transactions

Accelerated lung aging: a novel pathogenic mechanism of chronic obstructive pulmonary disease (COPD)

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Abstract

An enhanced or abnormal inflammatory response to the lungs to inhaled particles and gases, usually from cigarette smoke, is considered to be a general pathogenic mechanism in COPD (chronic obstructive pulmonary disease). Activation of leucocytes and the development of oxidant–antioxidant and protease–anti-protease imbalances are thought to be important aspects of this enhanced inflammatory response to cigarette smoke. The mechanisms involved in the perpetuation of the inflammatory response in the lungs in patients who develop COPD, even after smoking cessation, are not fully established and are key to our understanding of the pathogenic mechanisms in COPD and may be important for the development of new therapies. There is a relationship between chronic inflammatory diseases and aging, and the processes involved in aging may provide a novel mechanism in the pathogenesis of COPD. There is good evidence linking aging and COPD. During normal aging, pulmonary function deteriorates progressively and pulmonary inflammation increases, accompanied in the lungs by the features of emphysema. These features are accelerated in COPD. Emphysema is associated with markers of accelerated aging in the lungs, and COPD is also associated with features of accelerated aging in other organs, such as the cardiovascular and musculoskeletal systems. Cigarette smoke and other oxidative stresses result in cellular senescence and accelerate lung aging. There is also evidence that anti-aging molecules such as histone deacetylases and sirtuins are decreased in the lungs of COPD patients, compared with smokers without COPD, resulting in enhanced inflammation and further progression of COPD. The processes involved in accelerated aging may provide novel targets for therapy in COPD. The present article reviews the evidence for accelerated aging as a mechanism in the pathogenesis of COPD.

Introduction

COPD (chronic obstructive pulmonary disease) represents a major health problem which affects over 5% of the population over the age of 40 [1]. It causes considerable morbidity in those who suffer from it, and is associated with substantial mortality, with more than 30000 deaths in the U.K. per annum. Its morbidity, mortality and social and health care costs are projected to increase in the next two decades as the population continues to age [2]. The condition is characterized by chronic airflow limitation, as measured by the forced expiratory volume in 1 s (FEV_1), which progresses slowly but at an accelerated rate compared with the normal age-related decline in FEV_1. Current therapies can improve symptoms, particularly breathlessness, exercise tolerance and reduce attacks or exacerbations of the disease, but their effects are limited, and no treatments have been shown to reduce disease progression. There are a plethora of hypotheses relating to the pathogenesis of COPD [3] and we do not fully understand the basic mechanisms involved in the pathogenesis of COPD. However, a central feature is the change from the 'normal' inflammatory response to cigarette smoke in the lungs, which occurs in all smokers [4], to the enhanced or abnormal innate and adaptive immune responses in the lungs which characterize the development of COPD [5]. Two processes are considered to be important pathogenic mechanisms as part of this abnormal inflammatory response. These are a protease–anti-protease [6] and an oxidant–antioxidant imbalance [7] driven by the influx of inflammatory leucocytes (neutrophils and macrophages), as part of an enhanced innate inflammatory response and by lymphocytes which form part of the enhanced adaptive immune response [8]. Together with pro-inflammatory cytokine production and other inflammatory and immune responses, these processes result in apoptosis and failure of repair mechanisms, which result in the alveolar destruction in emphysema and remodelling of the small airways [9].

The mechanisms which result in the persistence of chronic inflammation in the lungs in COPD patients, even in the absence of the initiating factor of cigarette smoke, are not well established, but recent evidence suggests that this may

Key words: aging, chronic obstructive pulmonary disease (COPD), emphysema, oxidative stress, pathogenesis.

Abbreviations used: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; HDAC, histone deacetylase; MMP, matrix metalloproteinase; NF-κB, nuclear factor κB; PBL, peripheral blood leucocyte; SA-β-gal, senescence-associated β-galactosidase; SIRT1, sirtuin 1; SMP30, senescence marker protein 30; TL, telomere length; TNFα, tumour necrosis factor α.

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involve epigenetic mechanisms and mechanisms involved in cellular senescence which are also involved in aging. There are features of accelerated aging in COPD patients, particularly in the emphysematous phenotype of COPD. In addition, COPD is associated with systemic features such as increased risk of cardiovascular disease and osteoporosis, which also may be linked to accelerated aging. This, together with the fact that the presence of COPD is age-dependent, suggests a close relationship between the pathogenesis of COPD and aging processes [9,10].

Aging and cellular senescence

Aging or senescence has been defined as the progressive decline in homoeostasis which occurs after the reproductive phase of life and leads to increasing risk of disease or death. Biological aging, although normally linked to chronological age, can occur earlier in life and is thought to result from a failure of organ or cell maintenance or repair, particularly a failure to protect DNA against oxidative injury [11]. Thus aging results from an accumulation of molecular damage. The resulting cellular defects can in turn enhance inflammation and so worsen existing damage. Cellular aging, or senescence, results in a series of alterations in cell morphology and function, including the loss of proliferative activity, so-called proliferative/replicative senescence. A number of molecular and cellular mechanisms are associated with cellular senescence, including accumulation of DNA damage [12], impairment of DNA repair [13], epigenetic modifications in nuclear DNA [14], increased production of free radicals and protein damage [15], and telomere attrition [16]. Cellular senescence and cell arrest not only occur after exhaustion of a predetermined proliferative capacity (intrinsic senescence), but also can be induced by external stresses, such as oxidative stress.

Clinical evidence of accelerated aging in COPD

Several clinical observations support the hypothesis that accelerated aging may play a role in the pathogenesis of COPD. Lung function declines with age in healthy individuals and this is accelerated in patients with COPD [17]. COPD preferentially affects elderly individuals, with those >65 years having a higher disease rate than younger groups, independent of their history of exposure to tobacco smoke. The aging lung shows progressive distal air space enlargement, with loss of gas-exchanging surface area and the support of the alveolar attachments for peripheral airways [18]. Although these structural changes are thought to be non-destructive, in contrast with smoking-induced emphysema [19], they do have functional consequences, resulting in a loss of elastic recoil of the lungs, an increase in residual volume and functional residual capacity or over-inflation of the lungs. In addition, there is associated elastin fibre fragmentation [18,20]. This loss of elastin fibres is similar to that which occurs with aging in the skin, resulting in loss of elasticity and skin wrinkling which is enhanced by smoking [21]. Interestingly, the degree of skin wrinkling correlates with quantitative measurements of emphysema by CT (computed tomography) scanning [22]. Thus cigarette smoking produces elastolysis both in the lungs and systemically in the skin [23], suggesting that cigarette smoke may accelerate the aging process [24].

Cigarette smoking also results in cellular senescence. *In vitro* exposure of human epithelial cells [25] or lung fibroblasts [26] results in an increased expression of SA-β-gal (senescence-associated β-galactosidase), a marker of cellular senescence. Interestingly, cultured lung fibroblasts from patients with emphysema also show increased expression of SA-β-gal compared with those from healthy smokers [27,28]. Furthermore, the proliferative capacity of lung fibroblasts is reduced in patients with emphysema compared with control smokers, which is an indication of cellular senescence.

Cigarette smoking is an important risk factor in many age-related diseases (including COPD) and is associated with increased systemic inflammation and oxidative stress [7,29]. This is thought to contribute to the extrapulmonary manifestations of COPD, such as muscle wasting, cardiovascular disease and osteoporosis [30], which are interestingly also characteristics of aging [31]. These observations are compatible with COPD as a syndrome of accelerated aging.

Mechanisms of cellular senescence and aging in COPD

Telomeres

Telomeres are regions at the ends of chromosomes containing 5–10 kb of (TTAGGG) repeats [32], which protect DNA against degradation and recombination, thus supporting chromosomal stability [33]. In most somatic cells, telomeres shorten with every cell cycle because of the difficulty in priming DNA synthesis by DNA polymerase in this region. When telomeres reach a critical length, cell senescence is induced [34]. Oxidative stress and chronic inflammation enhance telomere shortening [35]. TL (telomere length) therefore reflects the length at birth and its attrition thereafter. The latter is as a result of replication history, but is also a reflection of accumulative oxidative stress and chronic inflammation acting on progenitor cells [34]. TL provides a marker of biological age, at least at the cellular level, shorter telomeres indicating increased biological age. PBLs (peripheral blood leucocytes) are often used to measure TL in humans, and TL in blood leucocytes also accords with that in other tissues [36]. PBL TL decreases with aging, on average by 20–60 bp per year [37]. Shorter telomeres in blood leucocytes correlate with poor survival [36,38].

Interestingly, there is a dose-dependent relationship between leucocyte TL and years smoked [39]. Furthermore, alveolar epithelial and endothelial cells [40] and fibroblasts [27] in emphysematous patients' lungs exhibit shorter telomeres compared with those from non-emphysematous subjects. Recent data also indicates that telomeres in circulating leucocytes from patients with COPD are

shorter compared with control subjects in any age range [41,42].

Proteases and oxidative stress

Oxidative stress is thought to play a critical role in aging [43]. In this free radical theory of aging, reactive oxygen species, formed during normal oxygen metabolism, induce DNA damage, the accumulation of which results in the changes of aging. Mitrochondrial dysfunction results in the production of reactive oxygen species by the respiratory chain, which can directly damage mitrochondrial DNA and contribute to aging [44]. In addition, mitrochondria can have indirect effects on cell survival, e.g. by mediating apoptosis. There is considerable evidence of increased oxidative stress in the lungs in COPD patients [7] which may enhance aging and cellular senescence.

In addition to oxidative stress, a protease–anti-protease imbalance is thought to be an important mechanism in the pathogenesis of COPD [6]. Peripheral blood monocytes and alveolar macrophages from COPD patients show an enhanced release of proteinases, such as MMP (matrix metalloproteinase) 9 [45,46]. MMPs are implicated in the development of emphysema [7] and are also implicated in the degradation of collagen in the skin in smokers [47] and in age-related remodelling of vascular walls [48].

Anti-aging molecules

Several anti-aging molecules may influence the aging process and may have relevance in the pathogenesis of COPD. SMP30 (senescence marker protein 30) is a 34 kDa protein, expressed in the liver and kidney, which increases in early life and progressively decreases with age [49]. *SMP30*$^{-/-}$ mice show decreased protection against TNFα (tumour necrosis factor α)-mediated liver apoptosis [50], decreased lifespan [51] and alveolar apoptosis and enlargement indicative of emphysema [52]. Consistent with the role of oxidative stress in aging [53] the lungs of *SMP30*$^{-/-}$ mice show age-dependent increases in protein carbonylation, a marker of oxidative stress. Chronic exposure of *SMP30*$^{-/-}$ to cigarette smoke results in a greater degree of emphysema compared with wild-type mice exposed to cigarette smoke [54], suggesting that aging in this model directly enhances the lung injury produced by cigarette smoke.

The *klotho* gene encodes a membrane protein that is a regulator of oxidative stress and cell senescence [55]. Mice with a defect in the *klotho* gene have a short lifespan, develop a syndrome resembling aging [56], with arteriosclerosis, skin atrophy, osteoporosis and emphysema [57]. The development of emphysema in mice with a defect in the *klotho* gene is associated with activation of MMP9 in the lungs [58], which has also been implicated in smoking-induced emphysema [6]. This *klotho* gene protein product has been shown to be down-regulated in PBLs in healthy elderly subjects and in chronic inflammatory diseases such as rheumatoid arthritis [59]. The role of klotho protein in COPD has not yet been determined.

Metabolic NAD^+-dependent histone/protein deacetylases (sirtuins) play an important role in a variety of processes, including stress resistance, metabolism, apoptosis, senescence, differentiation and aging [60]. Sirtuins are type III HDACs (histone deacetylases) and are structurally different from other HDACs and are inhibited by different compounds [61]. HDACs act on histone residues in DNA and thereby mediate gene silencing. SIRT1 (sirtuin 1) is essential for maintaining silent chromatin via the deacetylation of histones, but also regulates NF-κB (nuclear factor κB)-dependent transcription and cell survival in response to TNFα [62]. Activation or overexpression of SIRT1 increases the lifespan of a number of species [63]. Environmental stress, such as cigarette smoke exposure, decreases SIRT1 levels in both macrophages *in vitro* and rat lungs *in vivo*, associated with increased inflammatory cytokine expression [64]. SIRT1 has recently been shown to be reduced in lung cells from COPD patients as a result of post-translational oxidative modification by cigarette-smoke-derived components, leading to increased acetylation and enhanced inflammatory responses to cigarette smoke [65]. Thus SIRT1 may have an important role in the regulation of inflammation as well as being involved in aging and in the pathogenic mechanisms in COPD. In addition to sirtuins, HDAC2 (a type I HDAC) has also been reported to be an anti-aging molecule. Thus knockdown of HDAC2 induces cellular senescence by enhancing p53-dependent transrepression and transactivation of target genes [66]. HDAC2 has been shown to be reduced in the lungs of COPD patients compared with smokers who have not developed the disease [67,68]. Down-regulation of HDAC2 results in deacetylation of histone residues, unwinding of DNA and access of transcriptional factors such as NF-κB and also RNA polymerase to the transcription machinery, resulting in transcription of pro-inflammatory genes and inflammation [69].

Histone modifications are also implicated in cell senescence. Cell-cycle progression is controlled via CDKs (cyclin-dependent kinases) and their inhibitors such as $p16^{INK4a}$ and $p21^{Cip1/Waf1}$. Before senescence, cells inhibit an increase in $p21^{Cip1/Waf1}$, which decreases when the cells reach senescence, whereas expression of $p16^{INK4a}$ increases and is thought to be responsible for the final irreversible proliferation [70]. Thus $p21^{Cip1/Waf1}$ can initiate senescence which is primarily telomere-dependent, which is then maintained by $p16^{INK4a}$. It has been shown that endothelial cells and alveolar type II cells in lungs of emphysematous patients have an increased expression of $p16^{INK4a}$ and $p21^{Cip1/Waf1}$ [40,71]. Mice exposed to cigarette smoke *in vivo* and human cells exposed *in vitro* have increased expression of $p21^{Cip1/Waf1}$ [71]. In addition, increased expression of $p16^{INK4a}$ and $p21^{Cip1/Waf1}$ can also be shown by exposure of human fibroblasts to cigarette smoke [72]. The expression of $p16^{INK4a}$ and $p21^{Cip1/Waf1}$ is at least partially controlled through histone acetylation within promoter regions [73]. This suggests a role for HDAC inhibition in senescence by controlling both $p16^{INK4a}$ and $p21^{Cip1/Waf1}$. Increased $p21^{Cip1/Waf1}$ transcription through HDAC inhibition is linked to increased histone H3 acetylation in that region [74,75]. Elevated global acetylation of histone H3 has been detected in the lungs of ex-smokers with COPD [67] and of histone H4 in current smokers [68].

In addition, the lungs from rats exposed to cigarette smoke also show increased histone acetylation [71]. Thus these modifications of histones are important in cell senescence associated with emphysematous lungs.

Conclusions

There has been a recent focus of interest on the mechanisms of aging and cellular senescence and their role in the development of chronic diseases, including COPD. The links between signs of aging in smokers and patients with COPD, particularly those with emphysema, are striking. A number of animal models and exposure of human cells *in vitro* provide evidence that cigarette smoking results in cellular senescence. Markers of cell senescence and accelerated aging can be found in both lung cells and circulating leucocytes in patients with COPD. Anti-aging molecules have also been shown to be decreased in the lungs of COPD patients. There is therefore compelling evidence that mechanisms involved in accelerated aging processes are involved in the pathogenesis of COPD. Targeting these processes will lead to new therapeutic interventions for this condition.

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