Editorial

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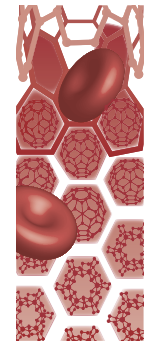

Advancements in nanotherapeutics targeting senescence in chronic obstructive pulmonary disease

Keshav Raj Paudel[‡,1], Meenu Mehta[‡,2], Shakti Dhar Shukla[2,3], Nisha Panth[1], Dinesh Kumar Chellappan[4], Kamal Dua[2,3] & Philip Hansbro*[,1]

[1]Centre for Inflammation, Centenary Institute and University of Technology Sydney, School of Life Sciences, Faculty of Science, Sydney, NSW, 2007, Australia

[2]Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Sydney, NSW, 2007, Australia

[3]Faculty of Health, Australian Research Centre in Complementary & Integrative Medicine, University of Technology Sydney, 2007, Ultimo, Australia

[4]Department of Life Sciences, School of Pharmacy, International Medical University, Bukit Jalil, Kuala Lumpur, 57000, Malaysia

*Author for correspondence: Tel.: +6 012 636 1308; philip.hansbro@uts.edu.au

‡First authors with equal contributions

"Senotherapies are potential new drugs that could be utilized to manage COPD"

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Chronic obstructive pulmonary disease (COPD) is a chronic airway disease. It is characterized by severe inflammation mediated by inflammatory cells such as macrophages, neutrophil influx, emphysema due to loss of alveolar-capillary units, and poorly reversible impairment in lung function [1]. The primary risk factor for COPD is cigarette smoking. Other risk factors include prolonged exposure to firewood/biomass smoke (commonly associated with indoor cooking in developing countries), air pollution such as traffic-related pollution and occupational exposure to coal dust, silica, asbestos and so on [2]. A 2017 report of the Global Burden of Diseases Study states that COPD accounted for 3.2 million deaths, placing it at seventh position for leading cause of years of life lost. Out of 545 million prevalent cases of chronic respiratory diseases (CRDs), approximately 50% were attributed to COPD, and COPD accounted for 81.6 million disability-adjusted life years [3].

The mechanisms of cellular senescence

Cellular senescence is a condition in which cells undergo growth arrest, resulting in premature aging due to continued exposure of the cells to stressful stimuli (both endogenous and exogenous), followed by cellular responses to these stimuli that result in either recovery or death of the cell(s) [4]. Cellular senescence is now well established as a crucial driving factor for COPD progression. Cellular senescence is primarily due to activation of p53 during cell replication and activation of $p16^{INK4a}$ during stress-related senescence, resulting in further activation of $p21^{CIP1}$ and impaired cell cycle process. These aging cells generate various inflammatory proteins, well known as the senescence-associated secretory phenotype, which leads to chronic inflammation and further facilitates senescence [5].

Apart from the activation of endogenous molecules during senescence, there are also important antiaging molecules, such as sirtuins (SIRT)-1 and SIRT-6, as their decreased expression may be pivotal in the promotion of cellular aging. The loss of SIRT function is due to oxidative stress that further reduces the expression of *PTEN* (a tumor suppressor gene) and activates PI3K and mTOR pathways. The PI3K-mTOR signaling pathway regulates *miRNA-34a*, which plays a vital role in reducing SIRT-1/SIRT-6. Therefore, using antagomirs to inhibit *miRNA-34a* can restore SIRT level, reduce the senescence-associated secretory phenotype and reverse cell cycle arrest in airway epithelial cells of COPD patients [6]. Similarly, *miRNA-570* is also associated with decreased expression of SIRT-1 and senescence and is induced by the p38 MAPK pathway. In addition, the potential of *miR-146a* to downregulate

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IRAK1 and TRAF6 promotes the negative feedback regulation for the senescence-associated mediators IL-1β, IL-6 and IL-8 [7]. These miRNAs are carried as cargo in extracellular vesicles, and their uptake by nearby recipient cells can promote senescence during cell-to-cell communication within the lung, hence promoting the progression of chronic lung diseases, including COPD [5]. p16 is another marker of cellular senescence, and its expression has been observed in lung epithelial and endothelial cells of COPD patients. In a study, patients with COPD had remarkably high alveolar type II cells and endothelial cells positive for $p16^{INK4a}$ and p21CIP1/WAF1/Sdi1 as compared with asymptomatic smokers and nonsmokers. Moreover, the length of telomeres in both cell types was notably shorter in COPD patients compared with asymptomatic nonsmokers. The degree of alveolar cell senescence was positively correlated with impairment in airflow [8].

Nanotherapeutics is an emerging medical field that utilizes the applications of nanotechnology in the therapy and diagnosis of a wide range of medical disorders. Nanotherapeutics such as polymeric nanoparticles, liquid crystalline nanoparticles, nanoemulsions, nanogels, nanostructured lipid carriers and dendrimers have recently gained considerable attention due to their versatility in targeting various disease, including respiratory disease [9]. Therefore, nanotherapeutics specifically and effectively targeting the markers of senescence mentioned above (and others) could be a promising approach to the management of COPD progression. These nanotherapies could be designed to achieve a decrease in the senescence markers or to promote the expression of antiaging molecules such as SIRT, to inhibit the PI3K-mTOR pathway, to inhibit specific miRNAs or to delete senescent cells with senolytic therapies. In the last decade or so, our understanding of the aging process has substantially improved, including identification of the molecular pathways involved in the process. Efforts have been made to deepen our knowledge in relation to cellular senescence in COPD. Although it is not feasible to reverse the normal aging process, it is very much possible to target the pathways that lead to or are involved in premature aging, thus slowing COPD progression and possibly associated mortality. Several therapeutic targets have already been recognized, paving the way for the emergence of senotherapies (drugs targeting senescence pathways) [10], which are further classified as either senostatics (senescence developed by oxidative stress) or senolytics (removal of senescent cells). Currently existing drugs such as metformin and rapamycin could very well be repurposed to be tested and used in treating COPD, as these block the PI3K-mTOR signaling pathway, and novel drugs could be produced through screening and rational drug design approaches [11].

Advancements in nanotherapeutics targeting senescence in COPD

Senotherapeutics could be combined with nanotechnological approaches that specifically target the intended cells/pathways in the lungs through a variety of nanocarriers [12]. Nanocarriers have distinct physicochemical properties that improve the bioavailability of the loaded bioactive compound and reduce adverse effects due to untargeted drug action [13]. For example, Agostini and colleagues employed capped mesoporous silica nanoparticles to deliver a cargo (magenta spheres) of galacto-oligosaccharide to senescent cells (X-DC1774 and X-DC4646 cell lines obtained from fibroblasts of X-linked dyskeratosis congenita patients and H460, a human non-small-cell lung cancer cell line) *in vitro* via β-galactosidase (β-gal) activity. Galacto-oligosaccharide is a substrate of the senescent biomarker, senescence-associated-β-gal, and releases the cargo upon entry into senescence-associated-β-gal expressing cells. However, the study failed to demonstrate specific cellular absorption of these nanoparticles by senescent cells after intravenous or subcutaneous delivery. This clearly highlights that senescent cells must be targeted with a mechanism-driven strategy for selective interaction and uptake of nanoparticles [14]. To address this challenge, Zhong and team studied the systemic and lung cellular absorption and bioavailability of poly(amidoamine) (PAMAM) dendrimers. Results showed that PEGylation of dendrimers improved dendrimer mobility through extracellular pulmonary barriers as well as the pulmonary epithelium, allowing dendrimers to reach endothelial cells and the systemic circulation more efficiently. Pulmonary administration resulted in a 52–75-fold increase in dendrimer concentration in lung tissue when compared with intravenous injection [15].

High levels of AMP and ADP in senescent cells may result in the activation of AMPK, which regulates energy-stress responses in the cells. Lewinska *et al.* formulated quercetin-loaded magnetic nanoparticles and assessed their senolytic and senostatic activity in human fibroblasts *in vitro* via oxidative stress-induced senescence. Results showed that the nanoparticles increased AMPK activity and reduced the number of hydrogen peroxide-induced senescent fibroblasts (senolytic activity), as well as suppressing the proinflammatory cascade (reduced secretion of IL-8 and IFN-β) that is associated with senescence (senostatic activity) [16]. This demonstrates that serotherapies, when conjugated with appropriate drug-delivery vehicles, could have meaningful biological effects and potentially translatable clinical benefits.

Mohamed *et al.* developed nanocomposite microparticles containing *miR146a* in order to suppress IRAK1 target gene expression. The study demonstrated that these polymeric nanoparticles downregulated the expression of IRAK1 by 40%, along with decreasing Interleukin-8 secretion [17]. Another study found that fluticasone propionate-loaded solid lipid nanoparticles were superior at controlling cigarette smoke-mediated oxidative stress due to their enhanced absorption and better retention of the drug (about 40% of initial drug loaded) inside the cells. Furthermore, the coated polymer enhanced fluticasone efficacy by inhibiting senescence-related pathways such as survivin expression and ERK1/2 pathway activation [18].

Inhalation of nickel compounds is a well-known occupational threat linked with the development of pulmonary disorders such as lung inflammation, fibrosis and cancer [19]. Therefore, Duan and team prepared nickel oxide nanoparticles and investigated whether SIRT-1–mediated cell death contributed to the cytotoxicity of nanoparticles. These nanoparticles were taken up by bronchial epithelial cells, which then released $Ni2^{+}$. Intracellular $Ni2^{+}$ deposition suppressed SIRT-1 production, which led to increased p53 acetylation on Lys382, resulting in p53 activation, which in turn activates Bax, resulting in cell death [19]. Another potential treatment for COPD could be cerium oxide–based nanoparticles, which have been proposed to treat COPD due to their senostatic activity, that is, their ability to prevent cells from reactive oxygen species (ROS). Cerium can exist in two states: reduced (Ce^{3+}) and oxidized (Ce^{4+}). They display superoxide dismutase mimetic activity by catalyzing superoxide radical anion in the +3 oxidized state, whereas in the +4 reduced state they exhibit catalase activity by degrading H_2O_2 to O_2 and H_2O, shielding the cells from damaging ROS [20].

Although it is too early to state what effects senotherapies could have on COPD, it is very likely that nanocarriers could provide an attractive translational alternative for senescent cells, which could be more efficient in managing COPD than the currently approved drugs.

Conclusion

COPD is considered a disease of the elderly, and the disease itself is associated with accelerated aging, as oxidative stress due to exogenous and endogenous factors increases cellular senescence markers and reduces antiaging molecules. Thus, senotherapies are potential new drugs that could be utilized to manage COPD. Advanced nanotherapeutics are evolving as a promising approach to the management of various diseases, including COPD. As such, these nanotherapeutics may be used to decrease senescence markers such as p16, p21 and p53 and to maintain the baseline level of antiaging sirtuins. Nevertheless, these collective scientific studies performed *in vitro* and *in vivo* in preclinical animal models create a platform on which researchers can further explore the clinical utility of these promising compounds in chronic respiratory disease.

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