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The role of immunity in susceptibility to respiratory infection in the aging lung

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Abstract

Respiratory tract infections, particularly pneumonia, are a leading cause of death in persons 65 years or older in both developed and developing countries. Because many attributes of immunity wane with advancing age, the elderly may be more susceptible to respiratory infections, even if they appear to be in good health. A decline in the ability of lymphoid tissues to mount an antigen-specific response (adaptive immunity) to specific microorganisms such as influenza virus or *Streptococcus pneumoniae* is thought to be an important factor in increasing susceptibility to respiratory tract infection with advancing age. However, abnormalities in innate immunity may also contribute to increased susceptibility to respiratory infections and have been poorly characterized in the elderly. Although changes in immune parameters such as T cell subsets and immunoglobulin concentrations have been observed in respiratory secretions from older healthy individuals compared to younger subjects, the significance of these changes for protective immunity in the lung is unknown. The incidence of pneumonia may be lessened by measures such as optimizing treatment of comorbid conditions, optimizing nutrition, and addressing swallowing disorders. The use of vaccines directed against the influenza virus and *S. pneumoniae* appears to have made an impact on the degree of morbidity and mortality, and perhaps, the incidence, of community-acquired pneumonia. However, better stimulation of specific immune responses with improved vaccines and more widespread use of these vaccines for protection of elderly individuals are needed. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Aging; immune system; Disease; pneumonia; Mammals; humans; Susceptibility; respiratory tract infections

1. Introduction

Individuals who are advanced in age are increasingly susceptible to airway hyperreactivity (Dow et al., 1992), chronic obstructive pulmonary disease (Hardy and Connolly, 1996), lung neoplasms (Hendrick and Hendrick, 1996), idiopathic pulmonary fibrosis (Coultas et al., 1994), and pneumonia (Marston et al., 1997). Elderly individuals may be more prone to these respiratory problems due to progressively impaired immune surveillance, depressed ability to mount an appropriate immune response, or inappropriate (dysregulated) immune responses. Respiratory tract

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infections, particularly pneumonia, rank high as a cause of death in the elderly, and mortality rates for community-acquired pneumonia are considerably increased in the elderly (Marston et al., 1997). Although the presence of lung disease or other medical conditions increases the risk of pneumonia in elderly populations, immunosenescence may also play an important role in the increased risk of respiratory tract infections. Additionally, age-associated decline in lung function (Chan and Welsh, 1998) may diminish pulmonary reserve and increase the impact and severity of pneumonia in aged individuals.

Although the waning abilities of the immune system in the elderly are likely linked to the increased risk of respiratory tract infection, relatively little is known about how compartmentalized innate or antigen-specific (adaptive) immune responses change in the aged human lung or how much of a role such age-associated changes in immune responses play in increasing susceptibility to respiratory tract infections. Many assumptions concerning changes in lung immunity associated with advancing age are made on the basis of animal studies and on studies of peripheral blood, but little research on immune responses within the aging human lung has been published to date.

2. Alterations in immune function with advancing age

Distinct, antigen-specific receptors develop on lymphocytes during intrauterine development, giving rise to specific or adaptive immunity (Delves and Roitt, 2000a,b). Adaptive immunity is mediated by T and B lymphocytes derived from pluripotent stem cells in fetal liver and bone marrow and is characterized by the generation of antigen-specific immunoglobulins by B cells and antigen-specific surface receptors by T cells. It is estimated that $\approx 10^{14}$ specific immunoglobulin and 10^{18} T cell receptors are generated via somatic gene rearrangement (Medzhitov and Janeway, 2000), but relatively small numbers of memory T cells are retained for any unique antigen. Although T cells must passage through the thymus to complete their development, adaptive responses are generated in secondary lymphoid tissues, which include the spleen, lymph nodes, and mucosa-associated lymphoid tissue. These mucosa-associated lymphoid aggregates are present throughout the lung and defend the mucosal interface with the external environment.

The innate immune system (Table 1), which does not rely on immunologic memory and is constantly active, is characterized by immediate responses which involve pathogen-specific, pattern-recognition receptors (e.g. mannan-binding lectins which bind carbohydrate moieties on gram-positive and gram-negative bacteria, fungi, and some parasites and viruses), signaling receptors (e.g. toll-like receptors which induce expression of cytokines and co-stimulatory molecules), phagocytes, the alternative complement pathway, and antimicrobial peptides (Medzhitov and Janeway, 2000). These highly conserved, pathogen-associated molecular structures, which are bound by innate immune system receptors are

Table 1
Elements of innate immunity

Antigen-presenting cells
Dendritic cells
B cells
Macrophages
Phagocytes
Macrophages
Neutrophils
Inflammatory mediator-secreting cells
Mast cells and basophils
Polymorphonuclear leukocytes
Monocyte/macrophages
Lymphocytes
Non-mobile cells
Natural killer lymphocytes
Pattern recognition receptors
Signaling receptors
Costimulatory molecules
Antimicrobial molecules
Nitric oxide
Glycoproteins
Surfactant-associated proteins
Peptides
Defensins
Complement

shared by entire classes of microbes and are not found on host tissues. These structures include lipopolysaccharide, peptidoglycan, lipoteichoic acids, glucans, bacterial DNA, and double-stranded RNA in addition to mannans. In contrast to the extremely large number of receptors expressed by lymphocytes which mediate adaptive immunity, pattern recognition receptors of the innate immune system are thought to number only in the hundreds (Medzhitov and Janeway, 2000). Innate immunity, particularly, the production of antimicrobial peptides (Huttner and Bevins, 1999) and other antimicrobial molecules by epithelial cells, plays a critically important role in protection against infection in the lung with its extensive epithelial surfaces. Additionally, innate immune mechanisms can produce signals, which trigger adaptive immunity or act in an adjuvant fashion to augment-acquired immune responses via expression of co-stimulatory molecules. However, relatively little investigation has been published concerning the effect of advancing age on innate immune mechanisms and protection against pulmonary infection.

The impact of advancing age on immunity has been predominantly studied for adaptive immune responses. There is consensus that the immune system displays primary alterations (those that occur in healthy as well as diseased individuals) with advancing age (Kirkwood and Ritter, 1997Ginaldi et al., 1999a–d). However, secondary changes (those caused by underlying disease or environmental factors) also occur, there is considerable interindividual variability in both primary and secondary changes, and many aspects of immunity remain relatively robust in centenarians (Franceschi et al., 1995). Nonetheless, numerous alterations in immune function have been observed for apparently healthy, aged individuals (Table 2). The thymus gradually involutes beginning shortly after birth and is almost completely replaced by fat by age 60 for all mammalian species (Hirokawa et al., 1994). Therefore, the T lymphocyte repertoire, which comprises the acquired, antigen-specific portion of immunity, is created early on in life, and generation of immunoreactive T cells in response to a given stimulus in an aged individual may be limited. With aging, the naive T lymphocyte populations decline and memory cells, which tend to be hyporesponsive in aged individuals, predominate (Jackola et al., 1994; Brosche and Platt, 1995; Linton et al., 1996). Moreover, the number of retained memory cells for a given antigen specificity is very small, and the host depends upon rapid clonal expansion in response to antigen exposure to mount an effective immune response to invading microorganisms which cannot be contained by innate immune response mechanisms alone.

Table 2
Altered immunity in the elderly individual

Adaptive immunity
Cell-mediated immunity
Involution of the thymus
↓ Naive T cell output
Altered thymocyte differentiation
↑ Peripheral blood memory T cells
Hyporesponsive memory cells (↓ proliferative responses to mitogens or antigens)
↓ T cell receptor repertoire diversity
Shift of Th1 to Th2 cytokine profile
↑ HLA-DR+
Decreased Fas-mediated apoptosis
Humoral immunity
↓ Helper T cell function
↓ B cell number
↓ Germinal center formation
Altered B cell repertoire expression
↓ Antibody responses to specific antigens
Altered generation of primary B cells
Impaired generation of memory B cells
↓ Ability to generate high-affinity protective antibody
↑ IgG and IgA
↓ Organ-specific autoantibodies
↑ Non-organ-specific autoantibodies
Innate immunity
↓ NK activity with impending morbidity

Investigations of lymphocyte dysfunction with advancing age have shown declines in cell surface co-stimulatory molecule expression or function and altered intracellular signaling pathways (Engwerda et al., 1994; Rea et al., 1996; Garcia and Miller, 1997). Antigen presentation by dendritic cells and cytokine production profiles are altered and less efficient (Miller et al., 1994; Pahlavani and Richardson, 1996). Additionally, the diversity of the T and B cell receptor repertoire appears to

decline (Nicoletti et al., 1991; Liu et al., 1997), T helper activity diminishes (Li et al., 1995), and memory cells are less responsive to stimuli (Flurkey et al., 1992). Additional alterations include a decline in Fas-mediated apoptosis (Zhou et al., 1995), a reduction of proliferative responses to antigens or mitogens (Lerner et al., 1989; Linton et al., 1997; Miller et al., 1997), increased expression of DR on T cells (Jackola et al., 1994), and a shift of type 1 helper T cell (Th1) to type 2 (Th2) cytokine profiles (Cakman et al., 1996; Table 2). Not only is antibody production in response to specific antigen depressed, but antibodies tend to have diminished affinity for their specific antigen (Song et al., 1997). It is, therefore, not surprising that elderly individuals display an age-related decline in protective immunity against various natural infections as well as less vigorous responses to vaccinations as a consequence of immunosenescence, and that infectious diseases (particularly pneumonia, bronchitis, influenza, and gastroenteritis) are a major cause of debilitation and death in the elderly. Nonetheless, despite evidence of declining immune function with advancing age in an unselected population of elderly individuals, many centenarians have fairly good immune function, including a relative persistence of naive T cells and well-functioning NK cells (Franceschi et al., 1995; Solana and Mariani, 2000).

Many interesting observations comparing healthy, ill, and centenarian individuals have been reported which suggest that some immune changes are associated with impending illness or decreased longevity, while others can be found in healthy individuals. Although peripheral blood lymphocyte number does not appear to correlate with age in healthy elderly people, the peripheral lymphocyte counts decline in over 90% of individuals at ≈ 3 years prior to death as compared to values obtained 5–10 years earlier (Bender et al., 1986). Another longitudinal study found that a cluster of four parameters (poor T cell proliferative responses, high CD8+ lymphocytes, low CD4+ lymphocytes, and low CD19+ (B) cells) predicted shortened survival, although no single parameter by itself was predictive (Ferguson et al., 1995). Finally, some individuals who appear to age more rapidly than their peers and demonstrate more physiologic impairment have been shown to have dysregulation of proinflammatory cytokines such as interleukin-1, tumor necrosis factor, and interleukin-6 (Verdery, 1992).

3. Lung immunity and advancing age

The lung has unique qualities, some of which are shared with the skin and the gastrointestinal tract, organs which are also constantly exposed to the external environment. One of these qualities is that the lung possesses large numbers of dendritic cells for antigen-presentation as well as large numbers of mucosal lymphocytes and draining lymph nodes, which would greatly facilitate adaptive immune responses. However, the innate immune system is a key component of respiratory tract defenses and provides constant and immediate protection against microbial invasion. Epithelia of the conducting airways in the lung (like the upper airway, skin, gastrointestinal and genitourinary tracts) produce diverse antibacterial peptides such as defensins and tracheal antimicrobial peptide (Huttner and Bevins, 1999). These peptides are microbicidal and in all probability are very important in conferring continuous protection to the host, complementing the protection provided by proteins such as secretory IgA from conducting airways or surfactant-associated proteins A or D produced by type II alveolar epithelial cells. Antigen-specific immune responses are apt to be triggered only if innate defenses are overwhelmed.

Unfortunately, little is known about innate immunity in the aging human lung and whether changes occur which increase susceptibility to respiratory infection. However, some changes in immune parameters of respiratory secretions as reflected by bronchoalveolar lavage have been reported (Table 3). Increased numbers of CD4+ memory T cells which express increased amounts of HLA-DR appear to accumulate on mucosal surfaces in healthy, elderly individuals (Meyer et al., 1996; Meyer and Soergel, 1999), and increased concentrations of immunoglobulins have also been observed in bronchoalveolar lavage

fluids (Thompson et al., 1992; Meyer et al., 1996). The increased immunoglobulin concentrations may reflect a tendency for older, but healthy individuals to display a shift toward Th2 cytokine profiles in the lung with increased Th2 cytokines such as interleukin-4 or interleukin-10 expressed, possibly accompanied by decreased Th1 cytokine (e.g. interferon-γ or interleukin-2) expression. Although interleukin-10 was more frequently present in bronchoalveolar lavage from old normal individuals (Meyer et al., 1996), Th1 vs. Th2 cytokine profiles have not been investigated in respiratory secretions or lung tissue from old vs. young, clinically normal individuals. Interestingly, increased numbers of neutrophils have also been observed in bronchoalveolar lavage fluids from clinically normal, elderly individuals (Meyer, 1998), suggesting that some degree of low-grade mucosal inflammation may be present in the aging human lung in healthy individuals. These changes may reflect heightened host responses which are a consequence of continued exposure to inhaled environmental agents (perhaps, augmented by longer retention in the lung due to diminished mucociliary clearance with advancing age), loss of regulatory suppression of inflammatory responses, and/or adaptive responses to subclinical aspiration due to depressed protective reflexes associated with advancing age. Because the individuals in these studies were healthy with normal lung function, the increased numbers of CD4+ memory T cells and immunoglobulins may represent a selection bias and characterize adaptive, protective changes in these healthy individuals.

Table 3
Bronchoalveolar lavage in healthy aged individuals

↑ Lymphocytes
↑ CD4+/CD8+ T cell ratio
↑ HLA-DR+ T cells
↓ B cells
↑ IgM, IgA, and IgG
↑ Total protein
↑ Neutrophils
↑ Interleukins (IL-6, IL-8)
↑ α_1-antitrypsin

4. Respiratory infection in the elderly

Respiratory infection, usually caused by bacteria, is a leading cause of morbidity and mortality (up to 20% for community-acquired pneumonia and 40% for nursing home residents) in elderly populations (Marrie, 1990; Feldman, 1999; Torres et al., 1999). However, various secondary changes and comorbidities appear to play major roles in predisposing the elderly individual to bacterial pneumonia in addition to age-associated alterations in immune status. These secondary changes and comorbidities include malnutrition, the presence of lung or heart disease, predisposition to aspiration due to swallowing disorders or depressed levels of alertness, alcoholism, immunosuppressive therapies, institutionalization, recent hospitalization, enhanced oropharyngeal bacterial colonization, and prior antibiotic therapy. The age-associated decline in mucociliary clearance (Incalzi et al., 1989) and relative blunting of glottic protective reflexes (Aviv, 1997) in concert with declining protective immune capacity may be particularly important in elderly individuals who appear to be healthy and lack comorbidities but nonetheless develop community-acquired bacterial pneumonia.

The spectrum of causative pathogens varies with the setting in which pneumonia occurs, and pneumonia severity and comorbid situations need to be considered in making treatment decisions. The most common pathogen identified as a cause of pneumonia in adults remains *Streptococcus pneumoniae*, but gram-negative bacilli, *Hemophilus influenzae*, *Legionella*, and *Staphylococcus aureus* are frequently identified as pathogens in community-acquired pneumonia. Decision guidelines regarding hospitalization and treatment vary according to age, severity of infection, and the presence of comorbid conditions. Of particular concern is the evolution of antibiotic resistance in *S. pneumoniae* and other bacterial pathogens. Pneumococcal isolates have been identified which are resistant not only to penicillin but to azithromycin or newer fluoroquinolones such as levofloxacin, and newer antibiotic classes such as the ketolides, which are more active against drug-resistant *S. pneumoniae*, may also gradually lose their efficacy with widespread usage.

Viral illness may also play an important role in predisposing the elderly individual to subsequent serious lower respiratory tract bacterial infection, as observed for influenza (Treanor and Falsey, 1999). In addition to influenza A and B, respiratory syncytial virus can cause serious infection in the elderly immunocompromised patient, the frail elderly, or those with cardiopulmonary disease. Parainfluenza virus can also cause significant infection, and rhinovirus or coronavirus can cause serious infection in the frail elderly. In addition to viral infections, tuberculosis presents a significant, worldwide problem for aging populations, and *M. avium-intracellulare* infections in seemingly normal individuals are being increasingly encountered (O'Brien, 1989).

5. Prevention of respiratory infection in the elderly

Influenza virus infection in the elderly has significant morbidity and mortality, increases the risk of associated bacterial pneumonia, and can greatly diminish functional status in the post-convalescence period. Because community-acquired pneumonia in the elderly is associated with increased severity of infection, increased likelihood of hospitalization and pulmonary complications, and increased mortality, immunization against influenza A and B and *S. pneumoniae* (which remains the most common bacterial pathogen identified as a cause of community-acquired pneumonia) should play an important role in pneumonia prevention. Indeed, the currently used 23-valent polysaccharide vaccine against *S. pneumoniae* appears to protect against bacteremia and decrease the incidence of community-acquired pneumonia due to *S. pneumoniae* in at-risk populations (Sims et al., 1988). Similarly, currently used influenza vaccines have been shown to be protective (Corrigan and Clancy, 1999). However, vaccination rates for elderly Caucasians are under 70% for influenza and 50% for *S. pneumoniae*, and vaccination rates are considerably lower for African Americans and Hispanics.

Novel vaccines and the use of mucosal surfaces to achieve immunization may improve vaccine efficacy. Live, attenuated influenza virus can be used to infect and replicate in the respiratory tract (e.g. intranasal application) and thereby, deliver a larger dose of immunogen to bronchus-associated lymphoid tissue, and a natural infection can induce cross-protective IgA antibodies to hemagglutinin to protect against influenza variants (Corrigan and Clancy, 1999). On the other hand, oral administration of inactivated virus, which depends upon Peyer's patches to mount a response may provide effective immunity (Pang et al., 1992), and a combination of parenteral inactivated virus and intranasal live attenuated virus may prove efficacious. Although the currently used pneumococcal polysaccharide vaccine confers some protection against *S. pneumoniae* respiratory infection, newer approaches such as the use of conjugate vaccines to elicit higher levels of antibody via T cell-dependent mechanisms and induction of larger numbers of memory B cells may increase protection (Butler et al., 1999). Additionally, vaccines directed against non-capsular antigens common to all pneumococcal serotypes such as pneumolysin, surface adhesin A, or surface protein A would provide protection against all pneumococcal serotypes, and DNA technology, wherein a DNA plasmid which carries a protein-encoding gene is incorporated into host cells, may prove particularly effective (Butler et al., 1999).

Although vaccinations play an important role in preventing respiratory infections in the elderly, other factors such as optimal nutrition, antioxidants, and caloric restriction can play an immunomodulatory role and may improve immune responses and resistance to pulmonary infections in the elderly (Table 4). Protein-energy malnutrition, which can occur in apparently healthy elderly individuals, can adversely alter lymphocyte subsets and cytokine release and even impair monocyte and polymorphonuclear leukocyte function (Lesourd, 1997). Additionally, micronutrient deficiencies (e.g. zinc, selenium, vitamin E, folate, B-6) have been shown to diminish various immune indices (Lesourd, 1997). Furthermore, dietary supplementation with vitamins E and/or C has been shown to antagonize or even restore age-associated decline in immune function (de la

Table 4
Preventing respiratory infection in the elderly

Improved vaccines
Influenza A and B
S. pneumoniae
Mycobacterium tuberculosis
Other bacteria and viruses
Optimization of nutrition
Adequate treatment of chronic disease states
Prevention of aspiration
Avoidance of unnecessary antibiotic pressure
Treatment of influenza
Avoidance of stress
Antioxidant vitamin supplementation
Optimization of treatment of hyperlipidemia
Caloric restriction

Fuente et al., 1998; Enioutina et al., 2000; Moriguchi and Moruga, 2000), likely on the basis of antioxidant properties, and vitamin E has been shown to significantly reduce influenza virus titers in aged mice (Han and Meydani, 1999). Caloric restriction, a significant modulator of the aging process in laboratory animals, also appears to attenuate age-associated immunosenescence (Pahlavani and Richardson, 1996). Interestingly, altered lipid metabolism has been suggested to be an important factor in optimal immune reactivity in the elderly (Wick and Grubeck-Loebenstein, 1997). A high cholesterol to phospholipid ratio in lymphocyte cell membranes impairs T cell responses, and low-density lipoprotein (LDL) receptors on cells from aged individuals have decreased sensitivity to plasma LDL, which can lead to increased cholesterol to phospholipid ratios in cell membranes of lymphocytes of aged individuals. These authors speculate that diet and lipid-lowering drugs may improve T cell responses in the elderly by maintaining or improving membrane fluidity.

Other measures taken to prevent pneumonia include optimizing the social situation and medical treatment of the elderly. Treating comorbid conditions, avoiding medications likely to depress alertness, decreasing aspiration risks, and dealing adequately with malnutrition are important interventions that can often be successfully implemented. Additionally, effective and relatively safe therapies using neuraminidase inhibitors given early in the course of illness for influenza virus infections may attenuate morbidity and mortality as well as prevent subsequent bacterial pneumonia. Similarly, the administration of immunomodulatory agents such as interferon-γ may improve outcome in mycobacterial infections, particularly those caused by drug-resistant or atypical organisms.

6. Summary

The declining immune responses observed systemically may help explain, in part an increased susceptibility to pulmonary infection with advancing age. However, secondary factors, particularly cigarette smoking and structural lung damage, also play a very important role in respiratory infections in elderly individuals. Although a combination of primary immunosenescence and secondary factors are probably involved in the increased susceptibility to pneumonia in the elderly, little investigation has been done on compartmentalized immune responses in the aging lung itself. Research, which focuses on the integrity of mucosal immunity in the aging lung may identify changes which increase susceptibility to respiratory tract infection. Evidence seems to be accumulating that dietary factors including caloric restriction (but avoidance of protein-energy malnutrition), micronutrient supplementation, and antioxidant usage may improve immune function in aging individuals. Avoidance of high fat diets and treatment of hyperlipidemia may also play a role in maintaining optimal immune function in the elderly. Clearly, the use of more effective vaccine strategies is needed and is likely to have a major impact on morbidity and mortality of respiratory tract infections in the elderly.

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