Accelerated ageing in COPD: New insights and targets

COPD is characterised by acceleration of the ageing process in lung parenchyma and airways and is commonly associated with comorbidities, such as cardiovascular and metabolic diseases, which also may share these mechanisms. There is now a much better understanding the signalling pathways and cellular events involved in ageing, including evidence of cellular senescence with telomere shortening, activation of phosphoinositide-3-kinase (PI3K)-mammalian target of rapamycin (mTOR) signalling, impaired autophagy, mitochondrial dysfunction, stem cell exhaustion, epigenetic changes and abnormal microRNA profiles. All of the hallmarks of ageing have now been identified in COPD patients and there is an accumulation of senescent cells in the lungs. It used to be thought that senescent cells were basically inert but it is now evident that they secrete a particular combination of inflammatory proteins, known as the senescence-associated secretory phenotype (SASP), including TNF-α, IL-1β, IL-6, CCL2, CXCL1, CXCL8, TGF-β, MMP-9, all of which are increased in COPD. Removal of senescent cells in old mice prolongs their lifespan and reduces the incidence of age-related diseases, such as cardiovascular disease and chronic kidney disease. COPD patients also show evidence for increased immunosenescence, with senescent CD4+ and CD8+ T lymphocytes (CD28null), which are less able to mount an immune response and associated with autoimmunity. Many of these ageing pathways are driven by chronic oxidative stress, a key driving mechanism of COPD pathology. There is also a reduction in endogenous anti-ageing molecules, which further accelerates the ageing process. Many endogenous anti-ageing molecules have been identified and all appear to be reduced in COPD, including histone-deacetylase-2, Nrf2, Klotho, SMP30. In COPD patients there is a selective reduction in sirtuin-1 and sirtuin-6, which may result in the characteristic changes in the lungs of COPD patients, but also in associated comorbidities. Reduced SIRT1 is linked to defective autophagy, reduced DNA repair, mitochondrial dysfunction, increased activation of inflammatory genes (through increased NF-κB), whereas decreased SIRT6 results in defective Wnt signalling, reduce telomere length and reduced Nrf2 expression.

It is now recognised that micro-RNAs and other non-coding RNAs, play a key role in the dysregulation of signalling pathways in chronic disease. In particular miR-34a has been shown to be an important regulator of SIRT1 and we have shown that it also regulates SIRT6, but not the other 5 sirtuins known. There is a marked increase in miR-34a in COPD lungs and cells, which correlates with reduced SIRT1/6 and increased cellular senescence and is driven by oxidative stress through activation of PI3K/mTOR signalling. By specifically blocking miR-34a with an antagomir, we can restore SIRT1/6 and reduce senescence in COPD small airway epithelial cells.

The same pathways are operative in other diseases of accelerated ageing, including cardiovascular diseases, chronic kidney disease and type 2 diabetes; it may be that these common pathways are coordinated through the release of extracellular vesicles, such as exosomes, which may spread senescence. This may account for the comorbidities of COPD and for multimorbidity. Understanding the molecular mechanisms involved in accelerated ageing has identified novel therapeutic targets and several drugs have already been developed that may reduce the ageing process, as well as lifestyle interventions, such as diet and physical activity. This indicates that in the future new treatment approaches may target the common pathways involved in multimorbidity.
References


