Lung Diseases of the Elderly: Cellular Mechanisms

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KEYWORDS

• Idiopathic pulmonary fibrosis • COPD • Aging • Cellular senescence • Stem cells

KEY POINTS

- Changes in the aging lung result in impaired protective mechanisms that predispose to chronic lung diseases.
- Genomic instability, telomere attrition, and epigenetic alterations are mechanisms that lead to accumulation of genetic errors that result in improper cellular division and development of lung disease.
- Cellular senescence can be induced by cigarette smoking and has been linked to idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease.

AGING LUNG

Aging is the natural process of growing older over a period of time and does not take place uniformly in cells, tissues, or organs.[1] In the lung, aging correlates with the development of chronic lung diseases.[2] Some of the factors that are involved are being characterized, including shorter telomeres, mitochondrial dysfunction, DNA damage, oxidative stress, and changes in markers of apoptosis. An understanding of changes in pulmonary pathophysiology and genomic differentiation in aging lungs may be key to identifying age-related risk factors in the development of lung disease.

INCIDENCE OF LUNG DISEASE INCREASES WITH AGE

As the percentage of persons more than 65 years old increases worldwide (5.87% in 1985, 7.28% in 2005, and 8.28% in 2015[3]), so does the incidence of lung disease.

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Although globally chronic obstructive pulmonary disease (COPD) is reported in 200 per 10,000 patients in individuals less than the age of 45 years, there are 1200 cases reported per 10,000 patients more than the age of 65 years. The predominance of cases in an older age group is also reported in patients with idiopathic pulmonary fibrosis (IPF), in which the incidence increases to about 4 to 17 diagnoses per 10,000 in patients more than the age of 75 years.[4] Overall, there is an almost 5-fold increase in incidence of IPF and COPD related solely to age.[4]

CHANGES IN THE HEALTHY AGING LUNG

There is a natural decline of pulmonary function with aging. Lungs achieve maximum function around 20 to 25 years of age, followed by a steady decline until death.[5] This decline is best shown by the nonlinear decline in forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) lung volumes. At approximately 35 to 40 years of age, FEV_1 is reduced 25 mL to 30 mL per year. By age 70 years, FEV_1 is reduced at a rate of 60 mL per year.[6] Total lung capacity remains constant with advanced age; however, an increase in functional residual capacity and residual volume effectively reduces the vital capacity.[6] Menopause also correlates with a greater decline in FVC than expected with age alone.[7] Differences in men and women regarding sex hormones and their apparent effects on lung function are not yet completely understood.[7] At present, there are limited studies evaluating asymptomatic elderly individuals with radiological imaging and pulmonary function tests; therefore, the full spectrum of the normal aging process remains unknown.

The molecular biology of aging involves multiple mechanisms. Over time, these mechanisms may lose their integrity, resulting in loss of protective strategies. The most studied mechanisms include genomic instability, telomere attrition, epigenetic alterations, proteostasis, nutrient sensing, mitochondrial dysfunction, cell senescence, extracellular matrix (ECM) deregulation, and stem cell exhaustion. Genomic instability may be a result of posttranscriptional changes leading to absent or defective protein products. Usually these defective proteins are eliminated by autophagy. However, if the means by which the cells undergo autophagy is saturated, then abnormal proteins accumulate within the tissue, preventing proper functioning. Telomeres are responsible for protection of chromosomes and assist in genetic stability. With each sequential cell proliferation, telomeres are shortened, and eventually they become too short, resulting in inaccurate cell proliferation. Likewise, stem cell exhaustion and inability to properly regenerate and mitochondrial dysfunction severely limit ATP production, resulting in abnormal cellular functionality.

The Wnt pathway is integral to cell aging.[8] It comprises a group of signal transduction pathways involved in proper regulation of stem cells and progenitor cells, and in maintaining homeostasis during repair from injury. The WNT pathway has been studied in several models of aging organs and is likely a ubiquitous pathway in aging. There are 19 evolutionarily conserved ligands identified.[8–10] The pathway activates β-catenin–dependent (canonical) or β-catenin–independent (noncanonical) pathways.[11] Lung development depends on the WNT pathway for embryogenesis and maintenance of healthy lung tissue. Knockout of this pathway (WNT2 or β-catenin) results in complete agenesis of lungs in mice.[12] Alternatively, when overexpression occurs there is dilation of distal bronchioles, which results in significant respiratory failure.[13] Significantly different levels of specific ligands in this pathway correlate with aging in mice.[14] Aged mouse lungs had different levels of expression of WNT3A at a transcriptional level with altered expressions of target gene *Nkd1* compared with young mouse lungs.[15] Similar changes in signaling of WNT pathway with advanced age