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Susceptibility of the Aging Lung to Environmental Injury

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Abstract

With an ever increasing number of elderly individuals in the world, a better understanding of the issues associated with aging and the environment is needed. The respiratory system is one of the primary interfaces between the body and the external environment. An expanding number of studies suggest that the aging pulmonary system (>65 years) is at increased risk for adverse health effects from environmental insult, such as by air pollutants, infection, and climate change. However, the mechanism(s) for increased susceptibility in this subpopulation is not well understood. In this review, we provide a limited, but comprehensive overview of how the lung ages, examples of environmental exposures associated with injury to the aging lung and potential mechanisms underlining the increased vulnerability of the aging lung to injury from environmental factors.

Keywords

aging lung; susceptibility; environmental injury

I. INTRODUCTION

In populations exposed similarly to air pollutants, pulmonary inflammatory and function responses are more severe in certain groups of individuals than in others, particularly for

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pregnant women, infants, children, and the elderly (1). The rapid growth in the number of elderly individuals in developed countries has major implications for public health, including the need to better understand the risks posed to older adults by environmental factors, such as by air pollution, infection and climate change (2). The respiratory system is one of the primary interfaces between the body and the external environment and, thus must satisfy unique demands to handle and detoxify inhaled gases, particles and infectious agents (3). It is generally agreed lung function declines with age, and that oxidant stress related to smoking, chronic lung inflammation, or cardiopulmonary diseases may increase the rate of decline (4,5). Furthermore, the decline in antioxidant capacity with age strongly correlates with increased risk of mortality from a wide range of entities (6). A growing number of studies suggest the aging pulmonary system (>65 years) is at increased risk for adverse health effects from environmental insults, such as air pollutants, airborne pathogens and other aeroallergens (4, 7). However, the mechanisms underlying increased susceptibility in the aging population are not well understood. In this review, we provide a brief overview of the aging lung, examples of environmental injuries and potential mechanisms by which the aging lung is believed to be more susceptible to these environmental insults. The goal of this review is to highlight those areas of investigation important to the field of pulmonary geriatrics.

II. THE AGING LUNG

II.A. Changing lung function and anatomy

The lung matures by 20–25 years of age. Thereafter, aging is associated with a progressive decline in lung function (8,9). The alveolar dead space increases with age, affecting arterial oxygen (8). The pulmonary transfer factor for carbon monoxide (TLCO), which is dependent on lung volume (TLC) and alveolar ventilation, declines with age (10). Older adults have decreased sensation of dyspnea and diminished ventilatory response to hypoxia and hypercapnia (11,12) accompanied by a decrease in CO₂ threshold (13).

Even in the absence of disease, the respiratory system undergoes a variety of anatomical and physiological changes with age (Table 1) (14). Structural changes include deformities of the chest wall and thoracic spine that impair respiratory system compliance and increased work of breathing (15). Diminished respiratory effort in response to upper airway occlusion and impaired perception of bronchoconstriction can occur with increased age (16). Respiratory muscle strength decreases with age and can impair effective cough, which is important in airway clearance (17). Deposition, retention and clearance of particulates in the airways also change with age. Adult aging *per se* does not appear to alter the regional deposition fraction of aerosols (18), however, changes in inspiratory peak flow may impair deposition of drugs in the elderly (8). The lung parenchyma loses supporting structure, leading to dilation of air spaces or “senile emphysema” (19). An age-related decrease in elastic fibers with an increase in type III collagen deposition within alveolar walls is indicative of an impaired repair mechanism which could play a significant role in the pathogenesis of senile emphysema (20,21).

Age-related changes in airway receptors, critical in airway homeostasis, are not well understood. For instance, substance P receptor (neurokinin-1 receptor) decreases with age in

normal sheep (22), while β -adrenoreceptor density remains unchanged, however, receptor affinity is significantly reduced (23). Changes in muscuranic receptor subtypes and receptor coupling to G proteins have been noted with senescence (24). Cysteinyl-leukotriene (CysLT1) receptors undergo functional changes with age and are less likely to respond to drugs that have been found to be effective in younger individuals to treat the same disorders (25–27). These aging-related structural and functional changes in the normal lung may predispose the elderly population to ventilatory failure during high demand states such as conditions of heart failure or pneumonia with potentially poor outcomes.

II.B. Oxidative stress and lung antioxidant defenses

A commonly held theory of aging is based on the free-radical or oxidative-stress hypothesis: the accumulation of reactive oxygen species (ROS) in cells with increasing age results in various forms of reversible and irreversible oxidative modifications of proteins (carbonylation or nitro-modifications), lipids (hydroperoxide lipid derivatives) and DNA (adducts and breaks) that eventually lead to loss of molecular function. The human lung is continuously exposed to oxidative stress. Particulates, such as cigarette smoke (28,29), ambient airborne aerosols (30), coal dust or silica (31), all possess intrinsic free radical activity. Diesel emission particulates also contain compounds that catalyze the generation of ROS (32), as well as other exogenous toxins that activate lung resident cells to produce ROS (33).

The lung has a remarkable array of responses and defenses to oxidative stress (34). Low level stress may invoke adaptive responses, including growth arrest and preferential expression of genes responsible for repair of damage (35). Oxidative stress results in the transcription of over 40 genes (36). The lung normally defends itself against ROS damage through the use of specific ROS-reducing mechanisms that encompass enzymatic reactions involving superoxide dismutase (SOD), glutathione peroxidases and catalases or non-enzymatic components such as vitamin A, C, and E; urate; ferritin; ceruloplasmin; surfactant; and ubiquinone (37).

As the lung ages, changes in antioxidant defenses will also occur. These changes include decreased ascorbic acid (38, 39), reduction in glutathione levels (40, 41), and decreased activity of SOD and glutathione peroxidase (42) in lung tissues. NF-E2-related factor 2 (NRF2) is a transcription factor that protects cells and tissues from oxidative stress by activating protective antioxidant and detoxifying enzymes (43). NRF2 expression has been found to be decreased in the alveolar macrophages of older current smokers and patients with COPD, compared with younger subjects (44). Heme oxygenase-1 (HO-1) is the rate-limiting enzyme that catalyzes heme and is known to be readily inducible to confer cytoprotection against oxidative stress (45). A recent study in mice demonstrated age-related defects in HO-1 induction in whole lung as well as in alveolar macrophages in response to lipopolysaccharide (46).

II.C. Immune system changes with aging

Immune mechanisms underlie many chronic degenerative diseases of the lung. Both innate and acquired immunity are affected by aging (14). The impact of age on innate and adaptive

immune responses is summarized in Table 2. The elements of innate immunity include the functions of antigen presenting cells, phagocytic cells, inflammatory mediators released from leukocytes, natural killer lymphocytes, antimicrobial molecules (such as nitric oxide), surfactant-associated proteins, defensins, lactoferrin, and complement (14,47). A number of reports have suggested that the total number and phagocytic activity of neutrophils and macrophages in the peripheral blood remain unchanged with age (48–50), however, the ability of neutrophils to self-proliferate as well as kill infectious agents is reduced in elderly subjects. In contrast, neutrophils in elderly subjects have increased ROS production and impaired apoptosis which may result in the prolonged presence of neutrophils in either the systemic circulation or in local tissue sites where they might induce local damage. Macrophages have been demonstrated to have impaired antigen presentation and reduced MHC II molecule expression in aged mice (50). Although the number of natural killer cells in circulation increases with age, the ability to perform cytotoxic effector functions and to produce IFN- γ and IL-8 in response to IL-2 declines *in vitro* (51,52). Dendritic cells (DC), which play a key role in initiating an adaptive immune response, are reduced in number in the peripheral blood and lymphoid follicles in the elderly (53). In addition, chemotaxis and phagocytosis of DCs are impaired, and therefore, stimulation of naïve CD41 T cells to generate an effective adaptive immune response to an antigen may fail (54).

Age-related changes to the adaptive immune system include a decrease in the number of T cells in the peripheral blood of older adults with significantly reduced T cell receptor repertoire (55). With aging, an increase in CD81 CD28null Tregs cells inhibits antigen-specific CD41 T cell responses, leading to a decline in the adaptive immune response and immunosenescence (56). Hematopoietic stem cell (HSC) production is another important component of immune system maintenance that slows with aging in both animals and humans. Older individuals are more likely to suffer toxicity such as prolonged myelosuppression in response to traditional cytotoxic chemotherapy drugs, suggesting a reduced marrow regenerative capacity (57–59). Moreover, the volume of hematopoietic bone marrow tissue decreases with aging (60), resulting in reduced production of B cells, which in older adults have a reduced capacity to proliferate and impaired ability to be activated. The quantity and efficacy of antibodies produced in response to antigen exposure in older adults are also reduced (61).

Changes in the composition of bronchoalveolar lavage fluid have also been noted in association with aging (Table 3). Some of these parameters reflect innate as well as acquired immune responses. The reduction in the adaptive immune system is associated with an innate immune system stimulated and up-regulated by external environmental insults or internal antigenic stimuli from oxidative stress, creating a chronic proinflammatory state with aging. Inflammation is central to the pathogenesis of obstructive lung diseases, including asthma, chronic bronchitis, and emphysema (14).

II.D. Endocrine changes with aging

Hormonal changes are thought to play a role in the loss of lung tissue mass, impaired respiratory and peripheral muscle function and reduced exercise capacity in the elderly. Changes in the hypothalamic pituitary–adrenal axis occur with age and attenuated diurnal

variability may account for some hormonal changes (62). Growth hormone (GH), insulin like growth factor, (63), estrogen (64), glucocorticoids (65), testosterone (66) and vitamin D (67) have been demonstrated to change with aging. An age-related decline in GH parallels changes in body composition, such as a reduction in lean body mass, bone mineral density and increased visceral fat (63). The loss in muscle protein mass, function and muscle quality also accompanies advancing age (68).

Hormonal changes hormones are associated with a decline in lung function. A recent study suggests alveolar hypoventilation and attendant arterial hypercapnia in healthy postmenopausal women are due in part to a reduction in circulating sex steroid hormone concentrations (69). Longitudinal analysis of the relationship between basal plasma cortisol concentration and FEV₁ over an average of 4.7 years revealed a significant ($p = 0.008$) relationship between the plasma cortisol concentration and the rate of decline of FEV₁ after adjustment for age, height, smoking status, and initial FEV₁ (65). Moreover, the authors' multivariate model predicted that subjects with cortisol concentrations one standard deviation (23.3 ng/ml) below the mean would experience FEV₁ declines of 71.6ml/year greater than subjects with cortisol concentrations one standard deviation above the mean. The difference was comparable to an estimated 69.5ml/year difference between current smokers and never-smokers (65). These data indicate that physiological concentrations of cortisol may modulate the process responsible for the deterioration of ventilatory function with aging. A separate study of 631 male participants in the normative aging study (age range 44–85 years) showed that 2 hour urinary excretion of serotonin, but not 5-hydroxy indole acetic acid (5-HIAA), decreased with age (70). Animal studies suggest that the serotonin-dependent augmentation of respiratory motor output is reduced in old rats (71). Current active smokers secrete significantly more serotonin than never-smokers, while former smokers did not differ significantly from never-smokers (70).

II.E. Body mass

Body mass is positively associated with airway hyperresponsiveness (72) and with progressive reductions in FVC, FEV₁ and FEV₁/FVC ratio (73). Cross-sectional (74,75) and longitudinal (76) studies have shown a relationship between asthma and obesity, particularly in women (77). Static lung volumes significantly increase following weight loss in middle-aged and older, obese men. In contrast, aerobic exercise has no effect on pulmonary function but does increase maximal oxygen uptake (VO₂ max) (78). The contribution of body composition, physical activity and smoking to lung function in older people has been investigated (79); fat free mass and physical activity both exerted significant independent effects on FEV₁. These results, in contrast to the former study (78), indicate that heavy intense physical activity may be more important in contributing to forced expiratory function than previously recognized (14).

II.F. Cellular senescence

Programmed senescence is a driving force behind aging of all organs in the body, including the lung (14). It is not clear what causes cells to undergo senescence, but studies have shown that senescence can be induced by a variety of stimuli (Fig 1.) (80). Dysfunctional telomeres trigger a classical DNA damage response (DDR) (81). The DDR enables cells to sense

damaged DNA, particularly double-strand breaks (DSBs), and to respond by arresting cell-cycle progression and repairing the damage if possible (Fig 2). It has been suggested that only one or a few such short of dysfunctional telomeres are sufficient to trigger senescence (82,83). One study showed that both current and former smokers had shorter telomeres than did age-matched nonsmokers (84).

Non-telomeric DNA damage occurs anywhere in the genome and damage that creates double-strand breaks causes many cell types to undergo senescence (85,86). Excessive mitogenic signals including those produced by oncogenes, such as RAS and other members of the RAS signaling pathway (RAF, MEK, MOS and BR AF), as well as pro-proliferative nuclear proteins (for example, E2F-1), cause senescence when over-expressed or expressed as oncogenic versions (which also cause DNA damage) (87–90).

Mechanisms proposed by which senescent cells contribute to aging include up-regulation of genes that encode extracellular-matrix-degrading enzymes, inflammatory cytokines and growth factors, which can affect the behavior of neighboring cells or even distal cells within tissues (80). The products of these genes can disrupt the normal tissue structure and function in cell-culture models (91,92), stimulate growth and angiogenic activity of nearby premalignant cells both in culture and *in vivo* (93–96). Therefore, senescent cells, although unable to form tumors, may fuel the progression of nearby premalignant cells and facilitate the development of cancer in aging organ systems.

III. INCREASED SUSCEPTIBILITY OF THE AGING LUNG TO SPECIFIC ENVIRONMENTAL INJURIES

III.A. Ozone

Exposure to ozone has been documented to cause decrements in lung function in healthy subjects (97). Numerous studies in both humans and animals have shown the susceptibility to the effects of ozone varies with age (98). Age-related changes recorded in response to ozone exposure include changes in pulmonary eicosanoid metabolism in rabbits and rats (99), altered ventilatory responses to CO₂ in rats (100), altered hydroxylation of salicylate in lungs of Fischer 344 rats (101), and altered lung mitochondrial respiration, reactive oxygen species (ROS) production and lung pro/antioxidant status in rats (102). Overall, the cellular and biochemical effects of ozone exposure appear greater in senescent Fisher 344 rats (24 months old) compared to juvenile or adult rats (39,103). Moreover, in aged rats, the increase in cytosolic SOD and GPx activities during ozone exposure was not sufficient to prevent impairment of mitochondrial function or the accumulation in lung 8-oxodG (102). In humans, many studies and meta-analyses have found an association between acute ambient ozone exposure and increased risk of death (104). In addition, ambient ozone has been associated with increased respiratory-related emergency department visits and hospital admission in the elderly (105,106). These findings suggest that the elderly are particularly susceptible to the effects of ozone. Previous studies have found that functional responsiveness to ozone has been no greater, and usually lower, among older adults than in young adults, but these studies typically include only healthy nonsmokers (107,108). Recent studies suggest that ozone has an acute effect on lung function in the elderly. Ozone-induced

effects may also be modified by the presence of specific polymorphisms in antioxidant genes (109) or other pre-existing health conditions, such as obesity and airways hyper-responsiveness (AHR) (110). The long-term effects of ozone on the human lung are not well established but appear to enhance aging (111).

III.B. Cigarette smoke

Smoking is well accepted as an important cause of lung cancer with the highest incidence occurring late in life between 60 and 70 years of age, at which time the lung may have lost its full competency for defense and immunity. Life-time cigarette smokers also have a higher prevalence of other common diseases, such as atherosclerosis and COPD with significant systemic impact (112). It has been estimated that cigarette smoking reduces life span by an average of 7 years, and tobacco consumption accounts for a shortening of disease-free life by 14 years (113). The exact mechanisms by which smoking causes disease and death are generally not well understood, but evidence continues to mount that cigarette smoking exhausts cellular defense and repair functions, leading to an accumulation of damage (e.g., mutations and malfunctioning proteins) (113).

There is increasing evidence that cigarette smoking is associated with premature aging. It has been proposed that cigarette smoke accelerates the aging of lung or worsens aging-related events in the lung by induction of senescence in alveolar epithelial cells and impaired re-epithelialization (114). Smoking also causes defective resolution of inflammation and consequently induces accelerated progression of COPD (115). A recent study suggests that aging also increases susceptibility to cigarette smoke-induced inflammation in a mouse model through robust mRNA upregulation and nuclear translocation of NF-kappaB in bronchiolar epithelium (116). The reaction of components of cigarette smoke with plasma and extracellular matrix proteins resulting in the formation of covalent adducts, such as advanced glycation end products (AGE), also has been shown to play a role in the development of many of the pathological sequelae of aging and diabetes, such as cardiovascular diseases and cancer growth and metastasis (117,118).

Other smoking-related effects on the lung that enhance lung aging include accelerated maturation of the fetal lung, impairment of lung growth, shortening of the plateau phase of FEV1 and acceleration of age-related declines in FVC and FEV1 (119). These effects have also been shown for cigar and pipe smoking (120). Smoking also increases the risk of bacterial pneumonias by impairing host immune response, which in turn contributes to the incremental declines in FEV1 associated with COPD (121). Some animal models also provide insights into the pathogenesis of these clinical observations. Mutant mice with accelerated senescence are more susceptible to smoke-induced emphysema than wild-type control mice (122,123). Old aged rats showed seriously impaired ability to resist oxidative damage by cigarette smoke, whereas the activation of polyaromatic hydrocarbons to their carcinogenic forms remains intact, which may predispose these rats to the development of cancer (124).

III.C. Particulates

Particulate matter (PM) is an important air pollutant of concern due to its contribution to adverse health effects. Use of motor vehicles has resulted in a consequent rise in exhaust-generated PM emissions in urban areas worldwide (125). Airborne PM varies in size and composition (heavy metals, PAHs, etc). Aging is associated with accumulation of particles and metals in the mammalian lung (126–128), and exogenous carbonaceous particles appear to accumulate progressively with age, but accurate quantification has not been achieved (14). Numerous studies over the past decades have observed associations between inhaled PM (PM₁₀ and PM_{2.5}) and various health outcomes, including mortality, hospitalization for respiratory and cardiovascular diseases, aggravation of asthma attacks, and adverse lung function (125).

One of the most sensitive subpopulations to the adverse health effects of inhaled PM is the elderly, typically individuals over 65 years of age (129). To what extent this increased susceptibility to PM exposure results from aging *per se* is not clear. It is likely that many factors play a role, including aging associated systemic effects discussed earlier. Progressive accumulation of particles in the lung throughout life and the increased incidences of serious respiratory, cardiac, and circulatory diseases in the elderly may also contribute to the increased sensitivity of older individuals to the adverse effects of inhaled pollutants (129).

The effects of PM on age-associated changes have been studied in rats and mice. Mauderly et al (130) exposed normal rats and rats with elastase-induced emphysema for two years to whole diesel exhaust at a soot concentration of 3500 µg/m³ beginning at 18 weeks of age. The study showed that the presence of emphysema protected the rats from particle-associated effects (measured by functional and biochemical parameters) and that there was a reduction in retained lung dust in the emphysematous animals (130). In another study, young (4 months) and aged (20 months) male Fisher 344 rats were exposed to concentrated Boston ambient particulate matter at an average concentration of 100 µg/m³ for 3 days (131). Total cell numbers in bronchoalveolar lavage fluid (BALF) were greater in both control and particulate-exposed young rats than in older rats. Sunil VR et al (132) exposed young (2 months) and aged (18 months) mice to diesel exhaust (300 and 1000 µg/m³) for 3 hours for 1 day or for 3 days. They found altered patchy thickening of the alveolar septa, increased IL-8 and decreased MnSOD expression in aged mice. They also found a small, but significant decrease in total cell numbers in BALF in old mice compared with young animals (132).

Studies of the short-term effect of PM on human health mostly focus on mortality and hospital admissions. Some of the most interesting findings are from studies that observed changes in daily death counts associated with short-term changes in PM air pollution. Most of the results suggest that a 10 µg/m³ increase in PM₁₀ is associated with a 0.5% to 1.5% increase in daily mortality (133–136).

Evidence of long-term effects on lung health from exposure to relatively low levels of air pollution has increased substantially during the past decade (137–139). One study investigating the effect of PM on longitudinal change in lung function showed that a greater decline in the forced expiratory volume in 1 second (FEV₁) in adults was associated with

residence near major roads (140). Another study demonstrated that reduced exposure to concentrations of PM less than 2.5µm in aerodynamic diameter (PM_{2.5}) was associated with a reduction in mortality from all causes - from cardiovascular causes and lung cancer (141). Downs et al (142) conducted a prospective study from 1991–2002 to examine the association between age-related decline in lung function and decline in exposure to PM₁₀ in Switzerland. The authors found that decreasing exposure to airborne particulates appears to attenuate the decline in lung function related to exposure to PM₁₀ and the effects are greater in small airways (142). These findings suggest that an accelerated decline in lung function in the elderly with higher exposure to PM, as compared with lower exposure, may represent a step toward increased mortality risk.

III.D. Infectious agents

The elderly are more susceptible to a wide variety of respiratory infections, particularly to those caused by newly emerging and re-emerging pathogens, which are often of greater severity. Sub-optimal nutrition, deteriorating lung mechanics and declined immunity with age all appear to play a role (14), among which the age-related senescence in the immune system, including both changes in innate immunity and adaptive immunity, is likely to be the most important factor associated with the increased susceptibility to the various respiratory infections. Group housing also plays a role in the elderly, contributing to the spread of diseases associated with influenza A and *Legionella* (47). In the case of influenza infections, even though the hospitalization rates for children less than 5 years and adults over 70 years of age are almost identical, individuals older than 70 years have a 35-fold increase in mortality (143,144). Vaccination can reduce the rates of hospitalization; however, protection induced by immunizations is diminished in the elderly compared to the adults as demonstrated by lower antibody titers and higher rates of respiratory illness (145). In addition, cell-mediated immune responses to vaccinations are decreased in the elderly (146–149). The elderly have an increased morbidity and mortality due to influenza as a result of secondary bacterial and viral infections (150). *Streptococcus pneumoniae* is most frequently associated with community- acquired pneumonia (CAP) (151). In developed countries, despite aggressive vaccination policies, *S. pneumoniae* remains a major medical problem in the elderly population, especially among those aged 65 or more. Pneumococcal pneumonia in the elderly is characterized by rapid onset, severity, and high case-fatality rate (152), which may be due to a priming effect of chronic inflammation and Toll-like receptor dysfunction with age (153). The generation of antigen-specific CD4⁺ T cell mediated immunity is delayed or impaired in old people (154), and poor CD4⁺ T cell mediated immunity may contribute to the increased susceptibility of the elderly to develop tuberculosis (155). The proportion of tuberculosis in the elderly has risen in recent decades with approximately one fifth of all tuberculosis cases in the U.S. (156). This is frequently overlooked and is commonly diagnosed post mortem (157). The prevalence of *Mycoplasma pneumoniae* has been reported to be low in the elderly (158), however, recent reports suggest that *M. pneumoniae* also accounts for 4–10% of cases of pneumonia in the elderly population (159,160).

III.E. Climate change

Like other environmental stressors, climate change can have differential effects on different subpopulations, depending on a variety of susceptibility factors (161). The impact of climate change on health is likely to be significant, particularly for more vulnerable subpopulations, such as the elderly due to their susceptibility to respiratory and cardiovascular diseases with aging (162,163). Older people do not tolerate drastic climatic changes well because they are more sensitive to temperature extremes, particularly heat (164,165). Individuals 65 years of age and older comprised 72% of the heat-related deaths in the 1995 Chicago heat wave (166). Over a 5-year period, from 1999 to 2003, a total of 3,442 heat-related deaths were reported in the U.S. (an annual average of 688) (167). In August 2003, in excess of 2000 deaths of older adults in England and Wales and nearly 15,000 deaths of mainly elderly people in France were caused by temperatures rising to more than 40°C (168).

The elderly are more likely to have preexisting medical conditions, such as cardiovascular and respiratory illnesses, which may put them at greater risk of severe morbidity or mortality from climate-related events or conditions. A 2004 rapid needs assessment of older adults in Florida found that Hurricane Charley exacerbated preexisting, physician-diagnosed medical conditions in 24% to 32% of elderly households (167). Storms and floods are also threats to the elderly because they have diminished response to stressors and are often less ambulatory, and thus less able to evacuate quickly and are more prone to accidents (169,170).

Climate change also indirectly affects human health through its impact on air pollution. A positive association has been found between temperatures greater than 32°C (>90°F) and ground-level ozone production (171). Increasing evidence suggests that ozone and high temperature affect mortality in a synergistic fashion. Similarly, heat wave mortality is greatest on days with high PM10 (172). As a result, the aging population will be more vulnerable to these environmental injuries and less able to adapt to dramatic climate change.

III.F. Lung injury during early life

Data accumulated data obtained from human genomic studies and genetic manipulation in rodents indicate that early abnormal lung development may be a significant susceptibility factor in selected respiratory diseases that become clinically detectable in later life, such as COPD, cystic fibrosis and asthma (173). Disturbances during lung development may result in transient or irreversible long-term effects in both lung function and immune response (174). Exposure to environmental insults during fetal development and early postnatal life is associated with adverse birth outcomes, including low birth weight, very low birth weight, preterm birth, intrauterine growth restriction, congenital defects, and intrauterine and infant mortality. Environmental insults in early life may also decrease lung growth, increase rates of respiratory tract infections, childhood asthma, behavioral problems as well as neurocognitive deficits (174). Intrauterine growth retardation and low birth weight have been linked to alterations of respiratory function at all stages of postnatal life (175). Intrauterine growth retardation may lead to increased susceptibility to air pollution exposure and other environmental factors (176), and low birth weight is an independent risk factor for COPD that is associated with poor lung growth and lung function during childhood and

adulthood (177). Frequent respiratory infections during childhood have been shown to play an important role in the occurrence of chronic airway diseases in adult life (178). Acute lung injuries produced by common pathogenic bacteria, for example *Staphylococcus aureus*, are usually associated with complete recovery and subsequent normal lung function. Viral infections, however, may produce more long lasting effects; notable among these are respiratory syncytial virus (RSV), adenovirus, and chlamydia. Children who survive these infections are likely to have unhealthy lungs that might predispose them to COPD in later life (179).

IV. CONCLUSIONS

The respiratory system represents a critical interface with the external environment and must meet unique demands to handle and detoxify numerous inhaled gases, particles and infectious agents (180). The lung must be ready to constantly mount a controlled and defensive response that preserves the primary function of gas exchange, while protecting the respiratory system from xenobiotic insults and potential injury. The health effects associated with exposure to environmental agents may range from subtle biochemical and physiological changes, to the exacerbation of pre-existing respiratory and cardiovascular disease or the genesis of a completely new disease. The aging lung must continually contend with changes that affect its ability to maintain homeostasis. With a growing elderly population and a strong correlation for increased susceptibility to environmental injuries, it is imperative to extend future research to better determine the effects of age on the respiratory system. Understanding the mechanisms behind the adverse effects of environmental factors on the aging lung will greatly assist in designing preventative strategies to enhance the quality of life, while further decreasing mortality and morbidity in the elderly.

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Figure 1. The Senescent Phenotype Induced by Multiple Stimuli

Mitotically competent cells respond to various stressors by undergoing cellular senescence. These stressors include dysfunctional telomeres, non-telomeric DNA damage, excessive mitogenic signals including those produced by oncogenes (which also cause DNA damage), non-genotoxic stress such as perturbations to chromatin organization and, probably, stresses with an as-yet-unknown etiology. The senescence response causes striking changes in cellular phenotype. These changes include an essentially permanent arrest of cell proliferation, development of resistance to apoptosis (in some cells), and an altered pattern of gene expression. The expression or appearance of senescence-associated markers such as senescence-associated β -galactosidase, p16, senescence-associated DNA-damage foci (SDFs) and senescence-associated heterochromatin foci (SAHFs) are neither universal nor exclusive to the senescent state and therefore are not shown. (Reprinted with permission from Campisi J et al, Cellular senescence: when bad things happen to good cells. *Nat Rev Mol Cell Biol.* 2007 Sep;8(9):729–40.)

Figure 2. Sources and Consequences of DNA Damage

DNA damage can be induced by exogenous physical agents, by endogenous chemical genotoxic agents that are the products of metabolism, such as reactive oxygen species (ROS), or by spontaneous chemical reactions, such as hydrolysis. Examples of DNA damage are ultraviolet (UV)-induced photoproducts (left), interstrand and intrastrand crosslinks, bulky chemical adducts (purple sphere), abasic sites, and oxidative damage such as 8-oxoguanine (8-oxoG). The consequences of DNA damage are essentially twofold. After misrepair or replication of the damaged template, surviving cells may be subject to

permanent changes in the genetic code in the form of mutations or chromosomal aberrations, both of which increase the risk of cancer. Alternatively, damage may interfere with the vital process of transcription or induce replication arrest, which may trigger cell death or cellular senescence, contributing to aging. Damage-induced cell death protects the body from cancer. G denotes guanine, and T thymidine. (Reprinted with permission from Jan H.J. Hoeijmakers. DNA Damage, Aging, and Cancer. *N Engl J Med* 2009;361(19): 1475–1485.)

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TABLE 1**The Aging Lung and Associated Environmental Influences**

Age-related changes	Environmental influences
Accumulated genetic injury	Oxidative damage, radiation, mutagens, carcinogens
Structural changes in chest wall and lung	Diet
alveolar matrix proteins	Obesity
senile emphysema	Hormonal changes
increased chest wall stiffness	
decreased respiratory muscle strength	
Impaired defense mechanisms	Inhaled irritants/particles
antioxidants	Cigarette smoke
immune cell function	Allergens
neural reflexes	Pathogenic organisms
clearance	Gastric contents
Impaired control of breathing	Cigarette smoke
	Alcohol
Pulmonary vascular remodeling	Cigarette smoke

Adapted from Green FHY & Pinkerton KE, 2003

TABLE 2

Altered Immunity in the Elderly

Cell-mediated immunity	Change with age
Involution of the thymus Naïve 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+	↑
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	
Neutrophils	
Impaired apoptosis and killing	
production of ROS	↑
Macrophages function	↓
Natural killer cells number	↑
cytotoxic activity	↓
Dendritic cells	
number of plasmacytoid dendritic cells	↓
B-cell stimulation	↓
Impaired capacity to capture antigen	
Impaired capacity to phagocytose apoptotic cells	

Adapted from Green FHY & Pinkerton KE, 2003 and Sharma G et al., 2009

TABLE 3

Changes in Bronchoalveolar Lavage Fluid in Healthy Aged Individuals

Parameter	Change
Lymphocytes	↑
CD4 ⁺ /CD8 ⁺ T-cell ratio	↑
HLA-DR ⁺ T-cells	↑
B-cells	↓
IgM, IgA and IgG	↑
Total protein	↑
Neutrophils	↑
Interleukins (IL-6, IL-8)	↑
α1-Antitrypsin	↑

Adapted from Meyer KC, 2001 and Green FHY & Pinkerton KE, 2003