The Ageing Lung

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Ageing is characterised by a progressive degeneration of the tissues that has a negative impact on the structure and function of vital organs and contributes to an incremental risk of disease and death. Ageing is among the most important known risk factors for most chronic diseases. However, ageing is not a disease itself, but increases vulnerability to disease. All organs tend to lose function with age and this is well described in the lung where there is a progressive decline in lung function after the age of 25. There is increasing evidence that chronic inflammatory conditions such as COPD represent an acceleration of the ageing process.

MECHANISMS OF AGEING

There are a number of cellular and molecular mechanisms that are thought to be involved in the ageing process and determine the ageing phenotype (Figure 1).

In general, ageing is determined by the interaction between injury and repair, and the balance between cell death and cell replacement in order to maintain organ integrity.

A common factor underlying ageing is the accumulation of molecular damage. Two of the main theories of ageing are the free radical theory and the replicative senescence theory.

Figure 1
The processes associated with ageing

PULMONARY EFFECTS OF AGEING

Lung function deteriorates progressively with age, resulting in an increased risk of shortness of breath and an increased prevalence of various pulmonary diseases in older individuals. With age there is progressive...
AGEING AND COPD

COPD and the ageing lung share similar features suggesting that COPD may be a condition of accelerated lung ageing⁴. Fletcher and Peto suggested that there is an accelerated decline in lung function with age of (50-100 ml FEV₁ per year) in susceptible smokers who develop COPD. However, recent studies show considerable individual variability in the decline in FEV₁ in COPD subjects, so that the development of chronic airflow limitation in COPD is not always as a result of an accelerated decline in FEV₁, but can be due, for example, to sub-optimal lung growth in childhood.⁵ This suggests that accelerated lung ageing may be a pathogenic mechanism in some, but not all COPD subjects.

RV is increased and respiratory muscle strength is also decreased in patients with COPD⁶ as also occurs with ageing. Furthermore, there is a good correlation between facial wrinkling, a feature of ageing, and emphysema. The latter is probably due to changes in collagen and elastin degradation both in the skin and the lungs. Moreover, elastin degradation in the skin is related to emphysema and to arterial stiffness in patients with COPD providing a link between skin ageing, COPD and cardiovascular risk.

Noxious inhalants, such as cigarette smoke can accelerate these age-related events in the lung due to increased modification of proteins, reduction in anti-ageing molecules and stimulation of pro-ageing molecules.⁷

Increased oxidative stress, which plays a key role in ageing and in the pathogenesis of COPD, is present in the lungs in COPD patients. Oxidative stress can lead to shortening of telomeres and shortened telomeres are present in current and former smokers compared with non-smokers, with a dose-dependent relationship between telomere length and pack years smoked. Circulating leukocytes from COPD patients have shorter telomeres, compared with control subjects in any age range. In addition parenchymal cells from emphysematous lungs have shortened telomeres, associated with increased cell senescence. Increased markers of cell senescence have been found in Type II epithelial cells and fibroblasts from emphysematous lungs that could contribute to the pathogenesis of COPD. Epithelial and endothelial apoptosis occurs in emphysema and is thought to result in loss of cells from the alveolar walls. Cellular senescence results in the loss of cell proliferation to replace cells lost by apoptosis. Senescent cells show activation of NFκB and consequent release of inflammatory cytokines, thus enhancing inflammation. There is a direct relationship between the extent of cell senescence and the severity of inflammation in emphysematous lungs.⁸

COPD is characterized by suppression of sirtuin expression both in large and small airway epithelial cells as a result of post-translational oxidative modification of the molecule that would also result in enhanced inflammation and cell senescence.⁹ In addition to sirtuins, HDAC2 has been shown to be an anti-ageing molecule that is decreased in the lungs of COPD patients compared with smokers, who have not developed the disease as a result of oxidative modification of the molecule. This would lead to both increased cell senescence and enhanced inflammation as a result of increased histone acetylation and consequent enhanced pro-inflammatory gene expression.¹⁰

CONCLUSIONS

Ageing is among the most important known risk factors for most chronic conditions. There are many similarities between the ageing process in the lungs and COPD. Understanding the mechanisms of ageing may provide novel target for treatment of this condition.

Bibliography