

Allergy and Immunology of the Aging Lung

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The alveolar membrane of the lung is one of the largest epithelial surface areas of the human body in contact with the external environment, and it is continuously exposed to various microorganisms and organic and inorganic particles. Like the skin or the gastrointestinal mucosa, the immune system of the lung is exposed to a host of foreign matters and differentiates potentially harmful agents from other innocuous materials.

The aging process is associated with progressively impaired immune surveillance and decreased ability to mount an appropriate immune response, which potentially leads to increased susceptibility to respiratory insults. Aged individuals are at increased risk for respiratory tract infections [1], interstitial lung disease [2], and pulmonary neoplasms [3]. Pneumonia ranks high as a cause for hospitalization and causes significant morbidity and mortality in older patients. The role of aged-based immune changes in increases in infection, interstitial lung disease, and neoplasms has not been linked clearly, but the increased incidence of infections in the older population does suggest a role for alterations in host immunity [4]. Although the senescence of the immune system in older adults is likely to play a contributing role in the pathogenesis of these disorders, little is known about how the innate and adaptive immune responses change in the aged human lung or how the changes are linked to increasing susceptibility to infections. Many previous assumptions about host defense of the aging human lung are based on either animal studies or ex vivo data from human peripheral blood. This article reviews the basics of pulmonary host

defense and some recently published research on the immune response within the aging lung.

Overview of human immunity

The human immune system has cellular and soluble protein components that interact in a highly complex manner and lead to the basis for innate and adaptive responses. The innate immune system provides the first line of host defense, and its function does not depend on prior exposure to the microbe. The innate immune defense includes the epithelial barrier, leukocytes (neutrophils, macrophages, and natural killer cells), circulating effector proteins (complement, collectins, pentraxins), and numerous cytokines released from these cells (ie, interleukin [IL]-12, interferon- γ , tissue necrosis factor, chemokines).

Upon exposure to an antigen, the innate immune system responds by recruiting neutrophils, macrophages, and natural killer cells and activating the complement pathway. The products of complement activation can serve various roles in host defense, with the primary one being opsonization, a process whereby the complement components bind to the microbial cell surface and facilitate uptake by phagocytic cells. The complement system enhances the immune response by facilitating chemotaxis for other effector cells. For example, the complement-activated product C5a is a potent chemotactic factor for neutrophils and is involved in the activation of phagocytic cells [5] and release of oxidants and granule-based enzymes [6–8]. The collectins are another group of related proteins that serve as opsonins for bacterial products in plasma and tissues. The group includes mannose-binding lectin and the lung surfactant proteins SP-A and SP-D. The collectins have a common structure of a globular-like

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domain and a collagen-like tail, and the binding of the collectins to the bacterial surface promotes phagocytosis by macrophages and neutrophils. Mannose-binding lectin binds carbohydrates with terminal mannose and fucose, which are typically found on the microbial cell surface, which results in activation of the alternate complement pathway and leads to accumulation of C3b on the microbial surface.

Innate immunity depends highly on recognition of conserved pathogen-associated molecular patterns of micro-organisms (eg, lipopolysaccharide, lipoteichoic acids, mannans, peptidoglycans, glucans, or bacterial DNA), which are often essential for the survival of microbes but are not present on mammalian cells. The ability of the human immune system to detect pathogen-associated molecular patterns limits the capacity of microbes to evade immune surveillance and allows differentiation of self from non-self antigens.

The Toll-like receptors (TLRs) are a family of membrane proteins that binds pathogen-associated molecular patterns and are a subset of pattern recognition receptors. Ten mammalian TLRs have been identified [9]. They recognize an array of bacterial, fungal, and viral products, including gram-negative bacterial lipopolysaccharides, gram-positive bacterial peptidoglycans, bacterial lipoproteins, lipoteichoic acid, zymosan, flagellin, heat shock protein 60, unmethylated CpG motifs, and double-stranded viral RNA. Although a single TLR is responsible for stimulating inflammatory responses to a particular microbial ligand, the repertoire of specificities of the TLR system is apparently extended by the ability of TLRs to heterodimerize with one another, which minimizes the chance of immune evasion by microbial products.

After the initial identification and description of the mammalian TLR family, extensive studies have been performed to evaluate the susceptibility to infections by human microbial pathogens using mice with engineered deletions of each TLR molecule. In some bacterial infection models, mice with defective TLR signaling capacity succumb rapidly to *Staphylococcus aureus*, *Listeria monocytogenes*, *Mycobacterium tuberculosis*, and *Salmonella* infections [10–13]. Several human studies have confirmed the important role that TLRs play in a protective immune response by comparing the phenotypes of various polymorphisms of TLRs. Certain polymorphisms of TLRs render patients highly susceptible to pyogenic infections with *S aureus* [14], pneumonia caused by *Legionella*

pneumophila [15], or *M tuberculosis* [16]. Others have identified polymorphisms of TLR 4 to be associated with susceptibility to gram-negative infections [17] and gram-negative septic shock [18].

The innate immune system also plays a critical role in activating and coordinating the adaptive immune response by up-regulating costimulatory molecules and secreting cytokines, which influence lymphocytic function. Acquired immunity involves the activation and proliferation of antigen-specific B and T cells. Antigen-presenting cells (ie, macrophages and dendritic cells) from the innate arm of host defense process microbial antigens and present antigen proteins in association with major histocompatibility antigens class I and class II molecules to circulatory lymphocytes. Once an antigen-specific B cell recognizes the appropriate ligand, the cell transforms into a plasma cell and secretes antigen-specific antibodies, which serve numerous functions, including direct binding to antigen and opsonization. T cells augment B-cell development and can eradicate intracellular pathogens directly by cytotoxic activity against virally infected cells. The adaptive immune system has a memory component that is lacking in the innate immune system. Together, the innate and the adaptive immune systems enable the host to respond to various antigens encountered and preserve effector function for rechallenge against the same antigens at a future time.

Innate immunity in the lung

Nonspecific clearance mechanisms and components of innate immune surveillance are constantly active in the lung, eradicating pathogens and preventing infection. Innate immune defenses include epithelial cells, antimicrobial molecules generated in the airways, and the phagocytic defenses provided by the resident alveolar macrophages. Mechanical host defenses represent the first-line barrier to the invading substances. Particles larger than 5 μm are trapped in the upper airways and cleared by ciliary movement. Particles smaller than 5 μm potentially can be cleared by antibacterial molecules, including lysozymes, defensins, immunoglobulins, complement, and collectins. Lysozyme is lytic to many bacterial membranes, lactoferrin excludes iron from bacterial metabolism, and the defensins are antimicrobial peptides released from respiratory epithelial cells and leukocytes.

Recent studies have defined a critical role for airway epithelial cells in innate immune response

in the lungs [19,20]. The epithelium lining the airway prevents the growth and colonization of inhaled microbes by several different mechanisms. A direct mechanical effect involves the ciliated cells moving trapped particulates upward and out of the lungs. The secretions produced in the airway contain lysozymes, lactoferrin, and antimicrobial defensins, which inhibit bacterial growth. Binding of pattern recognition receptors to pathogen-associated molecular patterns also stimulates epithelial cells to produce antimicrobial defensins and secrete chemokines, which serve to recruit neutrophils to the location of insult and provide further immune protection to the lung. Besides the mechanical factors and chemokines, epithelial-derived cytokines contribute to the host defense of the lung. Epithelial cells produce proinflammatory cytokines, including IL-1, -5, -6, and -8, RANTES, granulocyte-macrophage colony-stimulating factor, and transforming growth factor- β . One mechanism for production of epithelial cytokines is through lipopolysaccharide binding to TLR-9, which leads to nuclear factor (NF)- κ B activation and a dose-dependent up-regulation of cytokines, specifically IL-6 and -8, and human β -defensin 2 in the airways [21,22].

Skerrett and coworkers [23] constructed a mouse model to express a dominant negative I κ B construct in distal airway epithelial cells, preventing NF- κ B activation, which led to impaired neutrophilic recruitment to the lung after lipopolysaccharide challenge and diminished levels of tissue necrosis factor- α , IL-1 β , and macrophage inflammatory protein-2. This experiment confirmed the pathway of lipopolysaccharide recognition by distal airway epithelial cells and the importance of airway epithelial cells in the innate inflammatory response.

Alveolar macrophages are the first line of phagocytic defense against the infectious pathogens that escape mechanical and epithelial defenses [24]. These cells comprise up to 95% of the cellular constituents in bronchoalveolar fluid. Macrophages possess the ability to avidly phagocytose and are important for daily clearance of small microbial challenges and maintaining sterility of the lower airway. Some bacteria, such as *Mycobacterium* spp, *Nocardia* spp, and *Legionella* spp, can evade the standard microbicidal activity of the macrophagers and replicate intracellularly. In such a scenario or when pathogen load is too large, macrophages produce proinflammatory cytokines and initiate a localized inflammatory response by recruiting neutrophils from the lung

capillary networks into the alveolar space. Neutrophils then eradicate the offending pathogens. In some instances, however, such as mycobacterial disease, the immune response may contain the infection but not lead to a sterilizing response. Alveolar macrophages in concert with other elements of innate defenses can clear foreign particles and bacterial pathogens from airspace surfaces; however, augmented innate and specific adaptive immune responses may come into play to clear virulent encapsulated bacteria, viruses, or intracellular pathogens that are capable of surviving within alveolar macrophages and ultimately lead to a pool of cells capable of memory function.

Adaptive immunity of the lung

The adaptive immune response is essential for pulmonary host defense and builds on the innate response. After exposure to a novel pathogen, the immune system within the lung generates humoral and cellular components. The primary cell for generating humoral immunity is the B cell; after antigen exposure, local antibody responses have been described. Using a mouse model with intratracheally administered sheep red blood cells, Kaltreider and Curtis' group demonstrated that particulate antigens are taken up in the alveolar space by macrophages or other antigen presenting cells. These cells then migrate via lymphatics to regional lymph nodes, where the primary immune response occurs. Once antigen-specific B cells are formed, they traffic back to the lung, where they terminally differentiate and expand into either antibody-secreting plasma cells or memory B cells [25–27]. If the pathogen is encountered again, the lung has the ability to respond quickly through recruitment of resident antigen-specific memory B cells, a process known as the amnestic response. The authors have shown that after oral mucosal and intranasal vaccine challenge, circulating antibody-secreting cells can be detected 1 week after vaccination. These cells transiently traffic between systemic and mucosal circulation. Adaptive responses seen systemically are linked to mucosal immunity but also differ in the manner in which antigen is handled [28]. In the upper respiratory tract, IgA predominates and IgG is present in lesser amounts. IgA serves as an immunologic barrier between organisms and mucosal surfaces and provides immune protection against mucosally presented antigens. Once pathogens are bound to IgA, they may be taken up by airway macrophages through the phagocytic

process [29]. In the lower respiratory tract, immunoglobulins comprise the second largest class of proteins obtained from bronchoalveolar lavage (BAL) fluid after albumin [30], and IgG is of primary importance for its opsonizing and complement-activating properties [31]. Four IgG subclasses exist in BAL fluid in approximately the same proportions as found in serum. IgG1 represents approximately 60% to 70%, IgG2 represents 20% to 25%, and IgG3 and IgG4 represent less than 5% of the total IgG present in BAL fluid [31]. Protein antigens provoke IgG1 antibodies, whereas polysaccharide antigens predominantly give rise to the IgG2 subclass [32,33]. Smaller amounts of IgA and IgE are also found in the BAL fluid of normal persons [30].

Cell-mediated adaptive immunity in the lung is essential for clearing viruses, mycobacteria, and fungi. It is modulated by the humoral response and requires a coordinated action among T cells, natural killer cells, and dendritic cells [34]. Immature myeloid dendritic cells carry antigen from the pulmonary epithelial to regional lymph nodes and present them to naive T cells expressing the $\alpha\beta$ T-cell antigen receptor. Precursors of $\alpha\beta$ T cells are recruited from the bone marrow to the thymus, where they migrate from the cortex to the medulla and undergo positive and then negative selection, which ensures that their T-cell antigen receptor recognizes self peptide major histocompatibility complex but not with such strong affinity as to be autoreactive. During thymic maturation, T cells develop expression of CD8 or CD4, which is essential for antigen recognition in the context of class I or class II major histocompatibility. Most T cells in the lung are mature memory T cells [35] and mirror the predominance of memory B cells in the lung [25–27], which suggests that the lung is immediately available to respond to infections humorally and cellularly in an antigen-specific manner.

CD4 T cells can further be divided into T helper 1 (Th1) and T helper 2 (Th2) based on cytokine profiles involved. The differentiation of naive CD4 T cells into Th1 and Th2 populations is controlled by cytokines produced by antigen presenting cells and by the T cells themselves. The differentiation of Th1 effectors is stimulated by virus, intracellular bacteria, such as *Listeria* and mycobacteria, and by some parasites, such as *Leishmania*. Th1 responses are characterized by secretion of interferon- γ , IL-2, and tumor necrosis factor- α and they are especially crucial in the lungs because alveolar macrophages require exogenous interferons to activate STAT1-

dependent killing of phagocytosed microbes [36]. Th2 differentiation occurs in response to helminthes and allergens. It is characterized by the production of IL-4, -5, -9, -10, and -13. These cytokines favor antibody production with class switching to IgE and IgG4. Exaggerated Th2 responses are thought to contribute to atopic diseases in the lung, such as asthma. IL-4 and -13 are thought to be IgE switch cytokines that may contribute to allergen-induced development of asthma. Data also have suggested that Th2 profile may favor fibrosis [37]. The protective role of T-cell immunity is essential in the lung regardless of the cytokine profile being exhibited, however. The tight regulation between Th1 and Th2 allows for a nonconflicting response. For example, if an intracellular pathogen such as *Mycobacterium* induces secretion of IL-12 and interferon- γ for protective purposes, these same cytokines block Th2 induction, which ensures that a more appropriate antimicrobial response is generated to eradicate the offending microbe.

A third distinctive phenotype of T-cell response has been identified: regulatory T (T_{reg}) cells. They are a CD25+ CD4+ T-cell subset that expresses the Foxp3 transcription factor [38]. T_{reg} cells principally develop from thymocytes but also can be produced peripherally during chronic antigenic stimulation. T_{reg} cells can suppress CD4+ and CD8+ T-cell responses by an undefined contact-dependent mechanism [39]. T_{reg} -mediated suppression leads to immunologic self-tolerance and negative control of immune responses. Several explanations are possible for the mechanisms of T_{reg} -mediated suppression in vivo. First, expression of the high-affinity trimeric IL-2 receptor by T_{reg} cells might result in growth-factor competition and consumption of IL-2 [40,41]. Other than passive IL-2 deprivation, two major immunosuppressive cytokines (IL-10 and transforming growth factor- β) have been implicated as active effector mechanisms of T_{reg} cell-mediated suppression in vivo [42–44]. The primary purpose is to induce tolerance to an antigen and down-regulate an active response once a pathogen has been eradicated. This action ensures that no overactive immune response leads to increased cytokine activation beyond what is necessary, potentially preventing autoimmunity by controlling self-reacting T cells. One therapeutic approach using T_{reg} cells could include modulating the intensity of antimicrobial immune responses in acute and chronic infections to develop effective vaccines against microbes and prevent or treat allergic diseases. It is believed that one mechanism of down-regulating the

allergic response with allergen immunotherapy involves invoking T_{reg} function.

Lung immunity and aging

Aging brings about changes in the structure and function of the lung, but immune responses also systemically wane and can impact lung host defense. Most data in this area center around adaptive responses because they have been studied more extensively than the innate response in the aged. TLR expression and cytokine secretion of macrophages from splenic and activated peritoneal cavities decline in aged mice [45]. It is also observed in mice that the phagocytic ability of macrophages from aged animals declines in parallel with decreased levels of macrophage-derived chemokines macrophage inflammatory protein (MIP)-1 α , MIP-1 β , and MIP-2 and eotaxin [46]. In humans, the effect of aging on monocyte and macrophage function remains controversial and in many studies is unaffected. Monocyte/macrophage and lymphocyte recruitment to infected tissue was delayed in older individuals based on a study of cutaneous punch biopsies [47]. Monocytes from older patients are reported to display decreased cytotoxicity against tumor cells *ex vivo* after lipopolysaccharide activation, which is thought to be caused by decreased production of reactive oxygen intermediates [48]. Macrophage dysfunction with aging also may depress the feedback loop between macrophages and natural killer cells via factors such as IL-12. Superoxide production in neutrophils from aged individuals also decreases, which further compromises phagocytic function [49].

Recently, Van Duin and colleagues [50] demonstrated in humans that TLR1 surface expression in peripheral blood monocytes was reduced, whereas TLR2 was not affected. They also reported defective TLR-mediated tissue necrosis factor- α and IL-6 production in older subjects. Such observations could provide an explanation for increased infections in older patients and decreased vaccine response. A more detailed understanding of the impact of age on innate immunity is needed to overcome age-related defects and reduce disease morbidity in the aged population.

It is clear that the thymus involutes with age and is replaced by fatty tissue by 60 years of age, whereas the absolute numbers of CD3+, CD4+, and CD8+ cells decrease with age. The proportion of naïve T cells goes down and memory T cells increase. Although the number of memory cells increases, the cellular responses by these cells wane

[51]. Mouse data in aging animals have shown a diminished lymphocyte repertoire [52], reduced proliferative responses to mitogens and antigens [53,54], and a decline in Fas-mediated T-cell apoptosis [55]. In humans, increased CD45RO (memory marker) on T lymphocytes [56], shifting from a Th1 to Th2 cytokine profile [57], and declines in peripheral lymphocytes and soluble IL-2 receptors also have been reported [58]. These findings may explain why older adults often fail to elicit adequate immune responses to infection or immunization. In regard to B-cell function, antibody production is less efficient with advancing age and the antibodies produced tend to have reduced affinity for specific antigens as a result of age-related decline in somatic hypermutation because of defects in T and B cells [59].

The CD4/CD8 T-lymphocyte ratio in human peripheral blood tends to increase with advancing age [60,61], and similar changes have been reported in the lung. Myer and colleagues [62] investigated the BAL and peripheral blood subsets in clinically normal nonsmoking volunteers of two different age groups (19–36 and 64–83 years). The total cells per milliliter in BAL fluid were significantly increased in the older age group. The mean percentage of lymphocytes in BAL fluid was also increased in this group compared with the younger cohort. The ratio of CD4+ to CD8+ T lymphocytes in BAL fluid was significantly increased (with an absolute increase in CD4+ cells) in the older group and it was considerably higher than the peripheral blood CD4/CD8 ratio. Activated CD4+/human leukocyte antigen-DR+ lymphocytes were also increased. The authors speculated that the relative increase in CD4+ lymphocytes for older healthy subjects probably represented an accumulation of memory cells and primed T cells caused by cumulative antigenic stimulation at mucosal surfaces. As a result, activated lymphocyte subsets may play a role in age-related low-grade inflammation in the aging lung and contribute to alterations in lung matrix and function that are associated with the aging process. Although lymphocytes and lymphocyte subsets retrieved from the lung by BAL have been studied in disease and, to some degree, in normal individuals, little information exists as it relates to aging [63–65].

The model of low-grade chronic inflammation in the lung correlating with the immunologic changes seen in the aged individuals was furthered when Myer and colleagues [66] studied the BAL profile of normal individuals in discordant age

groups (20–36, 45–55, and 65–78 years). The authors measured the level of immunoglobulin (IgG, IgA, IgM), albumin, IL-6 and -10, cell surface antigen expression, and superoxide anion production in BAL fluid. A significant increase in total cell concentration, neutrophils, and BAL immunoglobulin content was observed in the oldest age group. They also demonstrated that mean lymphocyte subset (CD4+/CD8+) ratios were significantly increased in blood and, to a greater degree, in BAL for the oldest versus youngest age groups. Similarly, BAL-derived cells displayed increased phorbol myristate acetate-stimulated release of superoxide anion for the oldest versus youngest subject group, and mean BAL IL-6 concentrations were significantly elevated in aged individuals compared with younger individuals. These observations suggested that even in asymptomatic and clinically normal aged volunteers, altered inflammatory cell profiles reflect the presence of low-grade inflammation in the lower respiratory tracts based on significantly increased numbers of phagocytic cells, immunoglobulins, IL-6 concentration, and superoxide anion release.

Franceschi and coworkers [67,68] put forward a similar hypothesis. They studied centenarians as a model to address the immunologic and genetic basis of aging and suggested that immunosenescence was a remodeling of the immune system in which sustained, lifelong exposure to antigenic stresses leads to a gradual decline of naive T cells, an accumulation of memory T cells and effector CD8+/CD28– T cells, and decline in T-cell repertoire. In contrast, many aspects of innate immunity, such as phagocytosis, natural killer cell cytotoxicity, chemotaxis, and complement activities, showed less decline. Innate immunity was believed to become progressively more important to aged individuals as a means to fill the “immunologic gap” that appears as a result of declining adaptive immunity. The consequence of these changes was interpreted as a state of chronic low-grade inflammation driven by IL-6 production from the overrepresented effector cells. Such a state was termed “inflammaging.” Similar processes may be the common and most important driving forces of age-related pathologies, such as neurodegeneration, atherosclerosis, and diabetes [68].

Longevity correlates with fairly well-preserved immune responses in older patients [69]. Conversely, immune parameters were measured in a longitudinal study of a very old population of Swedish people, and decreased survival was associated with low numbers of CD4+ T cells

and CD19+ B cells, impaired T-cell proliferative response to mitogenic stimulation, and increased numbers of CD8+ cytotoxic-suppressor cells [70].

Likely there is no simple explanation for the increased susceptibility of older individuals to lung infection, but age-associated changes are thought to increase the risk to older patients for pulmonary infections. Other factors that place older adults at higher risk for respiratory infections include systemic diseases, impaired oral [71] and mucociliary clearance [72], predisposition to aspiration [73], malnutrition [74], and residence in long-term care facilities [75]. The pathogens that are frequently involved include atypical pathogens, such as *Legionella* spp, *Chlamydiae pneumoniae*, and influenza A and B, parainfluenza virus, respiratory syncytial virus, *Bordetella pertussis*, *Haemophilus influenzae*, and *M tuberculosis*.

Allergy of the aging lung

The incidence of asthma—primarily allergic asthma—is highest among young children: approximately 3000 in 100,000 individuals in the first year of life and 900 in 100,000 in years 1 to 4. The incidence rate remains at approximately 100 in 100,000 after the age of 20 years [76,77]. Epidemiologic studies have focused largely on children and young adults. Much less information has been available about the epidemiology of allergic asthma in older individuals. Studies have shown that asthma is common in older adults and may be associated with severe symptoms that require unscheduled physician visits and hospitalizations. Chronic airway obstruction seen in this population rarely goes into complete remission [76,78].

Factors responsible for development of asthma in older patients have not been defined fully. Usually there is no familial correlation for these groups of patients. Occupational exposures are important during the working years. Otherwise, common environmental allergens are thought to be less important with increasing age, because individuals at risk of becoming sensitized probably will have done so by the time they reach the later years. Asthma is associated with elevated serum IgE levels from childhood into old age, but skin test or specific IgE antibody test responses are often negative in adult-onset asthma [79–84]. In a large number of patients, their first asthmatic symptoms are frequently described as having been preceded by a concomitant upper respiratory viral infection. This factor suggests that an infectious trigger may play a role in the onset of asthma in older patients

[76]. The role of air pollution in the incidence of adult asthma is still controversial [85,86].

Lung function depends on precision and accuracy of the equipment, and longitudinal data may have some inherent measurement bias. Lung volumes being influenced by body size have shown some consistent patterns in normal cohorts. All lung volumes increase to a point of maximal development in childhood [87]. The total lung capacity after adjusting for height does not seem to change beyond this point [88]. Interestingly, functional residual capacity and residual volume seem to increase in cross-sectional studies [89–91], and FEV₁ begins to decline in adulthood. The age at which FEV₁ declines has changed as successive birth cohorts are being studied. Estimates of age of decline in cross-sectional studies suggest the early 20s [92,93], but longitudinal data report that the decline does not begin until age 36 [94,95]. Gottlieb and colleagues [96] conducted a longitudinal study in approximately 1000 middle-aged and older men with no history of asthma participating in the Normative Aging Study to investigate the relationship between allergy and decline in lung function. They examined the immediate cutaneous hypersensitivity to common aeroallergens, chronic respiratory symptoms, peripheral eosinophil counts, methacholine responsiveness, and subsequent rate of decline of lung function. The results suggested that cutaneous hypersensitivity to common aeroallergens is a significant independent predictor of lung function decline in this population. The rate of decline of FEV₁ in the nonallergic nonsmoking group was 30.4 mL/year, whereas in the allergic nonsmoking group it was 38.9 mL/year [96]. O'Connor and colleagues [97] did not find a relationship between atopy and level of FEV₁ in a similar Normative Aging Study cohort, however. The latter group defined atopy as skin test reactivity more than 5 mm, whereas the former study used the parameter of more than 2 mm. Other data have examined the relationship between atopy and lung function and shown mixed results. The discordance in the literature may be explained by methodologic differences to include the number of allergens used for testing, the type of allergens, and the scale on which atopy is measured.

Summary

Recent research on bronchoalveolar fluid has shed some light on the immune cell profile and acellular components of the aging lung, but the

exact impact of these changes on host defense against respiratory infections is largely unknown. A better understanding of the age-associated changes in pulmonary host defense mechanisms is imperative before we can focus on manipulating age-related immune defects to reduce the susceptibility of older patients to respiratory tract disease. Only then can we possibly reduce morbidity and mortality and the considerable health care burden posed by the increased incidence of pneumonia and other inflammatory diseases of the lung in this at-risk population.

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