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COPD as a Disease of Accelerated Lung Aging*

Kazuhiro Ito, PhD; and Peter J. Barnes, MD, FCCP

There is increasing evidence for a close relationship between aging and chronic inflammatory diseases. COPD is a chronic inflammatory disease of the lungs, which progresses very slowly and the majority of patients are therefore elderly. We here review the evidence that accelerating aging of lung in response to oxidative stress is involved in the pathogenesis and progression of COPD, particularly emphysema. Aging is defined as the progressive decline of homeostasis that occurs after the reproductive phase of life is complete, leading to an increasing risk of disease or death. This results from a failure of organs to repair DNA damage by oxidative stress (nonprogrammed aging) and from telomere shortening as a result of repeated cell division (programmed aging). During aging, pulmonary function progressively deteriorates and pulmonary inflammation increases, accompanied by structural changes, which are described as senile emphysema. Environmental gases, such as cigarette smoke or other pollutants, may accelerate the aging of lung or worsen aging-related events in lung by defective resolution of inflammation, for example, by reducing antiaging molecules, such as histone deacetylases and sirtuins, and this consequently induces accelerated progression of COPD. Recent studies of the signal transduction mechanisms, such as protein acetylation pathways involved in aging, have identified novel antiaging molecules that may provide a new therapeutic approach to COPD.

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Abbreviations: DNA-PK = DNA-dependent protein kinase; HDAC = histone deacetylase; IL = interleukin; MMP = matrix metalloproteinase; NF-κB = nuclear factor-κB; PI3K = phospho-inositide 3 kinase; ROS = reactive oxygen species; SMP30 = senescence marker protein-30; TNF = tumor necrosis factor

COPD is a major and increasing global health problem with enormous amount of expenditure of indirect/direct health-care costs.[1] COPD now affects > 10% of the world population over the age of 40 years,[1] and the burden of disease is particularly high in developing countries. There is still a fundamental lack of knowledge about the cellular, molecular, and genetic causes of COPD, and current therapies are inadequate because no treatments reduce disease progression or mortality. COPD is caused by long-term inhalation of noxious gases and particles, such as cigarette smoke, and a chronic inflammatory disease of the lower airways and lung parenchyma, which is enhanced during exacerbations.[2] The pathologic characteristics of COPD are destruction of the lung parenchyma (emphysema), inflammation of peripheral and central airways, and an increase in mucus-producing cells. Airflow limitation, measured by reduced FEV_1, progresses very slowly over several decades, so that most patients with symptomatic COPD are in late middle age or are elderly. Thus, the prevalence of COPD is age dependent,

*From Airways Disease Section, National Heart and Lung Institute, Imperial College London, UK.
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Correspondence to: Kazuhiro Ito, PhD, National Heart and Lung Institute, Imperial College School of Medicine, Dovehouse St, London SW3 6LY, UK; e-mail: k.ito@imperial.ac.uk
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suggesting an intimate relationship between the pathogenesis of COPD and aging.

Aging Process and Its Molecular Mechanism

Senescence or aging is defined as the progressive decline of homeostasis that occurs after the reproductive phase of life is complete, leading to an increasing risk of disease or death. Kirkwood[3] has advanced the concept of "disposable soma," in which aging, rather than being programmed and determined by selected genes, results from the stochastic interaction between injury and repair, as the result of the energy devoted by an individual to maintain organ integrity and protect DNA against oxidative injury. In this model, the failure of organ/cell maintenance/repair results from the integrated action among genes, environment, and intrinsic defects of the organism. Underlying the aging process is a lifelong, bottom-up accumulation of molecular damage. Kirkwood[3] also makes the point that cellular defects often cause inflammatory reactions, which can themselves exacerbate existing damage, so that inflammatory and antiinflammatory factors can play a part in shaping the outcomes of the aging process. Thus, aging-associated inflammation/structural change is the results of failure of reactive oxygen species (ROS) elimination, failure of repair of damaged DNA, and telomere shortening, as shown below.

Telomere Shortening

In many human somatic tissues and cells such as fibroblasts, there is a decline in cellular division capacity with age or a limited division potential before undergoing so-called *replicative senescence*. This appears to be linked to the fact that the telomeres, which protect the ends of chromosomes, get progressively shorter as cells divide. Oxidative stress has been found to have an even bigger effect on the rate of telomere loss,[4] and telomere shortening is greatly accelerated (or slowed) in cells with increased (or reduced) levels of oxidative stress.

Oxidative Stress and DNA Damage

Somatic mutations can occur in any of the cells of the body, and this somatic mutation and other forms of DNA damage have been demonstrated to be increased age dependently. Promislow[5] reported a general relationship between longevity and DNA repair. Thus, the capacity for DNA repair may be an important determinant of the rate of aging at the cell and molecular level.

Harman[6] suggested that ROS, formed during normal oxygen metabolism, induce damage, the accumulation of which accounts for progressive deleterious changes called *aging* or *senescence*. This hypothesis is called the *free radical theory of aging* and has later been extensively supported by numerous *in vivo* and *in vitro* studies[7–10] showing that age-related changes is accelerated under the influence of oxidative stress, while various antioxidants slow aging. This oxidative stress causes DNA damage and increases risk of cancer, as documented for the role of mammary gland senescence and the increased risk of breast cancer.

Antiaging Molecules: Recent advance in aging research is identification of antiaging molecules. Sirtuins are nicotinamide adenine dinucleotide-dependent histone/protein deacetylases and display differential specificity toward acetylated substrates, which translates into an expanding range of physiologic functions, such as gene expression, cell cycle regulation, apoptosis, metabolism, and aging.[11] Seven molecules have been identified in the human sirtuin family (SIRT1–SIRT7). As well as sirtuins (type III histone deacetylase [HDAC]), HDAC-2 (a type I HDAC) is also reported to be an antiaging molecule as knock-down of HDAC-2 induces cellular senescence by enhancing p53-dependent transrepression and transactivation of a subset of target genes.[12]

Homozygous mutant *klotho* ($KL^{-/-}$) mice have a short lifespan and have pulmonary emphysema as well as some other aging phenotypes, such as arteriosclerosis, osteoporosis, skin atrophy, and ectopic calcifications[13] (Table 1). The secreted Klotho protein can regulate multiple growth factor signaling pathways, including insulin/insulin-like growth factor and Wnt, and the activity of multiple ion channels. Klotho protein also protects cells and tissues from oxidative stress, yet the precise mechanism underlying these activities remains to be determined. The development of emphysema in KL−/− mice is due increased expression of matrix metalloproteinase (MMP)-9.

Senescence marker protein-30 (SMP30), a 34-kd protein originally identified from the rat liver, is a novel molecule that decreases with age in an androgen-independent manner. SMP30 is widely expressed in vertebrates and highly conserved. The SMP30 out (SMP30Y/–) mouse has a shorter life span, and has had senile lung with age-related airspace enlargement and enhanced susceptibility to harmful stimuli[14] (Table 1). Cigarette smoke exposure generates marked airspace enlargement with significant parenchymal destruction in the SMP30Y/– mice.[15] Protein carbonyl, a marker of oxidative stress that increases with aging, was also significantly increased after 8 weeks of exposure to cigarette smoke. Thus, SMP30 protects mice lungs from oxidative stress associated with aging and smoking.