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Changes in immune function in asthma in the elderly

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Abstract

Asthma is an inflammatory disorder of the airway. The airway inflammation of asthma is typically an allergic inflammation characterized by cells and mediators described as a “Th2” inflammatory response. There is a growing body of evidence describing changes in the function of immune cells upon aging, a phenomenon referred to as “immunosenescence”. Several studies utilizing animal models and human subjects with asthma have begun to explore age-related effects on the airway inflammation in asthma. This review explores the existing data on the presence and effects of immunosenescence or age-related changes in immune function in asthma.

Keywords

Asthma; allergy; immunology; immunosenescence

Introduction

Asthma is characterized by underlying airway inflammation with variable airflow obstruction and bronchial hyperresponsiveness[1]. Estimates of the prevalence of asthma are 8–10% in all age groups. As the elderly (>65 years old) population is rapidly increasing, the numbers of elderly with asthma are expected to double in the next 20 years[2]. While the mortality in most age groups is decreasing, the mortality of asthma in the elderly has remained constant[3], with a notable increase in elderly African-American women[4]. The reason for these disparities is not known. Identifying the differences seen in asthma in the growing elderly population will be important in the diagnosis of the disease, improvement in the morbidity and mortality, as well as determining optimal therapies. This review will address how age-related changes in the immune system contribute to the pathogenesis of asthma in the elderly.

Defining Asthma in the Elderly

There is not yet a consensus definition of asthma in the elderly. There are suggestions that asthma in the elderly represents a distinct phenotype and within this phenotype, subgroups exist. These subgroups include: asthmatics with a persistence of disease from childhood, a history of childhood asthma with quiescence during young adulthood, and late-onset asthma. Furthermore, there is no strict definition for late-onset asthma, with some defining it as onset after age 30 and others as onset after age 65.

Another frequent issue in the evaluation of airway obstruction in the elderly is the distinction between asthma and chronic obstructive pulmonary disease (COPD). There are guidelines to identify distinguishing features of asthma, which include presence of other allergic symptoms, bronchodilator reversibility, and presence of eosinophilia[5]. In contrast,

COPD is frequently associated with a history of tobacco smoking. However, it is also likely that an overlap syndrome exists in which features of asthma and COPD are both present, but this subset of patients have yet to be examined and is typically excluded from investigational studies.

Inflammation in Asthma

Typically, the inflammation found in asthma originating in childhood is allergic and consists of predominantly Th2 lymphocytes and mediators (IL-4, IL-5, and IL-13). Studies of sputum samples, bronchoalveolar fluid, and bronchial biopsies have shown baseline inflammation consisting of T-cells and eosinophils with a subsequent influx of additional inflammatory cells including eosinophils, neutrophils, and lymphocytes into the airway during an exacerbation of asthma[6]. In addition to these cells, the expression of a number of inflammatory mediators including cytokines, chemokines, and lipids (prostaglandins and leukotrienes) are significantly increased in the airway. Many of these mediators, such as IL-13 and leukotriene LTC₄, can directly induce the pathophysiological hallmarks of asthma, including airway hyperresponsiveness, goblet cell hyperplasia, mucus secretion, and smooth muscle cell hypertrophy[7;8].

Late-onset asthma is typically non-allergic in nature, and is referred to as “intrinsic” asthma [9]. It is recognized to be a more severe phenotype of asthma, with greater levels of obstruction, more frequent exacerbations, and a greater rate of decline in lung function. Despite the lack of allergen induced inflammation, the cells and mediators associated with intrinsic asthma are remarkably similar, with prominent T-cell and eosinophil involvement[10;11].

An important “trigger” of asthma exacerbations is viral upper respiratory infections. Estimates suggest that up to 80% of asthma exacerbations in adults are caused by viral upper respiratory infections[12]. Since immune function is important for the resolution of respiratory infections, the question arises regarding the impact of immunosenescence on the clinical features of asthma in the elderly. For example, are exacerbations more frequent or severe in the elderly due to an increased susceptibility or a persistence of viral respiratory infections?

Allergic Sensitization and IgE Levels in the Elderly

Anecdotally, it is thought that individuals “grow out” of their allergies, such that the typical nasal and ocular symptoms upon exposure to allergens diminishes with age. Furthermore, allergen triggered asthma symptoms also typically diminish with aging. The TENOR study examined the natural history of the disease in one of the largest groups of older (> 65 years old) patients to date and found when compared to their younger counterparts, older asthmatics had lower total IgE levels, fewer positive skin prick tests, and less concomitant allergic rhinitis or atopic dermatitis[13]. Several studies have demonstrated age-related declines in total IgE and allergen-specific IgE levels[14–19], suggesting that this may be the explanation for the decline in allergy symptoms. There is also evidence for age-related decline in skin-prick test responses to allergens[20]. In addition, these patients also have a poor perception of their asthma symptoms when compared to their younger counterparts which likely contributes to their morbidity[21;22]. However, the relationship between total IgE and allergic disease persists in the elderly, such that subjects with elevated IgE levels remain more likely to have allergic rhinitis or asthma[23;24].

Given the changes in allergic inflammation with aging, one might conclude that asthma in the elderly should be milder or become nonexistent. However, there are numerous other common triggers for exacerbations of asthma including irritants (e.g. cold air) and

respiratory infections. These other triggers often exhibit inflammatory features in common with allergic triggers, but they are not necessarily identical.

Immunosenescence

Numerous studies suggest that immune function declines with aging, a phenomenon frequently referred to as “immunosenescence”. This is thought to manifest in the elderly as more frequent infections[25], increased incidence of autoimmune disease[26], and increased incidence of malignancy due to impaired immune surveillance[27]. Immunosenescence has been described for both adaptive and innate arms of the immune response.

The most extensively studied component of the immune system with regards to immunosenescence is the T-cell population. The involution of the thymus gland begins shortly after birth and undergoes replacement by fatty tissue that is nearly complete by 60 years of age. As a result, a decline in the numbers of naïve T-cells gradually occurs, and memory T-cells (CD45RO⁺) eventually predominate, although memory cell responses may also gradually decrease with aging[28]. T-cell receptor repertoire diversity appears to diminish and T helper cell activity declines[29]. Other observations of the T-cell population with aging include reduced proliferative responses[30], a decrease in CD8⁺ T cell levels[31], a shift of Th1 to Th2 cytokine profiles upon stimulation with PMA (phorbol myristic acid) [32], a decline in Fas-mediated T-cell apoptosis[33], and increased DR expression on T-cells[34]. In addition, an increased proportion of FOXP3⁺ CD4⁺ T regulatory cells with intact suppressive capabilities have been found in elderly subjects, which may help explain the decreased T-cell functional activities described above[35]. Whether any of these age-related changes is more or less pronounced in specific inflammatory disorders, such as allergic diseases or asthma, is not known.

A decreased production of B-cells with aging has been observed in mice and likely to be true for humans[36;37]. This supports the notion that the distribution of B-cell subsets present in the elderly differs from that of younger individuals. More specifically, there is a transition from the presence of naïve B-cells to “antigen-experienced” B-cells[38]. In mice, it appears that the functional ability to produce antibody remains intact with aging[39]; however, the quality of antibody produced is lower, i.e. the antibodies exhibit lower affinity and avidity for antigen[40]. This observation is likely due to deficient somatic hypermutation, which is responsible for enhancement of antibody specificity for antigen[41].

Several neutrophil functions are unchanged with aging including adhesion, migration into inflammatory tissue, and phagocytosis. However, the ability of neutrophils to kill phagocytosed organisms is diminished in the elderly compared to younger individuals[42], which may be due to a decrease in the production of reactive oxygen species (ROS)[43;44]. In addition, it has been observed that neutrophils in the elderly are more prone to undergoing apoptosis, which may be due to a deficiency in the cytokine-mediated signaling pathways to protect the neutrophils[45;46]. Therefore, neutrophils may be less abundant in acute inflammatory responses due to greater apoptosis, and those that are present may have diminished anti-pathogen activity. Both of these changes with aging may contribute to more frequent and more severe respiratory infections.

A cell often associated with allergic inflammation is the eosinophil. The presence of eosinophils in the airway has been shown to be a marker for disease activity and its decrease with therapies has served as a predictor of clinical responsiveness[47;48]. In a study examining age-related changes in eosinophil function, it was found that peripheral blood eosinophils from older asthma subjects exhibited decreased degranulation in response to

cytokine stimulation and a trend for decreased superoxide production[49]. Thus, eosinophils may have a diminished role in the airway inflammation of older asthma patients.

No studies have been performed to assess whether an increase in susceptibility to infections due to immunosenescence is associated with increased severity of asthma. Respiratory pathogens such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and rhinovirus (RV) have been proposed to be a contributory factor to asthma severity[50;51]. Moreover, *Chlamydia pneumoniae* in sputum and in the airway has been associated with persistent airflow limitation in non-atopic adult-onset asthma, disease severity and a poor clinical outcome[52]. Furthermore, RV infection early in life is a strong predictor of subsequent wheezing, suggesting that RV might also be important in the pathogenesis and chronicity of asthma[53]. Whether the increased susceptibility to infectious disease associated with immunosenescence contributes to the pathogenesis and/or severity of asthma in the elderly has yet to be determined.

Interestingly, there are suggestions that individuals with less features of immunosenescence with fairly well-preserved immune responses in the very old corresponds to a prolonged survival[54]. Conversely, decreased survival was associated with features of immunosenescence including impaired T-cell proliferative response to mitogenic stimulation, increased numbers of CD8⁺ cytotoxic/suppressor cells, and low numbers of CD4⁺ T-cells and CD19⁺ B-cells[55].

Another component of immunosenescence is the presence of a chronic systemic inflammation, often referred to as “inflamm-aging”, which is characterized by increased serum IL-6 and TNF- α [56]. The inflamm-aging is typically associated with more “frail” individuals and the precise etiology of the increased serum IL-6 and TNF- α is not known. However, the elevated levels of these cytokines may certainly contribute to organ-specific or systemic inflammatory processes, including asthma.

The presence of immunosenescence raises the question of its impact on inflammatory diseases such as asthma. Given the roles of immune cells in asthma, there are several mechanisms by which immunosenescence could affect asthma: 1) baseline airway inflammation may be altered, 2) airway inflammatory responses to an allergen trigger may be altered, and/or 3) airway inflammatory responses to a respiratory pathogen may be altered. In fact, it is likely that immunosenescence affects all these aspects of immune function in asthma. Thus, the clinical consequences of these effects are likely to be an important consideration for management of asthma in the elderly.

Animal Models

There are several studies that have examined the effect of aging on the airway inflammatory responses in animal model systems. In a study utilizing Brown-Norway rats, ovalbumin (OVA) sensitization in young (6–8 weeks) rats resulted in greater levels of serum total IgE than sensitization in aged (100–120 weeks) rats[57]. Furthermore, a subsequent intranasal OVA challenge and bronchoalveolar lavage (BAL) demonstrated an attenuated airway inflammation in the aged rats. While the young rats had marked increase in total BAL cells including both eosinophils and neutrophils, the aged rats had significantly less total cellularity and essentially an absence of eosinophils in the BAL fluid. However, the neutrophil influx was comparable in both the young and aged rats. Since eosinophils are typically associated with Th2 inflammatory responses, the interpretation of this observation was a diminished Th2 inflammatory response with aging.

In a study of BALB/c mice, splenic T-cells were examined for age effects on inflammatory responses[58]. The secretion of Th2 cytokines (IL-4, IL-5 and IL-13) from purified T-cells

stimulated with anti-TCR β was greater in young (5–6 weeks) mice compared to aging (32–48 weeks) mice. In contrast, secretion of a Th1 cytokine (IFN- γ) was greater in the aging mice, suggesting an age-related “skewing” of the T-cells to a Th1 phenotype of cytokine secretion. Further examination of the signaling pathways indicated that impaired function of the GATA-3 transcription factor in the aging mice was the mechanism for the transition to preferential Th1 responses with aging. In another study utilizing BALB/c mice, sensitization with OVA at different ages (1, 4, 8, 20, and 40 weeks) was followed by an aerosolized OVA challenge[59]. Sensitization at an older age corresponded to the OVA challenge causing less airway obstruction and hyperreactivity as well as a BAL cytokine profile of decreased IL-4, decreased IL-5, increased IFN- γ , and increased IL-10. This cytokine profile is consistent with an increased Th1 and T regulatory cell response and decreased Th2 response with aging.

When BALB/c mice were sensitized and challenged with OVA at different ages (6, 24, 48, and 72 weeks)[60], a Th1 predominant response was observed in the older mice, with increased IFN- γ and decreased IL-4 and IL-13 mRNA expression in the lung. However, there was also a finding of increased IL-5 mRNA expression and eosinophils in BAL of older mice. Despite the increased IL-5 expression and presence of eosinophils, airway hyperreactivity (AHR) was not increased in the older mice. This suggests that the relationship between pulmonary inflammation and eosinophils is not a direct one and Th2 cytokine generation may be blunted resulting in decreased AHR. Thus, this study showed that selective differences exist in Th1 and Th2 inflammatory responses with aging.

These studies indicate that in animal models of asthma, a decrease in airway hyper-reactivity and increase in Th1 responses is exhibited. However, there were conflicting results regarding the Th2 responses with selective decreases found in IL-4 and IL-13. Two of the studies found IL-5 expression to be decreased while one study found an increase in IL-5 expression. The reasons for this discrepancy are unclear but may be related to differences in sensitization/challenge protocols. The general finding of increased Th1 response in the animal models of airway inflammation is in contrast to the human T cell studies which revealed an increase in the Th2 response in a non-asthmatic population. This may be due to the use different stimuli, i.e. allergen versus PMA. However, it is intriguing to consider the possibility that these differences may occur because of disease specific inflammation.

Although identical age-related inflammatory changes were not observed in each of the animal model studies, a consistent feature was an alteration of inflammation with aging. One concern regarding the animal studies is that they more likely represent late-onset asthma. The allergic sensitization is performed in aged animals, which is then followed by a challenge to represent allergic airway inflammation. In humans, allergic asthma in older adults is typically the culmination of allergic sensitization in childhood with a lifetime of allergy-driven asthma. Thus, another model of interest for the study of asthma in the elderly would be an animal sensitized at a young age, challenged intermittently throughout life (for example, weekly), and analyzed upon challenge at an old age. However, there are many technical limitations to such a study, including the propensity of mice to develop tolerance to chronic antigen challenge. Furthermore, animal models utilizing alternate triggers for asthma exacerbations, such as respiratory infections, have not yet been examined in the context of aging.

Human Studies

The aging process has been shown to exhibit changes in airway inflammation. An examination of the cellular composition of bronchoalveolar fluid from 19 to 83 year old subjects, without history of allergies, pulmonary disease or gastroesophageal reflux, showed

an increased airway neutrophilia as well as increased numbers of CD4+ T-cells [61;62]. Furthermore, the T-cells also appeared to be more activated in the elderly with increased expression of HLA-DR and CD69. This increase in airway neutrophils has also been observed in asthma subjects[49]. In asthma subjects, it is unclear whether the increased airway neutrophils contribute to airway inflammation during exacerbations. Since there is a phenotype of severe asthma characterized by a predominantly neutrophilic airway inflammation[63], the question arises whether the increased presence of neutrophils contributes to a greater severity of asthma in the elderly.

A cohort of 2280 men, ages 21–80 at enrollment in 1961, from the Boston area were followed in the Normative Aging Study. Of note, these subjects did not have any chronic diseases, including asthma, at enrollment. In a study of case-controlled subsets of subjects from the Normative Aging Study (mean age 61 years), it was shown that allergic sensitization to cat was a predictor for the subsequent development of airway hyperresponsiveness or asthma[64]. Other studies have found asthma in the elderly to be associated with increased allergic sensitization to cockroach[65] and dust mite[24]. Another report found that chronic respiratory symptoms and airway hyperresponsiveness were associated with elevated peripheral blood eosinophil counts[23]. Thus, several studies have identified predictors for asthma, including allergic sensitization, total IgE and elevated eosinophil counts, that are also considered important for asthma in younger subjects.

One of the recent tools to provide a noninvasive assessment of airway inflammation is the measurement of exhaled nitric oxide. In a study examining 2200 subjects, 25–75 years of age, it was found that an increase in exhaled nitric oxide was associated with aging[66]. This increase may be reflective of the altered distribution of inflammatory cells or the altered activity of inflammatory cells in the airway. In either case, this demonstrates another important and perhaps clinically relevant difference between younger and older asthma subjects.

The Absence of Evidence Based Recommendations for Asthma in the Elderly

It is striking that the majority of published clinical trials on the treatment of asthma exclude subjects over the age of 65. As a result, current guidelines for the management of asthma in the elderly are the same as younger adults[1]. However, there are concerns about the use of inhaled corticosteroids (ICS) and beta-agonists in the elderly as there is a potential for adverse side effects to occur[67]. Since these medications are the mainstay of asthma therapy, the exploration of alternate treatment options and the safety of current therapies are needed. This would provide the necessary evidence base for guidelines in the management of asthma in the elderly.

There are only a handful of reports examining the efficacy of asthma therapies in an older population. The older subjects enrolled in ACCEPT (Accolate clinical experience and pharmacoepidemiology trial) were analyzed separately to demonstrate that the leukotriene receptor antagonist, zafirlukast, is effective in asthma subjects above 65 years old[68]. Interestingly, the traditional outcome measure of pulmonary function was only slightly improved in the older subjects, rather, symptoms scores demonstrated the statistically significant efficacy. Whether anti-cholinergics should have a greater role in the treatment of asthma in the elderly has been debated. In a study comparing a β -agonist, salbutamol, to an anti-cholinergic, ipratropium, it was found that nonallergic subjects older than age 60 tended to respond better to the ipratropium, while younger allergic subjects responded better to salbutamol[69]. In another study of pooled subset of older subjects (> 50 years) from several trials utilizing omalizumab for the treatment of asthma, the omalizumab was effective in the

older subjects, specifically reducing rates of exacerbations and beta agonist use [70]. In the TENOR (the epidemiology and natural history of asthma: outcomes and treatment regimens) study, which examined asthma outcomes in subjects recruited from allergy or pulmonary practices, the older subset of asthma subjects (> 65 years) had lower baseline lung function (in terms of percent predicted), used higher doses of inhaled corticosteroid, and had better quality of life symptom scores compared to the younger asthma subjects[13].

These clinical studies of asthma in the elderly suggest that the traditional therapies may be effective; however, the traditional outcome measures for asthma improvement may not be ideal for the older asthma population. It should also be noted that these clinical trials excluded older patients with significant comorbidities. This raises a concern that the studies may not be representative of typical older asthma patients that may have multiple comorbidities and may be taking several medications for their comorbidities. It is possible that the comorbidity itself or the medication treatment may have a significant impact on the asthma outcome measures. This is a theoretical issue affecting all studies in the elderly, but has not yet been addressed in asthma studies.

Future Directions

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[5]. The members of the panel recognized the lack of data to support evidence-based recommendations. Thus, a significant emphasis in the working group report was an urgent need to design studies to examine the safety and efficacy of current therapies and to define the natural progression of the disease with respect to the epidemiology as well as the cellular and molecular mechanisms. Unfortunately, the following decade has not provided the evidence base needed.

The existing data from animal models and human studies suggest that the inflammation associated with asthma in the elderly differs from younger asthmatics. This has implications for both the diagnosis and treatment of asthma in the elderly. With the expected increase in the elderly population including elderly asthmatic patients, there is an urgent need to study these individuals with particular attention to the differences from younger patients in terms of inflammatory mechanisms and responses to therapy. Furthermore, studies of novel asthma therapies should also include subjects above 65 years of age to validate their use in the elderly.

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Executive Summary

Introduction

- Asthma is an inflammatory disorder of the airway.
- Immune function has been shown to change with aging, referred to as “immunosenescence”.
- Whether immunosenescence affects the clinical presentation or management of asthma in the elderly remains to be answered.

Defining Asthma in the Elderly

- The definition encompasses: persistent asthma originating in childhood, asthma in childhood with period of quiescence followed by return in older age, and late-onset asthma.

Inflammation in Asthma

- The airway inflammation of asthma is present at baseline and increased upon exposure to a trigger, which could be exposure to allergen, cold air, or respiratory virus.

Allergic Sensitization and IgE Levels in the Elderly

- The levels of total and specific IgE decline with aging.
- There is a decline in response to skin-prick testing for allergic sensitization in the elderly.

Immunosenescence

- The T-cell population transitions to more memory T-cells with aging. The functional response of T-cells declines and the T-helper cell profile shifts from Th1 to Th2.
- The B-cell population declines in numbers with aging. Although the quantity of total antibody production is unchanged, the quality declines with less avidity of the antibody for its antigen.
- The neutrophil population exhibits less microbicidal activity and undergoes apoptosis more easily with aging.
- The eosinophil population exhibits less degranulation and superoxide production with aging.

Animal Models

- In rat and mouse models, the use of OVA sensitization and challenge in young and older animal has shown changes in airway inflammatory responses.
- There is less or defective Th2 inflammation with aging upon allergen stimulation. This is in contrast to the human studies showing increased Th2 responses with generalized stimulation of T-cells with PMA.

Human Studies

- Normal aging is associated with increased airway neutrophils and activated CD4+ T-cells.

- Several studies have shown the presence of the typical Th2 inflammatory markers associated with asthma in older subjects; however, the relative levels differ from younger subjects.
- Exhaled nitric oxide levels increase with aging.

The Absence of Evidence Based Recommendation for Asthma in the Elderly

- Most clinical trials exclude older asthma subjects and those with comorbidities.
- A few trials have examined the use of a leukotriene receptor antagonist, omalizumab, and inhaled corticosteroid. All showed efficacy in an older population, but there were suggestions that symptom reports were better than the traditional lung function measures in assessing efficacy.

Future Directions

- Further characterization is needed to determine the effects of immunosenescence on airway inflammation.
- Further studies are needed to establish the efficacy and safety of traditional and novel asthma therapies in an older asthma population.