Is Chronic Obstructive Pulmonary Disease an Accelerated Aging Disease?

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Abstract

Aging is one of the most important risk factors for most chronic diseases. The worldwide increase in life expectancy has been accompanied by an increase in the prevalence of age-related diseases that result in significant morbidity and mortality and place an enormous burden on healthcare and resources. Aging is a progressive degeneration of the tissues that has a negative impact on the structure and function of vital organs. The lung ages, resulting in decreased function and reduced capacity to respond to environmental stresses and injury. Many of the changes that occur in the lungs with normal aging, such as decline in lung function, increased gas trapping, loss of lung elastic recoil, and enlargement of the distal air spaces, also are present in chronic obstructive pulmonary disease (COPD). The prevalence of COPD is two to three times higher in people over the age of 60 years than in younger age groups. Indeed, COPD has been considered a condition of accelerated lung aging. Several mechanisms associated with aging are present in the lungs of patients with COPD. Cell senescence is present in emphysematous lungs and is associated with shortened telomeres and decreased antiaging molecules, suggesting accelerated aging in the lungs of patients with COPD. Increasing age leads to elevated basal levels of inflammation and oxidative stress (inflammaging) and to increased immunosenescence associated with changes in both the innate and adaptive immune responses. These changes are similar to those that occur in COPD and may enhance the activity of the disease as well as increase susceptibility to exacerbations in patients with COPD. Understanding the mechanism of age-related changes in COPD may identify novel therapies for this condition.

Keywords: aging; chronic obstructive pulmonary disease; chronic obstructive pulmonary disease pathogenesis; immunosenescence

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Aging is characterized by the loss of physiological integrity, decline in homeostasis, progressive degeneration of the tissues, and reduced capacity to respond to environmental stimuli, which contribute to an incremental risk of disease and death (1). The age demographics of the world's population are changing markedly. The proportion of the world's population over the age of 60 years will double from around 11% in 2000 to 22% in 2050, resulting in an absolute increase from 600 million to 2 billion individuals older than age 60 years over the same period (2). Since aging is one of the most important risk factors for most chronic diseases (3), this change will pose a challenge to society in the future, with an increased need for healthcare for chronic diseases in the aging population.

Chronic obstructive pulmonary disease (COPD) is one such chronic disease that has been linked with aging. Many of the features of aging in the lungs are similar to those that occur in the lungs of patients with COPD, and many of the mechanisms associated with aging also feature in the lungs of patients with COPD. In this review, I describe the hallmarks of aging and their relationship to COPD.

Concepts of Aging

In general, aging is determined by the interaction between injury and repair and the balance between cell death and replacement to maintain organ integrity (4). There are many theories of aging, and there is interaction between the different theories. One theory of aging, known and the "antagonistic pleiotropic theory of aging" (5), suggests that there are pleiotropic genes that are beneficial in early life but become detrimental in later life. For example, both the p53 and the mammalian target of rapamycin (mTOR) pathways have been suggested as antagonistically pleiotropic gene systems (6). A further concept of aging, the "disposable soma" theory (7), proposes that organisms devote energy resources to ensure optimal growth and fertility in early life but that insufficient maintenance and repair occurs in later life, resulting in increased cellular damage.

A further theory of aging is the "free radical theory," which proposes that aging results from accumulated damage

inflicted by reactive oxygen species (ROS) (8). Evidence is accumulating that an optimal amount of ROS, which can trigger proliferative and survival signals in response to physiological and stress signals, is required for successful aging (9). However, with aging, ROS levels increase in an attempt to maintain survival (10) until they reach a level where they enhance rather than alleviate age-related damage (11). Excess ROS can induce DNA damage, accelerate replicative senescence, and activate redox-sensitive transcription factors, which regulate the transcription of several genes, including those for proinflammatory cytokines (12). The accumulation of inflammatory tissue damage, combined with an increasingly dysregulated immune system and senescent cells that secrete proinflammatory cytokines, is termed *inflammaging* (13). Senescent cells remain metabolically active and secrete various inflammatory mediators in what is known as the senescence-associated secretory phenotype. The accumulation of senescent cells with age, resulting in a senescence-associated secretory phenotype–induced proinflammatory state, is similar to what is observed in COPD (14).

Lung Aging and COPD

With increasing age, there is a progressive deterioration in lung function (15) (Figure 1), resulting in an increased risk of breathlessness and an increased prevalence of chronic pulmonary diseases in older individuals (16). Aging is associated with a progressive reduction in FEV_1 of approximately 20 ml/yr, together with a reduction in FEV_1/FVC ratio and an increase in residual volume with preserved total lung capacity (17, 18). These changes in lung function result in lower oxygen levels and decreased ability to eliminate carbon dioxide due to decreases in chest wall compliance, lung elastic recoil (19), and respiratory muscle strength (19, 20). These changes in lung function with age resemble those that develop in COPD. The changes in lung physiology with age are associated with structural changes in the lung involving alveolar enlargement, resulting in a decrease in the area available for gas exchange. However, this

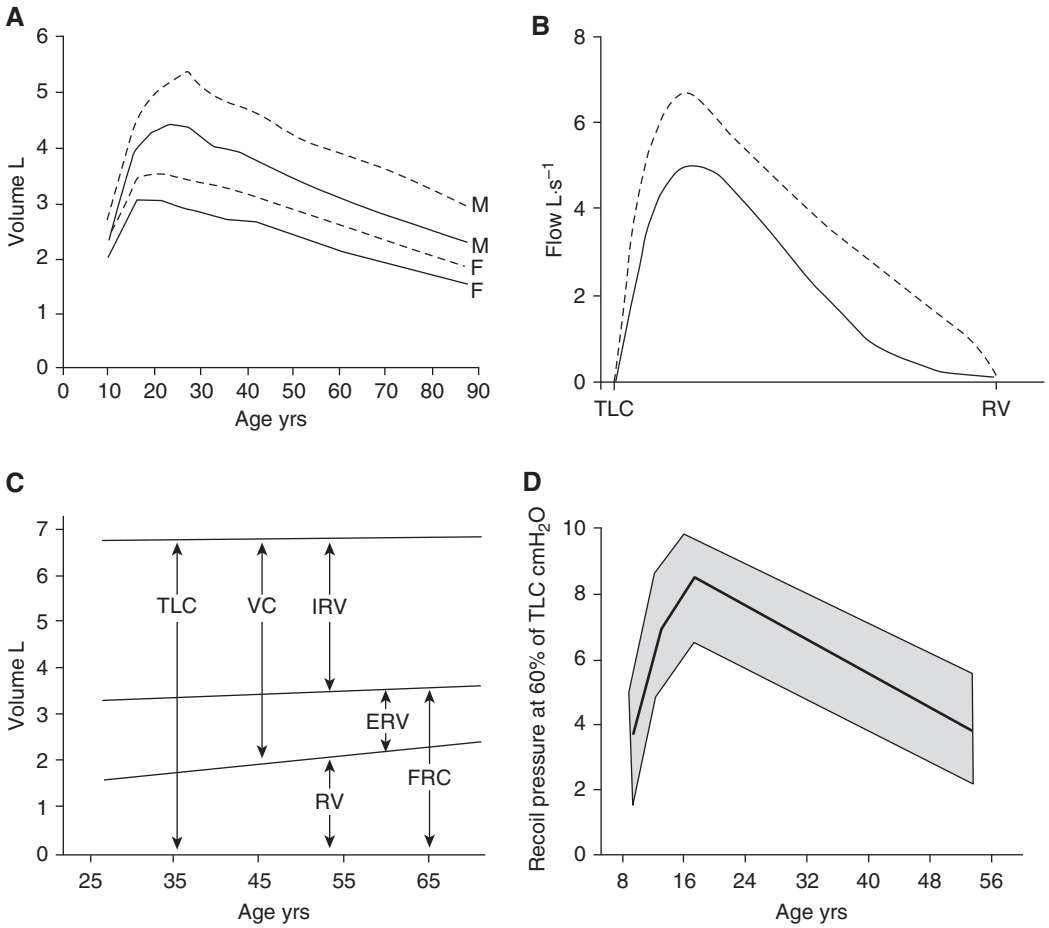

Figure 1. (*A*) Changes in lung function shown as evolution of FEV_1 (*solid lines*) and FVC (*dashed lines*) as a function of age. (*B*) Changes in the expiratory flow–volume curve with age. Data are derived from 10 older subjects (mean age, 71 yr; *solid line*) and 10 younger subjects (mean age, 24 yr; *dashed line*). (*C*) Evolution of lung volume with aging. (*D*) Static elastic recoil as a function of age. Static elastic recoil was measured at 60% of total lung capacity. *Shaded area* shows ±1 SD of plotted means. ERV = expiratory reserve volume; FRC = functional residual capacity; IRV = inspiratory reserve volume; RV = residual volume; TLC = total lung capacity; VC = vital capacity. Reproduced by permission from Reference 17.

alveolar enlargement is unlike that which occurs in COPD, because there is no destruction of alveolar walls in the aging lung, as occurs in emphysema in COPD (Figure 2). Since the classic epidemiological studies of Fletcher and Peto (15), it has been considered that, in susceptible cigarette smokers who develop COPD, there is an accelerated decline in lung function with age of 50–100 ml of FEV_1/yr. However, it is clear from recent studies that there is marked individual variability in the decline in FEV_1 in subjects with COPD and that the development of the persistent airflow limitation characteristic of COPD is not always a result of accelerated decline in FEV_1 (21, 22), but can be due, for example, to suboptimal lung growth in childhood (23). Thus, accelerated lung aging may not be a pathogenic mechanism in all individuals with COPD.

The incidence of COPD dramatically rises with age. The rate of newly diagnosed COPD in patients increases from around 200 cases per 10,000 patients younger than 45 years of age to 1,200 cases per 10,000 patients 45 years or older. The greatest increase occurs in patients aged 65–74 years (24).

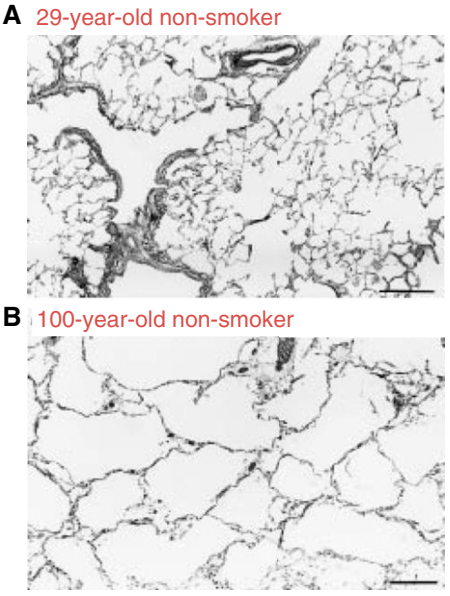

Figure 2. Lung parenchyma from (*A*) a nonsmoking 29-year-old subject and (*B*) a 100-year-old nonsmoking patient. Note the marked enlargement of alveoli without any inflammatory infiltrate or alveolar wall destruction. Reproduced by permission from Reference 17.

Hallmarks of Aging in COPD

López-Otín and colleagues (25) proposed nine hallmarks of aging (Figure 3). These are genomic instability, telomere attrition, cellular senescence, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, stem cell exhaustion, and altered cellular and intercellular communication. In the following sections of this review, the hallmarks of aging are described in relationship to COPD, with a particular focus on human studies. A review of animal models of aging in relationship to COPD can be found elsewhere (26).

Genomic Instability

Aging has been considered to result from accumulation of genetic damage and defects in DNA repair. Oxidative stress is recognized as a mechanism for the DNA damage of premature aging in the free radical theory of aging (8). Increased oxidative stress is known to occur in the lungs of patients with COPD, as shown by the increased presence of biomarkers of oxidative stress (27). Smokers and patients with COPD also have increased evidence of oxidative damage to DNA in the lungs, as shown by an increase in the concentration of 8-hydroxy-2-deoxyguanosine in the peripheral lung and type II pneumocytes (28, 29). In addition, there is an increase in the number of double-stranded DNA breaks, as shown by an increase in phosphorylated histone 2AX foci in lung endothelial cells, which also express an increase in p16 (a marker of cellular senescence).

There is also evidence of a failure of DNA strand break repair in COPD (28). This imbalance between oxygen-induced DNA damage and repair in COPD may result in increased cellular senescence, although the pathogenic link with DNA damage in COPD may be more related to the increased risk of lung cancer (28).

Telomere Attrition

Telomeres are the regions at the ends of chromosomes containing 1–5 kb of TTAGGG repeats that protect DNA against degradation and recombination and thus support chromosome stability (30, 31). In most somatic cells, telomeres shorten with every cell cycle, and this can be prevented by telomerase, an enzyme complex that maintains telomere length. However, telomerase activity is insufficient to completely maintain chromosome length, and therefore shortening of telomeres leads to progressive loss of telomere-protective sequences at the ends of chromosomes.

Telomere length reflects the length at birth and its rate of attrition thereafter. The latter is a result of the replication

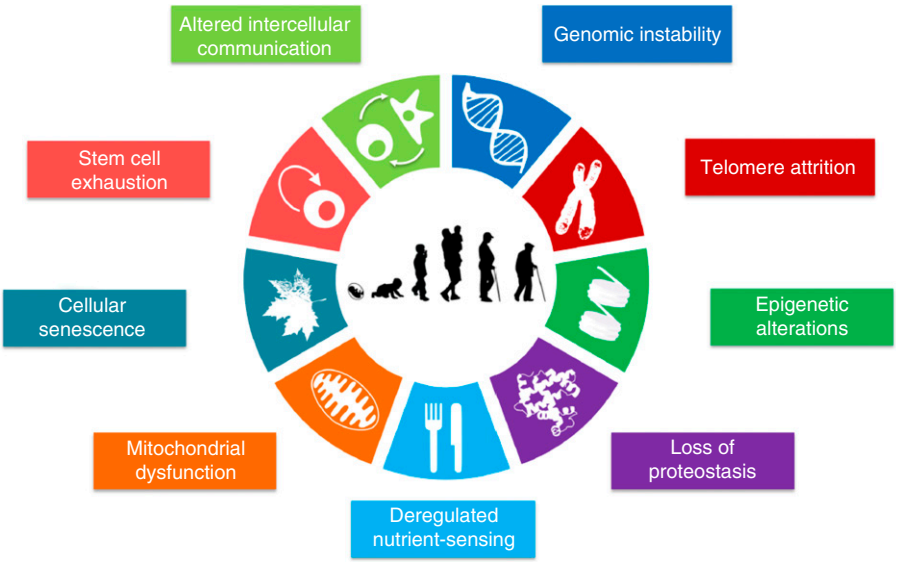

Figure 3. The hallmarks of aging. Modified by permission from Reference 25.

history, but it is also a reflection of a number of other factors, such as cumulative oxidative stress and chronic inflammation acting on progenitor cells (32). With successive cell divisions, telomere shortening in chromosomes occurs until cells are no longer capable of dividing, which results in either cellular senescence (replicative senescence) or cell death by apoptosis. Telomere length has been considered as a measure of biological rather than chronological age or, more recently, as a biomarker of somatic redundancy that is the body's capacity to absorb damage (33).

There is a strong relationship between short telomeres and the risk of mortality. Shortened telomeres are also associated with increased oxidative damage because shortened telomeres induce p53, which suppresses two gene products (the proliferator-activated receptor-γ coactivator-1α and -β gene) whose expression is needed for mitochondrial function and survival. This would therefore result in mitochondrial dysfunction with elevated free radical production.

Shortened telomeres have been described in current and former smokers in comparison with nonsmokers, probably as a result of increased oxidative stress from inhalation of cigarette smoke, since there is also a dose-dependent relationship between telomere length and pack-years of smoking (34).

Circulating leukocytes from patients with COPD have been shown to have shorter telomeres than those of control subjects in any age range (35, 36). Parenchymal lung cells from emphysematous lungs also show shortened telomeres associated with increased cell senescence (37) and an increase in lung inflammation (38, 39).

A meta-analysis of 14 studies showed a significant negative association between telomere length and COPD and positive associations between spirometric indices of airflow limitation and telomere length (40) (Figure 4). An observational study of 45,000 Danish subjects also indicated that shortened telomeres were associated with reduced lung function, although the associations were attenuated after age and multivariable adjustment (41). Recently, a hereditary telomerase mutation was identified in families with combined pulmonary fibrosis and emphysema (42, 43).

Telomere shortening in COPD may be a result of increased oxidative stress, which is known to impair telomerase activity and to directly affect telomere shortening. Shortening of telomeres results in activation of p21, leading to cellular senescence and release of proinflammatory mediators.

Pulmonary endothelial cells from patients with COPD have reduced telomerase activity, which is associated with shorter telomeres and increased p21 and cellular senescence compared with cells from the lungs of age-matched nonsmoker control subjects, in association with increased release of cytokines (38).

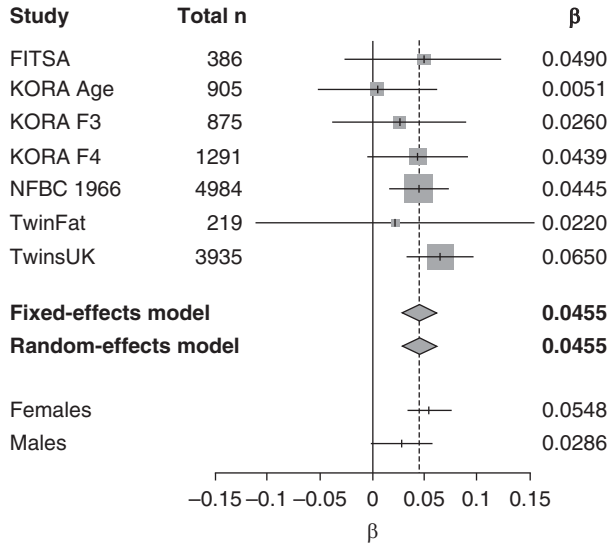

Figure 4. Telomere length is associated with FEV_1. Forest plots show comparison of effects between studies and combined effects in fixed-effects models as well as in random-effects models. Sex-stratified results are based on random-effects models. Ninety-five percent confidence intervals are given for all estimates. FITSA = Finnish Twin Study on Ageing; KORA = Cooperative Health Research in the Regional Ausburg Region; NFBC = Northern Finland Birth Cohort Study. Reproduced by permission from Reference 40.

Cellular Senescence

In response to stresses such as ROS, cells are directed toward cell arrest or, if the damage is beyond repair, toward cell death. Cellular senescence is a process in which cellular stresses converge toward cell-cycle arrest associated with stereotyped phenotypic changes (44). In addition to replicative senescence, where progressive telomere shortening leads to senescence (45), oxidative stress–induced DNA damage can promote cell arrest, or so-called stress-induced premature senescence (46).

Senescent cells, unlike apoptotic cells, remain metabolically active and exhibit the senescence-associated secretory phenotype (45). Senescent cells show activation of nuclear factor κβ, a transcription factor that regulates inflammation, and release increased amounts of inflammatory cytokines (46). Type II epithelial cells, endothelial cells, and fibroblasts from emphysematous lungs show increased evidence of senescence (47) (Figure 5). Exposure of human epithelial cells to cigarette smoke, the main etiological factor in COPD, results in cell senescence, as shown by increased senescent markers such as senescence-associated β-galactosidase and p21 protein (47). A direct relationship has been shown between the extent of p16-positive cell senescence and the severity of inflammation in emphysematous lungs (39).

Epigenetic Alterations

A range of epigenetic alterations, such as DNA methylation, histone modification, and noncoding RNAs, are thought to be a hallmark of aging, resulting in chromatin remodeling and alteration of gene expression (25). Cigarette smoke and

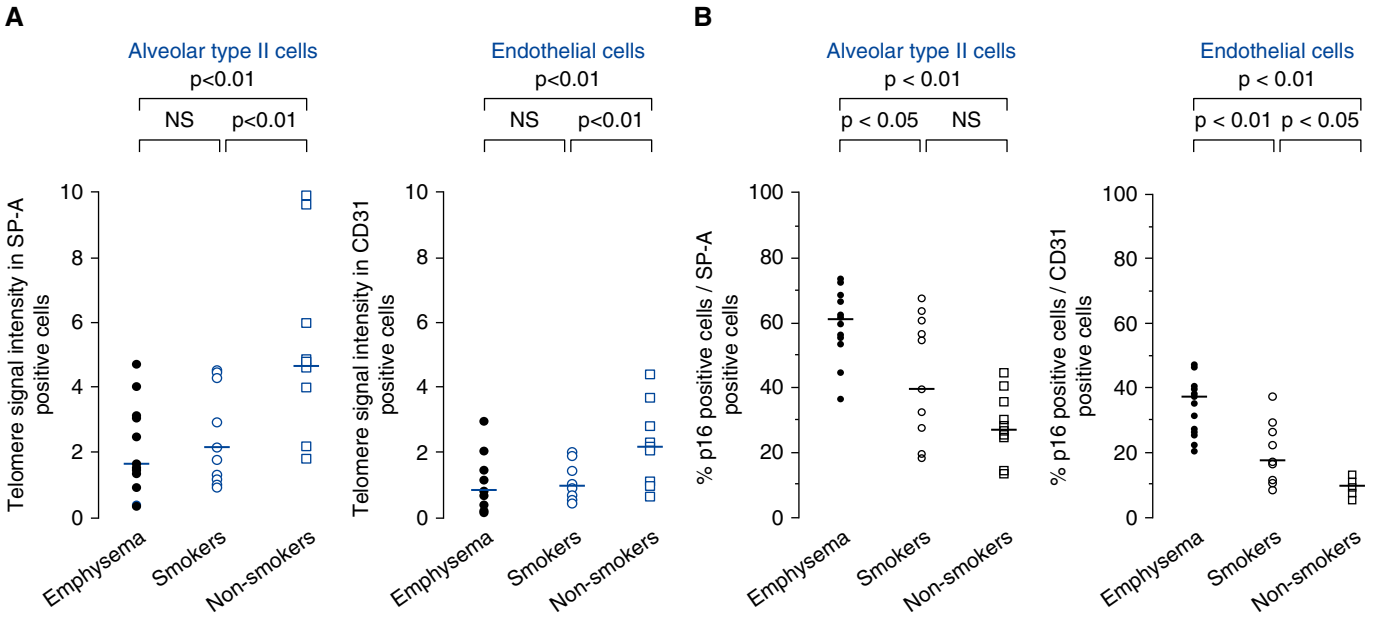

Figure 5. (*A*) Telomere length and (*B*) cell senescence (p21-positive cells) in type II alveolar (surfactant protein-A [SP-A]) epithelial and endothelial cells from lung tissue of nonsmokers, smokers, and patients with emphysema. Reproduced by permission from Reference 37.

wood smoke inhalation induce changes in DNA methylation and have been associated with an increased risk of the development of COPD (48, 49). DNA methylation has also been described in small airway epithelial cells (49), and differential DNA methylation has also been detected in lymphocytes from patients with COPD compared with healthy control subjects and is correlated with the severity of COPD (50, 51). Whether these changes are a cause or consequence of COPD is yet to be determined.

The histone deacetylase (HDAC) sirtuins are involved in these epigenetic mechanisms and have been studied as potential antiaging factors. Sirtuins are type III HDACs and act on histone residues in DNA that are essential to maintenance of silent chromatin during histone deacetylation. Sirtuin-1 is suppressed in both large and small epithelial cells from patients with COPD compared with smoking and nonsmoking control subjects as a result of post-translational oxygen modification of the molecule that results in enhanced inflammation and increased cellular senescence (52, 53) (Figure 6).

In addition to sirtuins, HDAC2 has been shown to be an antiaging molecule because knockdown of HDAC2 induces cellular senescence (54). HDAC2 has been shown to be reduced in the lungs of patients with COPD compared with smokers who have not developed the disease (55), owing to oxidative modification of the molecule (56), and this would lead to cell senescence and enhanced inflammation as a result of increased histone acetylation and consequent enhanced proinflammatory gene expression (57).

Loss of Proteostasis

Aging and some age-related diseases have been linked to impaired protein homeostasis or proteostasis (58). Proteostasis involves a range of processes by which cells stabilize correctly folded proteins or restore or remove misfolded or unfolded damaged proteins by the proteasome or lysosome systems (59).

The two principal proteolytic systems involved in degrading and removing damaged protein are the autophagy-lysosome system and the ubiquitin-proteasome system. Both of these systems have been shown to decline with age (60, 61), such that normal protein turnover is impaired with age and can lead to accumulation of altered proteins, which contributes to the pathophysiology of a number of age-related conditions.

In COPD, ROS from cigarette smoke can produce oxidative modifications of cellular proteins, such as histone deacetylases, resulting in loss of function and degradation by the proteasome system or by the autophagy pathways (62, 63). Proteasome function is reduced in patients with COPD and correlates inversely with the loss of lung function (64). Autophagy has a protective role in the response to exogenous stress. However, prolonged and excessive autophagy has been associated with cell death.

Inhibition of autophagy increases susceptibility to oxidative damage and apoptosis, whereas activation of autophagy leads to inhibition of apoptosis (65). Alveolar macrophages from cigarette smokers showed defective autophagy that could contribute to the accumulation of damaged proteins, abnormal mitochondrial function, and defective clearance of bacteria (66). There is evidence of increased markers of autophagy in lung tissue from patients with emphysema, suggesting that autophagy may be contributory to the apoptosis and alveolar destruction in emphysema (64). Increased activation of autophagic vacuoles (autophagosomes) has been found in COPD. Although this may indicate that autophagy has been initiated, it is not clear if autophagy has been completed, a process known as autophagic flux. Some studies have shown a defect in autophagic flux in smokers that results in the accumulation of the substrate of autophagy p62 and increased

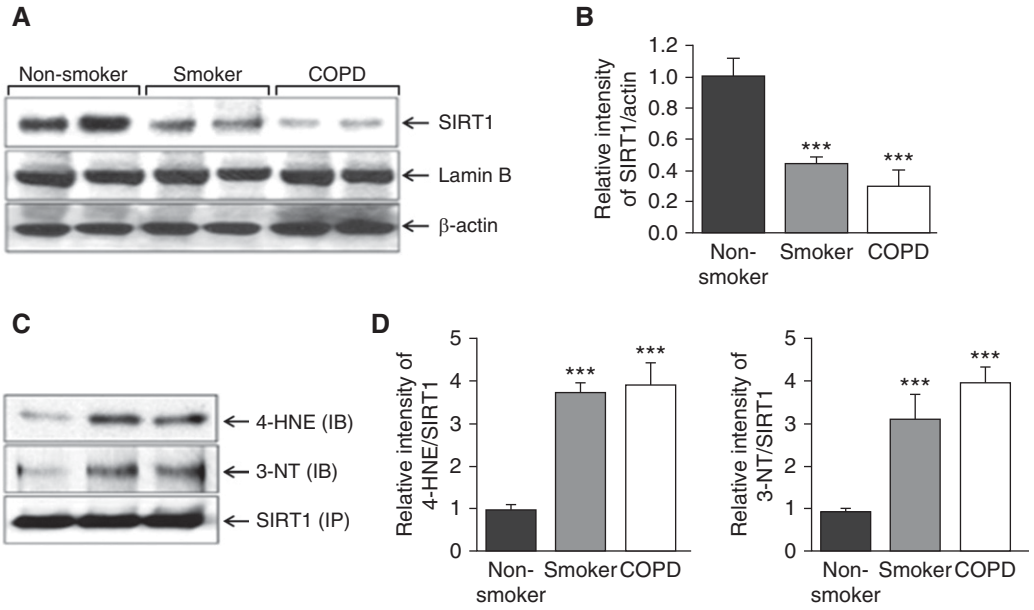

Figure 6. Decreased levels of sirtuin (SIRT1) protein in lung tissue of smokers and patients with chronic obstructive pulmonary disease (COPD). (*A*) Western blot analysis of SIRT1 nuclear proteins from the lung tissue of nonsmokers, smokers, and patients with COPD. (*B*) Densitometric analysis shows the relative level (as a percentage of control tissue) of SIRT1 in the lung tissue of smokers and patients with COPD. (*C*) The levels of SIRT1 adducts with 4-hydroxy-2-nonenol (4-HNE) and nitration of tyrosine residues in SIRT1 analyzed by immunoblotting (IB) with anti-4-HNE and anti-3-nitrotyrosine (3-NT) antibodies, respectively. (*D*) Relative intensity of 4-HNE/SIRT1 and 3-NT/SIRT1 protein in lung tissue of smokers and patients with COPD compared with nonsmokers. Results are expressed as mean ± SEM. ***$P < 0.001$ compared with nonsmokers. IB = immune blot; IP = immunoprecipitated. Reproduced by permission from Reference 52.

misfolded proteins with an associated dysfunction in lysosomal digestion of the autosomal burden caused by the reduction in the lysosomal protein LAMP2 (66). Autophagy is also impaired through the activation of phosphoinositide 3-kinase (PI3K)-mTOR signaling in COPD (67) and may contribute to defective phagocytosis of bacteria in COPD (68).

Deregulated Nutrients Sensing

With aging, deregulated nutrient sensing occurs that involves the PI3K-AKT-mTOR pathway, which integrates signals on nutrient availability to regulate cellular growth (69). The mTOR pathway has an important role in cellular senescence and aging, and inhibition of this pathway extends the lifespan of many species (69).

The mTOR pathway has multiple downstream effects that include inhibition of forkhead box O (FOXO) transcription factors, which are linked to longevity. In epithelial cells from the lungs of patients with COPD, there is evidence of PI3K activation with an increase in downstream phosphorylated AKT, which in turn activates mTOR. Activation of the insulin-like growth factor 1/AKT/mTOR pathway suppresses autophagy, but it also counteracts activation of FOXO transcription factors, which are central regulators of metabolized and stress-resistant cell-cycle progression in programmed cell death (70).

Diminished expression of FOXO3 protein has been shown in the lungs of smokers and patients with COPD (and in the lungs of smoke-exposed mice) (71, 72), and FOXO3 ablation in mice enhances the development of smoke-induced emphysema (72). In addition, abnormal epidermal growth factor receptor signaling inhibits FOXO3A activation in COPD airways, leading to enhanced IL-8 signaling (73). These data suggest that dysregulated nutrient sensing, together with loss of proteostasis, may contribute to the pathogenesis of COPD.

Mitochondrial Dysfunction

Mitochondrial dysfunction may contribute to aging by increasing production of ROS as part of the free radical theory of aging (74). Mitochondria also regulate cellular homeostasis through their membrane potential by making acetyl coenzyme A and by their removal by mitophagy (75).

Aging is associated with the accumulation of mutations in mitochondrial DNA (76). There is evidence of increased mitochondrial ROS and reduction in mitochondrial numbers in COPD (75). Cigarette smoke alters mitochondrial structure and function (77, 78). Mitochondrial structure and function have also been shown to be altered in airway epithelial cells from cigarette smokers (79). The mitochondrial stress markers Parkin and phosphatase and tensin homolog–induced protein kinase 1 have also been shown to be increased in patients with COPD (80).

Stem Cell Exhaustion

Stem cell exhaustion is thought to be a major factor in several age-related diseases (81). In COPD, basal progenitor cells that are necessary for airway epithelial differentiation have a reduced regenerative capacity (82, 83). Circulating progenitor cells—in particular endothelial progenitor cells from smokers and COPD—show evidence of DNA damage and senescence,

reducing their repair capacity (84). However, conflicting studies have shown decreased hematopoietic progenitor cells with unchanged numbers of circulating endothelial progenitor cells in patients with COPD (85, 86).

Altered Cellular and Intercellular Communication

There is an increase in low-grade systemic inflammation characterized by increasing higher levels of circulating proinflammatory cytokines, such as IL-1, IL-6, IL-8, and tumor necrosis factor-α, in elderly individuals, which may contribute to several age-related disorders (as part of the inflammaging hypothesis of aging) and as a common biological factor responsible for the decline and onset of disease in the elderly (87). Changes in the innate as well as the adaptive immune responses are characteristic features of COPD. Age-related changes in the immune system, referred to as *immunosenescence*, are also thought to be responsible for the predisposition of elderly patients with COPD to exacerbations (88–90).

Conclusions

There are many similarities between the aging process in the lungs and COPD, and many of the hallmarks of aging are present in COPD, suggesting that accelerated aging may be a pathogenic mechanism in COPD. Understanding the mechanisms of aging may provide novel targets for the treatment of this condition. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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