory functions of leukotriene D₄, were noted in older healthy subjects.⁽⁴⁵⁾ Although not specifically examining leukotriene production by AM, the levels of LTC₄ were not significantly higher in BALF cells or peripheral blood stimulated with Ca ionophore A23197 collected from atopic asthmatics >60 years of age compared with those 20-59 years.⁽⁴⁶⁾ Therefore, it is possible that regulation of leukotrienes may be altered with aging.

Mast cells

Mast cells are widely distributed throughout many tissues including blood vessels, the central nervous system, smooth muscle and epithelium. In many asthma phenotypes, mast cells are important in the early-phase bronchoconstriction and induction of subsequent inflammatory cell influx. The effect of age on mast cell number and function has been studied in some other human diseases asthma, and their murine models, and depends upon the tissue source and species. In the human brain, mast cell numbers in the ventricular choroid plexus were decreased in older patients expiring from non-central nervous system or cardiovascular causes.⁽⁴⁷⁾ Similarly, dermal mast cell number decreased with age in humans.⁽⁴⁸⁾ Numbers of mast cells in the lamina propria of jejunal biopsies, collected from subjects > 70 years with gastrointestinal symptoms, but without immunological, allergic, infectious, neoplastic etiology, were similar to normal controls (ages 20-50 years).⁽⁴⁹⁾ In contrast, vein samples removed in aortocoronary bypass or varicose vein surgery demonstrated greater numbers of mast cell numbers in older patients.⁽⁵⁰⁾ Young (6-week) and aged (3-12 months) C57BL/6 mice had similar dermal mast cell numbers.⁽⁵¹⁾ Liver mast cells increased to a greater extent after acute liver injury in young (2 and 6 months) compared to aged (12 and 19 months) rats.⁽⁵²⁾

The effect of age on mast-cell degranulation is unclear. Ear tissue mast cell degranulation and edema after PGE injection was significantly increased in aged (>6 months) compared to young (2 month) mice. However, both aged and young mice had similar edema and mast cell degranulation in ear tissue after IgE-dependent passive sensitization.⁽⁵¹⁾ The authors concluded that age modulates mast cells via non-FcR pathways. In addition, peritoneal mast cells obtained from aged (72-94 weeks) compared to younger (6-8 weeks old) C57BL/6 mice had a decrease in Fc γ RIIB/III (negative regulator) expression and a higher non-specific IgG-mediated degranulation after incubation with 2.4G2.⁽⁵³⁾

Eosinophils

Currently, there is very little reported on the age-associated changes in eosinophil number and function. However, it appears that the aged eosinophil may have altered effector functions and be less important in airway hyperresponsiveness. Although antigen sensitized

and challenged aged mice developed greater BALF eosinophilia in comparison to younger mice, the airway hyperresponsiveness was lower in the former.⁽¹⁹⁾ In a study examining age-related changes in eosinophil function, it was found that peripheral eosinophils from asthma subjects (55 to 80 years of age) exhibited decreased degranulation in response to IL-5 stimulation and a trend for decreased superoxide production, when compared to cells from patients 20 to 40 years of age.⁽³²⁾ However, a comparison of another *in vitro* eosinophil effector function, LTC₄ production, revealed no difference between older and younger asthma subjects.⁽⁵⁴⁾ Furthermore, older asthma subjects with evidence of atopy continue to exhibit sputum airway eosinophil levels comparable to younger asthma subjects.⁽³²⁾ In a study comparing subjects >64 years with either COPD (n=28) or asthma, defined by medical history and a lack of smoking history, who also had fixed airway obstruction (FEV1/FVC<70% after bronchodilator) (n=21) those with asthma had significantly elevated blood and sputum eosinophils and eosinophilic cationic protein (ECP) levels.⁽⁵⁵⁾ In addition, chronic respiratory symptoms and airway hyperresponsiveness to methacholine challenge were associated with elevated peripheral blood eosinophil counts in males (mean age 60years) enrolled in the Normative Aging Study.⁽⁵⁶⁾ Thus, eosinophils may be less functional in the elderly, but continue to be associated with asthma.

AGE-RELATED CHANGES IN ADAPTIVE IMMUNITY

Dendritic cells

Dendritic cells lie at the interface between the innate and adaptive immune responses and are categorized as plasmacytoid (pDC) or myeloid (mDC). Experimentally, monocytes can be differentiated *in vitro* (MDDC) to an mDC-like phenotype. MDDC derived from monocytes from older subjects exhibited decreased phagocytosis of CFSE-labeled apoptotic T-cells and decreased pinocytosis of FITC-labeled dextran.⁽⁵⁷⁾ A recent study demonstrated decreased TLR function of pDC and mDC from older (age ≥ 65 years) compared to young (21-30 year old) volunteers.⁽⁵⁸⁾ Defects in DC function correlated with a poor antibody response to influenza immunization in the older subjects. The impact of dendritic cell age-related changes in asthma is not clear. However, it is possible that diminished function impairs a robust adaptive immune response, leaving the inciting antigen or pathogen to evoke further innate responses.

T cells

Thymic involution—Thymic involution is a well characterized feature of immunosenescence. After approximately one year of life in humans, the thymopoietic space, which contains thymocytes and supporting thymic epithelial cells, is replaced with fatty tissue. By 70 years of age, the thymopoietic space is reduced to approximately 10% of the total thymus.⁽⁵⁹⁾ There are several consequences of thymic involution. First, T-cell receptor (TCR) diversity decreases from approximately 2×10^7 different TCR β -chains prior to 60 years of age to 200,000 after 70 years.⁽⁶⁰⁾ Decreased TCR diversity in aged (>18 month) C57BL/6 mice after infection with influenza virus A epitopes, decreased viral clearance.⁽⁶¹⁾ Thymic output of naïve cells CD4+CD45RO+ also diminishes by >95% after the age of 70 years.⁽⁶⁰⁾ As a result in mouse models, naïve CD4 cells maintained a longer life-span with increased resistance to apoptosis, but decreased response to antigen.⁽⁶²⁾ Additionally, in aged mice, recent thymic emigrants (RTE) produced by the aged thymus secreted less IL-2, had decreased proliferation, weak expression of early-activation markers, and decreased intracellular Ca²⁺ following TCR stimulation.^(63;64) Despite defects in RTE from aged mice, new CD4+ T cells generated from aged bone marrow stem cells, when transplanted into young hosts, function normally and generate normal memory responses.⁽⁶⁵⁾ In addition to the diminishing thymic output of naïve cells, the maintenance of the naïve T cell pool with aging may be compromised. Although it is controversial whether IL-7 levels decrease with

age, it is clear that it is critical for naïve and memory T cell maintenance and survival. IL-7 increased telomerase activity in naïve peripheral CD4⁺ cells of healthy aged adults, protecting against telomere loss and apoptosis.⁽⁶⁶⁾

Increased Memory T cells—Although thymic output of naïve cells decreases with aging, the total numbers of T cells remain relatively constant due to the survival of memory cells. The increased survival of memory CD4⁺ was reported to be due to changes in the aged mouse microenvironment.⁽⁶⁷⁾ Numbers of memory CD8⁺ T cells may be increased due to chronic viral stimulation.⁽⁶⁸⁾ Despite prolonged survival, memory CD4⁺ and CD8⁺ cells from aged mice may have poor antigen response.^(69;70) In humans, defective effector CD4⁺ cell responses after influenza vaccination was noted in healthy subjects > 65 years.⁽⁷¹⁾

Alterations in cytokine profile—Aging has been associated with a chronic pro-inflammatory state characterized by elevated IL-1, IL-6 and TNF- α , which may predict morbidity and mortality in the elderly.^(72;73) However, the effect of increased age on the balance between type 1 and type 2 cytokine lymphocyte expression is difficult to determine as it can be altered by many factors including the presence of co-morbid diseases. Although some studies suggest increased IFN- γ secretion by activated peripheral CD4⁺ and CD8⁺ cells⁽⁷⁴⁾, several others have shown a shift towards Type 2 cytokine production. In a study of healthy subjects in three different age groups (between 21-30 years, 80-81 years, and 100-103 years), flow cytometry was used to evaluate both CD4⁺ and CD8⁺ T-cell populations with respect to intracellular IL-4 (Th2) and IFN- γ (Th1) expression upon PMA (phorbol myristic acid) stimulation.⁽⁷⁵⁾ When the ratio of IFN- γ /IL-4 producing cells was examined, there were no age-related differences in the CD4⁺ T-cells; however, the IFN- γ /IL-4 ratio in the CD8⁺ T-cells was lower in both the older age groups suggesting an age-related shift from Th1 to Th2 cytokine profiles. The cytokine secretion of IFN- γ and both IL-4 and IL-10 (Th2) were measured following α -GalCer stimulation of NKT cells isolated from younger and older subjects.⁽³⁶⁾ The ratios of IFN- γ /IL-4 and IFN- γ /IL-10 were both significantly decreased in the older subjects suggesting a transition to a greater Th2 response with aging.

Decreased T cell signaling—One of the essential functions of T cells is the recognition of specific antigen in the context of an antigen presenting cell followed by proliferation and cytokine secretion. The aging of T cells in humans typically corresponds to a loss of CD28 expression, an accessory molecule for TCR signaling. The consequences of the CD28 loss include decreased IL-2 secretion and increased apoptosis upon activation.^(76;77) An *in vitro* loss of CD28 can be achieved with repeated antigen stimulation.⁽⁷⁸⁾ Furthermore, type I interferons (IFN- α and IFN- β) and TNF- α can also decrease CD28 expression.^(79;80) Therefore, the loss of CD28 is thought to reflect a lifetime of antigen or pathogen exposure.

Th17 cells—Th17 cells are a subgroup of T cells which secrete IL-17A, IL-17F, IL-22 and TNF- α . Th17 cells are differentiated from naïve T cells under the presence of IL-6 (increased expression associated with aging, see above) and TGF- β , which upregulates the transcription factors retinoid acid-related orphan nuclear hormone receptor- γ t (ROR- γ t) and STAT3.⁽⁸¹⁾ Th17 cells are maintained by IL-23. Several murine models of allergic asthma have suggested that IL-17A and IL-17F are important in airway inflammation, particularly neutrophilia^(82;83), enhance Th2 associated eosinophilia,⁽⁸⁴⁾ increase AHR and increase airway MUC-5AC expression.^(85;86) IL-17A and IL-17F are expressed in the airways of asthmatic patients.^(87;88) Besides playing a role in antigen induction of airway inflammation, the IL-23-Th17 axis is important for host response to respiratory bacterial infection and potentially viral infection.⁽⁸⁹⁾ Therefore, it is possible that Th17 cells may be involved in the

exacerbation of asthma or in pathogenesis of LOA late-onset asthma after respiratory infection.

The effect of aging on Th17 cells has been recently investigated and most work suggests increased IL-17 expression with aging. Aged (18-20 month) C57BL/6 and BALB/c mice infected with HSV-2 or murine cytomegalovirus produced higher levels of serum IL-17A, accompanied by an increase in liver neutrophil accumulation and mortality compared to infected young (2-4 months) and middle-aged (8-10 months) mice.⁽⁹⁰⁾ Conversely, IL-17 neutralization or neutrophil depletion reduced liver damage and prevented death in these models of viral infection. Aged (16-18 month) DBA/2 or BALB/c mice infected with the gram-negative bacteria *Brucella abortus* had significantly increased IL-17 and IL-6 splenocyte expression compared to similarly infected young (2-3 month) mice who displayed a Th1 expression.⁽⁹¹⁾ Additionally, aged (18-23 month) CBA (H2^k) and C57BL/6 mice demonstrated increased IL-17 spleen cell production after stimulation with irradiated donor spleen cells compared with strain-matched young (2-4 month) mice.⁽⁹²⁾ The role of Th17 cells in the pathogenesis of late-onset asthma in a murine model or in older humans with asthma has not been reported.

Regulatory T cells—T regulatory (Tregs) cells suppress several effector functions of the T-cells subsets including Th1, Th2 and Th17. Tregs may protect against autoimmune diseases such as multiple sclerosis and diabetes, but excessive numbers and function may lead to increased susceptibility to infection and cancer. Treg cells found in the lung are in the CD4+CD25^{hi} population. Natural Tregs (nTregs) are derived from the thymus, express the transcription factor Foxp3, and mediate suppression primarily via cell contact. Peripheral antigen-induced adaptive Tregs (iTregs) are either Foxp3+ or Foxp3-, and their major suppressive action is mediated via IL-10 and TGF-β. The precise role of nTregs and iTregs in asthma is not clearly established, but most studies in murine models of asthma and in humans suggest a protective role.⁽⁹³⁻⁹⁵⁾ Additionally, antigen tolerance in murine models of asthma, induced by inhalation or low-dose oral feeding of allergen to young mice has been shown to suppress several features of allergic asthma and may involve Treg cells.⁽⁹⁶⁻⁹⁸⁾

The effect of age on the Treg pool number and function is less clear. Numbers of cord blood CD4+CD25^{hi} are elevated at 2.3-9.5% of the total CD4+ T-cells (suggested to support fetal development of the immune system), decline within the first 36 months of life, and then remain stable in young and middle aged healthy adults.⁽⁹⁹⁾ In older patients, the change in Treg numbers is less investigated, and studies in humans have been limited to peripheral blood. Some investigators have shown an increase in CD4+CD25+ and CD4+Foxp3+ T cells^(100;101) in healthy elderly compared to younger subjects, whereas, other groups have found no significant differences in numbers of CD4+Foxp3+ T cells.⁽¹⁰²⁾ The proportion and numbers of CD4+Foxp3+ cells have been shown to be increased in lymphoid organs, but not in lungs and blood of aged (> 20 month) C57BL/6 mice compared to younger mice.^(101;103) Earlier studies suggested that the suppressive activity of Treg cells declined with increasing age,⁽¹⁰⁴⁾ but more recent studies have suggested that it is preserved or even enhanced.^(100;102;103)

The importance of Treg cells in airway inflammation in older patients with asthma is not widely investigated. However, aged mice fed low-dose OVA prior to antigen sensitization and challenge developed decreased AHR, antigen-specific serum IgE, BALF eosinophilia and mucus hypersecretion compared to age-matched non-tolerant mice. Additionally, the percent of lung tissue CD4+CD25+Foxp3+ cells were increased in antigen tolerant aged mice. (Busse PJ, manuscript in preparation)

B-cells—The potential to generate new naïve B-cells may diminish with age. In a study of 662 bone marrow biopsies from subjects ranging in age from 2 months to 92 years, a decline in the numbers of B-cell precursors was observed.⁽¹⁰⁵⁾ In mice, there is a transition from naïve B-cells to “antigen-experienced” B-cells⁽¹⁰⁶⁾. However, in mice, the ability to produce antibody remains intact with aging⁽¹⁰⁷⁾; but the quality of antibody produced has decreased affinity and avidity for antigen⁽¹⁰⁸⁾. This observation is likely due to deficient somatic hypermutation, which is responsible for enhancement of antibody specificity for antigen.⁽¹⁰⁹⁾ However, there are also defects on aged T-cells which may also account for altered immunoglobulin production. Transfer of aged stimulated murine CD4 T cells into young hosts resulted diminished B cell activation, lower levels of antigen-specific IgG and decreased expansion of the lymph node germinal centers. These alterations were secondary to reduced CD154 (CD40L) expression.⁽¹¹⁰⁾ Therefore, the age-related decline in diversity and quality of antibody, particularly in the setting of new antigen exposure, may impact the ability to clear pathogens and provide protection against a repeat exposure to the pathogen.

ALLERGEN SENSITIZATION IN OLDER ADULTS

Approximately 80% of young children in the United States with asthma are allergen sensitized, and atopy in this age group increases disease morbidity.^(111;112) The role of allergen-specific sensitization in the pathophysiology and severity in older patients is not well understood. It is generally accepted that total IgE declines with increasing age. Several cross-sectional studies of randomly selected individuals from the Tucson Epidemiological Study and the National Health and Nutrition Examination Survey (NHANES 2005-2006) have demonstrated that total serum IgE peaks by 20 years of age and is lowest after 70 years.^(113;114) However, some studies have not supported this trend.^(115;116) Studies also suggest that younger populations tend to have a higher prevalence of allergen-specific IgE sensitization than older groups.^(115;117) The decrease in total IgE and allergen-specific IgE with increasing age may be due to both age and cohort effects. The effect of increased age on alterations in total and allergen-specific IgE production are most likely due to several factors of immunosence, including alterations in cytokine profiles and changes in B cell antibody production, and are described elsewhere in the text. A cohort effect is due to the observation that over time there has been an increased prevalence of atopic diseases, possibly due to environmental factors. Therefore, more recent birth cohorts may have higher rates of allergen sensitization due to environmental conditions present at the time of birth and in early childhood, and not completely due to a younger age. There have been several longitudinal studies from cohorts of randomly selected subjects from Tuscon,⁽¹¹⁷⁾ Nottingham,⁽¹¹⁸⁾ Copenhagen,⁽¹¹⁹⁾ and in the European Community Respiratory Health Survey⁽¹²⁰⁾ that support a cohort effect along with an aging effect to explain differences in IgE among age groups.

For many years, asthma in older patients was characterized as non-atopic or intrinsic.⁽¹²¹⁾ However, over the past two decades, there have been a few reports looking at older patients with asthma, which have demonstrated that atopy is not uncommon in this group. The reported percentage of older patients with atopic versus non-atopic asthma varies and may depend upon the characteristics of the population studied. Studies in non-minority populations suggest that 28% to 74% of older adults with asthma (not classified based upon age of onset) are sensitized to at least one antigen.^(4;122-124) Additionally, it appears that there is a higher rate of allergen sensitization in older patients with asthma compared to age-matched controls.^(4;123)

Two studies have specifically looked at antigen sensitization rates in older asthmatics from inner-city populations. Rogers *et al* demonstrated in a study of 45 patients > 65 years of age recruited from an asthma clinic in New York City, that 60% had at least one detectable

allergen specific IgE (including outdoor allergens) and 47% were sensitized to cockroach.⁽¹²⁵⁾ Among these patients, cockroach sensitization was associated with more severe asthma as measured by airflow limitation and hyperinflation. However, this study did not compare rates of sensitization of elderly versus younger asthmatics. Another study looked at adult inner-city patients with moderate to severe persistent asthma, and found that 41% of those greater than 60 years of age were sensitized to at least one antigen, whereas 73% between 18-35 years of age were sensitized.⁽¹²⁶⁾ The most common aeroallergen to which older patients are sensitized is not consistent among reports and has been cat,⁽¹²⁴⁾ dust mites,^(123;126) and cockroach⁽¹²⁵⁾. Whether the differences in specific antigen sensitization are due to socioeconomic status, geographic location and environmental exposures, is not well established. Additionally, the role of allergen exposure in asthma pathogenesis and severity in sensitized older patients is not completely understood.

Some studies have suggested that antigen sensitization may play a role in late onset asthma.^(127;128) In the Normative Aging Study, men developing airway hyper-responsiveness after 49 years of age were more likely to be sensitized to cat (23.9% versus 4.4%) compared to age-matched controls.⁽¹²⁷⁾ However, sensitization to other indoor allergens (dust mite, mouse) were not significantly different. Nearly 50% of the forty patients in the Tucson Epidemiologic study of obstructive lung diseases who developed asthma after the age of 60 years were skin prick positive to at least one antigen, compared with 26% of the age-matched control population without asthma.⁽⁴⁾ In a study of 21 patients with asthma onset after 65 years of age, 81% demonstrated a positive skin prick test to at least one allergen compared to a group of 14 patients developing asthma < 65 years in whom 57% were allergen sensitized.⁽¹²⁸⁾ A French study recruited 1,485 patients (mean age 73 years) from a total of 379 lung specialists with a diagnosis of asthma to examine disease characteristics. 14.7% of those developing asthma after 65 years of age were sensitized to at least one antigen by skin prick testing, whereas 60.1% of those developing asthma prior to 21 years of age were antigen sensitized.⁽¹²²⁾

CLINICAL IMPLICATIONS AND SUMMARY

Older patients with asthma are a difficult population to treat and clinical management is addressed in detail elsewhere (see article by Reid in this issue). Treatment is complicated by co-morbid conditions, side-effects of medications and potential physical impairments decreasing effective drug delivery (i.e. difficulty administering an inhaler due to arthritis). Additionally, asthma in this population is frequently severe and increased age may affect cellular responses to corticosteroids, leukotriene inhibitors, anticholinergics, beta-agonists or anti- IgE. There have been limited numbers of studies specifically addressing the role of asthma medications on airway inflammation and asthma outcomes in older patients. Additionally, whether the asthma is long-standing or late-onset most likely also plays a role in medication response. Corticosteroids work in some, but not all older patients. A large database review of patients 65 years old hospitalized at least once for asthma and followed 12 months after discharge, demonstrated that those given inhaled corticosteroids had a 29% reduction in asthma readmission and a 39% reduction in all-cause mortality.^(129;130) However, some older patients with asthma may have a component of fixed airway obstruction.⁽¹³¹⁾ The National Institute of Health National Asthma Education and Prevention Program (NAEPP) sponsored a working group report on the topic of asthma in the elderly in 1996 which recommended that older patients be administered a 2 week trial of oral corticosteroids (0.3-0.5mg/kg) and have repeat lung function after the course to assess for possible benefit.⁽¹³²⁾ Although a reduction in anti-inflammatory lipoxin A₄ with aging has been reported,⁽⁴⁵⁾ the improvement in asthma with leukotriene receptor antagonists appears to be more beneficial in younger patients. Zafirlukast decreased asthma symptoms

regardless of age, but had its greatest effects on adolescents and adults, and did not change lung function in older patients.^(133;134)

In September 2008, the NIH National Institute on Aging and National Heart, Lung, and Blood Institute co-sponsored a conference with experts on asthma in older individuals. Existing data from animal models and human studies was reviewed and it was concluded that inflammation associated with asthma in the elderly differs from younger asthmatics. Age-related changes in immune function have been observed for components of the innate and adaptive immune responses. These changes may have implications for the clinical features of long-term asthma and late-onset asthma as well as asthma exacerbations (Figure 1). Furthermore, with the expected increase in the elderly populations, including elderly asthmatic patients, there is an urgent need to study these individuals with particular attention to the differences in inflammatory mechanisms and responses to therapy.

Abbreviations used

AA	Arachidonic acid
AHR	Airway hyperresponsiveness
AM	Airway macrophage
BALF	Bronchoalveolar lavage fluid
LOA	Late-onset asthma
OVA	Ovalbumin
PMA	Phorbol myristic acid
PMN	Polymorphonuclear leukocytes
ROS	Reactive oxygen species
Tregs	T regulatory cells

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KEY CONCEPTS

- Age-related changes in immune function have been observed for components of the ***innate immune response***, including epithelial cells, neutrophils, monocytes, macrophage, mast cells, and eosinophils.
- Age-related changes in immune function have also been observed for components of the ***adaptive immune response***, including dendritic cells, T cells, T regulatory cells, and B-cells.
- The age-related changes in immune function in ***human asthma subjects*** and the corresponding clinical consequences have yet to be fully characterized.
- Asthma in older patients is not uncommon and may either develop in childhood or later in life, termed late-onset asthma (LOA).
- Current pharmacological interventions and those in development for the management of asthma are increasingly focused on specific inflammatory pathways. Therefore, an understanding of age-related changes in inflammatory responses will be essential to establish rational approaches to the treatment of asthma in the elderly.

figure 1.

Table 1**Summary of Immunosenescence Features**

Neutrophils	Reduced phagocytosis Reduced ROS production
NK	Increased Reduced numbers Reduced cytotoxicity
NKT	Reduced numbers Reduced proliferation
Monocytes/Macrophage	Reduced phagocytosis Reduced cytokine and chemokine secretion Reduced generation of nitric oxide and superoxide
Eosinophils	Reduced degranulation Reduced superoxide production
Dendritic Cells	Reduced phagocytosis and pinocytosis Increased IL-6 and TNF- α production Diminished TLR expression and function
T cells	Reduced response and proliferation Reduced CD28 expression Accumulation of CD8+CD28+ T cells Reduced TCR diversity Reduced signal transduction
B cells	Production of low affinity antibodies Increased oligoclonal expansion Reduced surface MHC class II molecule expression