Inflammation, ageing and diseases of the lung:

Faniyi, Aduragbemi A.; Hughes, Michael J.; Scott, Aaron; Belchamber, Kylie B. R.; Sapey, Elizabeth

DOI:
10.1111/bph.15759

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Faniyi, AA, Hughes, MJ, Scott, A, Belchamber, KBR & Sapey, E 2021, 'Inflammation, ageing and diseases of the lung: Potential therapeutic strategies from shared biological pathways', *British Journal of Pharmacology*. https://doi.org/10.1111/bph.15759

Received: 27 June 2021 | Revised: 7 October 2021 | Accepted: 8 November 2021

DOI: 10.1111/bph.15759

THEMED ISSUE REVIEW

Inflammation, ageing and diseases of the lung: Potential therapeutic strategies from shared biological pathways

Aduragbemi A. Faniyi | Michael J. Hughes | Aaron Scott | Kylie B. R. Belchamber | Elizabeth Sapey

Birmingham Acute Care Research Group, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK

Correspondence
Elizabeth Sapey, Birmingham Acute Care Research Group, Institute of Inflammation and Ageing, University of Birmingham, Birmingham B15 2GW, UK.
Email: e.sapey@bham.ac.uk

Funding information
Health Data Research UK; Alpha-1 Foundation; British Lung Foundation; National Institute for Health Research; Wellcome Trust; Medical Research Council, Grant/Award Number: MR/S002782/1

Lung diseases disproportionately affect elderly individuals. The lungs form a unique environment: a highly elastic organ with gaseous exchange requiring the closest proximity of inhaled air containing harmful agents and the circulating blood. The lungs are highly susceptible to senescence, with age and 'inflammageing' creating a pro-inflammatory environment with a reduced capacity to deal with challenges. While lung diseases may have disparate causes, the burden of ageing and inflammation provides a common process that can exacerbate seemingly unrelated pathologies. However, these shared pathways may also provide a common route to treatment, with increased interest in drugs that target ageing processes across respiratory diseases. In this review, we will examine the evidence for the increased burden of lung disease in older adults, the structural and functional changes seen with advancing age and assess what our expanding knowledge of inflammation and ageing pathways could mean for the treatment of lung disease.

KEYWORDS
inflammation, lung, mechanics, physiology, senescence, therapeutics

1 | INTRODUCTION

1.1 | The epidemiology of lung disease in the elderly

While age is a risk factor for most diseases, the lungs have been described as the worst affected organ for disease in the elderly (Budinger et al., 2017). Older people are at a greater risk of developing acute and chronic lung diseases and suffer worse outcomes from these conditions.

Approximately 1% of the UK population is diagnosed with community acquired pneumonia (CAP) annually (The National Institute for Health and Care Excellence, 2021). Over 70% of hospital-treated CAP occur in those aged over 65, and the 30-day mortality is approximately 20% in this age group (Daniel et al., 2016; Grudzinska et al., 2017, 2019). Across Europe, the annual incidence of CAP in adults is 1.2 per 1000 person-years but 14 per 1000 person-years in those aged over 65 years (Torres et al., 2013). In the United States, approximately 1.6 million adults are estimated to be hospitalised with CAP with a median age of 68 and a 1-year mortality as high as 30% (Ramirez et al., 2017).

The ongoing coronavirus disease 2019 (COVID-19) pandemic demonstrates the potential impact of respiratory viruses on the

Abbreviations: AATD, α-1 antitrypsin deficiency; AECIIs, alveolar epithelial type II cells; ATF6, activating transcription factor 6; CAP, community acquired pneumonia; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DNMT-1, DNA methyl transferase 1; DQ, dasatinib plus quercetin; ECM, extracellular matrix; ER, endoplasmic reticulum; HDAC, histone deacytelases; IGF-1, insulin-like growth factor 1; IPF, idiopathic pulmonary fibrosis; mTOR, mammalian target of rapamycin; PBMCs, peripheral blood mononuclear cells; PINK1, PTEN-induced kinase 1; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SASP, senescence-associated secretory phenotype; sIgA, secretory IgA; UPR, unfolded protein response.

elderly. To date, there have been 235 million cases and 4.8 million deaths globally with over 73% of deaths occurring in those aged 65 or older (World Health Organisation, 2021). Approximately 70% of hospitalised COVID-19 patients in the United Kingdom are above 50 years, with 80% of deaths seen in those aged over 60 years of age (Escher et al., 2021; Sapey et al., 2020). A similar trend can be seen across Europe where there is a hospitalisation rate and hospitalised case fatality rate of approximately 80% in those over 60 years of age (European Centre for Disease Prevention and Control, 2021). In the United States, 80% of those who have died from COVID-19 are over the age of 65 (Centre for Disease Control and Prevention, 2021a).

The severity of infectious disease depends on the virulence of the infecting organism, the dose or route of infection and the response of the host. Given that exposure to infectious agents may be unchanged or reduced (with potentially less social contact) with advanced age, the increased burden and poorer outcomes seen from both CAP and COVID-19 suggest an increased susceptibility to becoming infected and developing severe disease. Indeed, in a recent systematic analysis across infectious diseases as diverse as tuberculosis, polio, typhoid, influenza, Middle East respiratory syndrome (MERS), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), smallpox, chickenpox, measles, infectious mononucleosis, hepatitis and HIV, a higher prevalence, severity and increased deaths were reported in older adults, with a trend towards poorer outcomes starting after the age of 50 (Glynn & Moss, 2020).

Chronic lung diseases are also more common in older adults. This not only reflects that these diseases are incurable; onset is more common with older age (Li, Cao, et al., 2020). One such example is chronic obstructive pulmonary disease (COPD). The international GOLD group defines COPD as a common, preventable and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation that is due to airways and/or alveolar abnormalities and lung and systemic inflammation (Global Initiative for Chronic Obstructive Lung Disease, 2020). According to the Global Burden of Disease (GBD) study, COPD is already the third leading cause of death worldwide, something that the World Health Organisation had not predicted to occur until 2030 (Lozano et al., 2012), and globally, the burden of COPD is projected to increase because of continued exposure to risk factors and our ageing population. In the United Kingdom, the average age of diagnosis of COPD is 67 years (James et al., 2014). In the absence of screening, symptoms precede diagnostic tests, and the first symptoms suggestive of COPD are often described in patients in their late 40s or early 50s (Yip et al., 2021). The average age of hospitalised patients with COPD in Europe was 70 years, with an average inpatient mortality of 250 deaths per 100,000 inhabitants (Atsou et al., 2011). In the United States, as elsewhere, the death rate for COPD is highest in those aged over 75 years (Thannickal et al., 2015).

A similar pattern is seen with interstitial lung disease (ILD) where the risk of developing it is 6.9 times higher (95% confidence interval [CI]: 5.9–8.0) in those aged over 70 than those in their 40s (Choi et al., 2018). Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing interstitial lung disease with a median survival from diagnosis of 2 to 5 years (Strongman et al., 2018), although the course of the disease is highly variable. IPF is diagnosed mostly in older adults (Strongman et al., 2018), with approximately 75% of those diagnosed aged over 73 years, both in the United Kingdom (British Lung Foundation, 2020) and in the United States (Raghu et al., 2006; Thannickal et al., 2015). In registry studies, the age of symptom onset was reported to be in people aged 60 and over (Hoyer et al., 2019).

Asthma is often considered a disease of children, but mortality is currently greatest in those aged over 55. This group also experience the most symptoms, more severe disease, more emergency presentations and a worse quality of life compared with younger adults (Hoyer et al., 2019; Plaza et al., 2000). The impact of age on pulmonary malignancies has been widely described and will not be discussed further here.

These lung diseases have a huge global economic burden. The annual cost of lung disease in Europe is estimated to be €380 billion with pneumonia accounting for €46 billion and COPD alone accounting for €140 billion (Gibson et al., 2013). In the United States, the annual cost of pneumonia is estimated to be over $17 billion (File & Marrie, 2010), and the annual cost for COPD, $50 billion (Centre for Disease Control and Prevention, 2021b).

Acute, communicable lung diseases such as CAP and COVID-19 have recommended treatment regimes. The mainstay of CAP treatment is anti-microbial agents with national guidelines highlighting the most commonly identified pathogens and their resistance patterns (National Institute for Health and Care Excellence, 2021). Poor responses to these therapies in older patients do not appear to be due to differences in virulence or resistance patterns in different age groups, and in general, our ability to diagnose CAP and initiate supportive treatments has improved (Grudzinska et al., 2020). This suggests that the poorer outcomes are more likely to be due to host responses rather than the insult per se.

In chronic lung diseases, there are treatments to support compromised respiratory function and reduce symptomatic burden, and these appear effective across age groups (Ferguson et al., 2020; Hanania et al., 2021). However, there are few drugs that impact on the biological processes that drive these conditions. Examples of disease-modifying treatments are anti-**IL-5** strategies for asthma. IL-5 is the main mediator of the inflammatory cascade in eosinophilic asthma, exerting its effects by binding to the α chain of the **IL-5 receptor** (IL-5R), and controlling eosinophil development and maturation in the bone marrow, as well as mobilisation. Anti-IL-5 has been shown to be highly effective in subsets of patients with severe asthma and eosinophilia. Although anti-IL-5 was shown to be effective across all age groups, a systematic review of 10 studies demonstrated that, in subjects with a high blood eosinophil count, the efficacy of these therapies were reduced in older patients (Principe et al., 2019).

In summary, older age is associated with an increased susceptibility to lung disease, the outcomes of lung disease are worse and some treatments appear less efficacious in older adults. With our population ageing and diseases of older age likely to become even more common globally, it is important to understand why this is and then mitigate these factors where possible. There are a number of potential

TABLE 1 Summary of common lung mechanics and physiology tests and how they change with increasing age

Lung function measurement	Description	Type of test	Changes with increasing age	Reference
FEV_1	Force expiratory volume = amount of air that can be exhaled in 1 s	Spirometry	Declines with increasing age, leading to longer exhalation and at worst, gas trapping	(Thomas et al., 2019)
FVC	Forced vital capacity represents the amount of air that can be forcibly exhaled after taking the deepest breath	Spirometry	Declines with increasing age, but less so than FEV_1	(Thomas et al., 2019)
FEV_1/FVC	The ratio of FEV_1 to FVC	Spirometry	Declines with increasing age and can become obstructed	(Thomas et al., 2019)
PEF	Peak expiratory flow—The maximum speed at which air can be exhaled from the lungs	Spirometry	Declines with increasing age reflecting airflow obstruction	(Thomas et al., 2019)
TLC	Total lung capacity—Maximum volume of air after maximum inhalation	Lung volume test	Decreases with older age, declining from age 50 onwards	(McClaran et al., 1995; Sharma & Goodwin, 2006)
RV	Residual volume—Volume of air left in the lungs after maximum expiration	Lung volume test	Increased in the elderly. An increased RV reflects an inability to fully empty the lungs due to a stiff chest wall and 'senile hyperinflation' with increased airspace size	(Sharma & Goodwin, 2006)
VC	Vital capacity—Volume of air exhaled after the deepest inhalation	Lung volume test	Decreases with increasing age. Functional residual capacity and residual volume increase with age, resulting in a lower vital capacity	(McClaran et al., 1995; Sharma & Goodwin, 2006)
MV	Minute ventilation—Volume of air inspired per minute	Lung volume over time test	Maintained with age as older people increase the number of breaths taken per minute	(McClaran et al., 1995)
Chest wall compliance	The relative change in volume of the chest wall to change in pressure	Mechanical	Decreases with increasing age. Reduced height of the thoracic vertebrae. Stiffening of the thoracic cage from calcification of the rib cage and age-related kyphosis places the diaphragm at a mechanical disadvantage to generate effective contraction	(Janssens et al., 1999)
Lung compliance	Compliance is change in volume relative to change in pressure in the lung	Mechanical	Increased to unchanged with increasing age due to loss of elastin fibres	(Sharma & Goodwin, 2006)
Respiratory muscle function	Diaphragm strength and maximal inspiratory pressures	Mechanical	Reduced by age and thought to reflect muscle atrophy and age-related decrease in fast twitch fibres	(Polkey et al., 1997)
DLCO	Diffusion capacity for carbon monoxide (gaseous exchange across capillary membrane)	Lung function	Diffusion across the alveolar–capillary interface is inversely proportional to the alveolar–capillary membrane thickness. The DLCO declines with age suggesting alteration with the membrane thickness	(Stam et al., 1994)
PaO_2	Partial pressure of oxygen in arterial blood	Gas diffusion test	Older people demonstrate a 50% reduction in the response to hypoxia	(Ebihara et al., 2016)
$PaCO_2$	Partial pressure of carbon dioxide in the blood	Gas diffusion test	Older people demonstrate a 40% reduction in the response to hypercapnia	(Ebihara et al., 2016)

(Continues)

TABLE 1 (Continued)

Lung function measurement	Description	Type of test	Changes with increasing age	Reference
VO_2 max	Exercise capacity	Exercise test	Maximum oxygen consumption reduces with age, even in the physically active. Reduced heart rate responses, cardiac output and peripheral muscle mass loss may also contribute	(McClaran et al., 1995)

Note: A non-exhaustive list of changes in lung mechanics and physiology with advancing age.
Abbreviations: DLCO, diffusion capacity of carbon monoxide (a measure of the conductance or ease of transfer for CO molecules from alveolar gas to the Hb of the red blood cells in the pulmonary circulation); FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; MV, minute ventilation; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; PEF, peak expiratory flow; RV, residual volume; TLC, total lung capacity; VC, vital capacity; VO_2 max, maximal oxygen consumption.

mechanisms that might make older adults more susceptible to the effects of acute and chronic lung insults and diseases, and these are often host based, including structural changes to the lungs, lung physiology, alterations to inflammatory pathways, changes to how immune cells function and how the host can repair damaged cells and tissues, which are impacted with age. Of importance, these mechanisms are often shared, irrespective of lung disease, offering the potential for shared therapeutic strategies, targeted more at the ageing process rather than the specific lung disease. These will be discussed, below.

2 | INCREASED SUSCEPTIBILITY TO LUNG DISEASE: CHANGES IN LUNG STRUCTURE AND PHYSIOLOGY WITHIN AN AGEING HOST

There are broad structural and functional lung changes that occur during older age (lung senescence) that are implicated in the pathogenesis or progression of acute and chronic lung diseases. The changes impact on every aspect of lung function, reducing the resilience of the host when dealing with challenges. The impact of ageing on lung structure, including senile emphysema, has been recognised for over 60 years (Rappaport & Mayer, 1954), and a number of reviews have commented on the causes and consequences of structural lung changes with age (Janssens et al., 1999; Sharma & Goodwin, 2006), but a non-exhaustive list of changes and potential consequences is described in Table 1. Specific examples include the rate of decline in FEV_1 (being 25–30 ml·year^{-1} from age 35–40 years but doubling to 60 ml·year^{-1} after the age of 70 years) (Sharma & Goodwin, 2006). This would amplify the airflow obstruction seen with COPD or asthma. Another example is the reduction in gas transfer across the alveolar–capillary membrane in old age, which would further exacerbate hypoxia in the presence of pneumonia or diseases of ventilation/perfusion mismatch such as a pulmonary embolus or emphysema (Stam et al., 1994). Further, the reduced response to hypoxia seen in the ageing host (with less compensatory increase in the minute volume) might further exacerbate hypoxia, placing additional strain on end-organs (Polkey et al., 1997). There are known differences in lung function with age by sex (Becklake & Kauffmann, 1999), but less is known about how sex might impact on the mechanisms underlying the ageing lung and therefore will not be discussed further in the context of this review.

3 | PROTECTING THE AIRWAYS

3.1 | Cough reflex and aspirations

As well as the structural and functional changes described above, elderly people may lose protective facets for lung health. This includes the cough reflex and the mucociliary escalator.

The respiratory muscles involved in the cough reflex are weaker in the elderly (Kim et al., 2009). The 'urge to cough' decreases with normal ageing and is severely reduced in the frail elderly, even with strong stimuli (Ebihara et al., 2016). A reduced cough reflex places the person at risk of aspiration. Aspiration is the movement of gastrointestinal content from the mouth or stomach into the respiratory tract, caused by poor swallowing (dysphagia) of food and oropharyngeal secretions. Inflammation is thought to contribute to the risk of chronic aspiration seen in the elderly (Ebihara et al., 2016). It has been proposed that chronic micro-aspiration induces inflammation in the lung and the recruitment of leukocytes to airways containing aspirate, which secrete VEGF-related cytokines and TNF-α, among other mediators (Costa et al., 2007). These elevated inflammatory cytokines are associated with a reduction in muscle mass and strength, termed sarcopenia, which is associated with frailty in the elderly (Wilson et al., 2020). Sarcopenia of swallowing muscles is directly associated with dysphagia and aspiration (Maeda & Akagi, 2016).

Dysphagia is very common among patients with chronic respiratory disease and can manifest as aspiration pneumonia (Verin et al., 2017). Dysphagia is prevalent in COPD, for example, and is associated with frequent exacerbations (Terada et al., 2010).

3.2 | The mucociliary escalator

The epithelial surface of the respiratory tract is continually exposed to pathogens and particulates. In health, the airways produce

approximately 20–30 ml of secretions each day. The airway surfaces are lined by ciliated epithelial cells and covered with an airway surface layer (ASL), which consists of a mucus layer that entraps inhaled particles/foreign pathogens, and a low viscosity periciliary layer (PCL) that lubricates airway surfaces and facilitates ciliary beating to enable mucus clearance (Shei et al., 2018).

Mucociliary clearance decreases with age (Proença de Oliveira-Maul et al., 2013). In elderly individuals, the frequency of cilia beating is slower and the time taken to clear mucus is longer (Ho et al., 2001). Environmental exposure to cigarette smoke (Pavia et al., 1971), pollution (Pedersen, 1990), repeated infections (Look et al., 2001) and chronic lung diseases (Lam et al., 2013) have all been shown to impact on ciliogenesis. The mechanisms underpinning this appear again associated with inflammation and degranulation by recruited immune cells. Neutrophil proteinases, for example, damage ciliated cells (Amitani et al., 1991), leading to DNA damage responses over time (Johnson & Collis, 2016), which hinder the effective replenishment of cilia (which occurs approximately 14 days after injury, usually; Tilley et al., 2015). This process is exacerbated in lung diseases, which are often associated with submucosal gland hypertrophy and goblet cell hyperplasia, impairing mucociliary clearance, leading to mucostasis (Williams et al., 2006). Mucostasis inhibits clearance of inhaled pathogens, which favours microbial lung infection, airway muco-obstruction and a progressive decrease in lung function as well as localised inflammation, the recruitment of immune cells, proteinase degranulation and subsequent damage to other ciliated cells, in a vicious cycle of damage (Lewis et al., 2019).

4 | INCREASED SUSCEPTIBILITY TO LUNG DISEASE: CHANGES IN THE IMMUNE SYSTEM, MICROBIOTA AND TOLERANCE IN AN AGEING HOST

4.1 | The checks and balances of a healthy immune response

The lungs are exposed to approximately 8500 L of air each day and studies describe air holding approximately 10^5 viral or bacterial particles per 1000 L (Prussin et al., 2015), suggesting significant exposure to potential pathogens, without considering other organic and inorganic matter. Particles of less than 3 μm have the capacity to evade the innate structural defences of the lungs and penetrate deep into the small airways and alveoli. Not all these inhaled particles represent a threat to host, and lung health requires a careful balance been immune tolerance and activation. This balance is essential. A diminished response to a potentially pathogenic virus or bacteria may lead to microbial replication and severe infection, leading to lung damage, sepsis and even host death. An exaggerated response to a benign foreign particle can lead to the accumulation of recruited and activated leukocytes. Their activation can result in proteinase and ROS release through leukocyte degranulation, frustrated phagocytosis (so called 'sloppy eating') and release of neutrophil extracellular traps (NETosis), which will lead to the degradation of host tissues, further inflammation and tissue scarring.

When a potentially pathogenic particle reaches the lung tissues, it is exposed to the defence functions of the airway epithelium and submucosa. The airway epithelium can recognise pathogens via a variety of receptors including pattern recognition receptors (PRRs) and then modulate their environment through barrier tightness, secretion of mucus and antimicrobials, and cytokine, chemokine and growth factor production to enable systemic leukocytes to be recruited to the local environment. Secretory IgA (sIgA) is the main antibody found in lung secretions and it has unique structural and functional features not observed in other antibody classes, enabling sIgA to protect the host through immune exclusion and immune activation. Immune exclusion refers to the ability of sIgA to prevent microbial pathogens and antigens accessing the respiratory epithelium through agglutination (essentially clumping of antibody around the pathogen), entrapment in mucus and/or clearance. For example, sIgA can coat and sterically hinder microbial adhesins from interacting with the epithelium as well as inhibiting specific pathogens by direct recognition of receptor-binding domains (Helander et al., 2003). sIgA also mediates bacterial translocation to dendritic cells for immune-mediated responses including those leading to pathogen clearance and those leading to immune tolerance of that specific inhaled particle (Diana et al., 2013).

Alveolar macrophages line the alveoli and interstitium, where they phagocytose organisms and release inflammatory or anti-inflammatory mediators to control immune response (Belchamber & Donnelly, 2020). There is considerable cellular crosstalk involving alveolar macrophages as the resident sentinel immune cell and dendritic cells that project their dendrites into the airway lumen. These mononuclear phagocytes have the ability to take up antigen, process it for presentation on major histocompatibility complex (MHC)-I or II, migrate and effectively activate and polarise naïve T cells. Intra-epithelial lymphocytes (predominantly cytotoxic T cells) are seen between epithelial cells, with CD4+ helper T cells and collections of B lymphocytes organised into follicles known as inducible bronchus associated lymphoid tissue (iBALT), which can initiate protective humoral and T cell responses following infection.

A further facet of lung defence is the lung microbiota. The lung is colonised by microorganisms that maintain a symbiotic relationship with the host, creating an ecological community. In healthy lungs, there is a relatively low bacterial replication rate caused by antimicrobial peptides in mucus, sIgA and resident immune cells, but the microbiota is continually renewed and replaced, with the majority of microbe genera including *Prevotella*, *Streptococcus*, *Veillonella*, *Neisseria*, *Haemophilus* and *Fusobacterium* (Dickson et al., 2016). The microbiome helps maintain the structural integrity of the epithelium. Tight junctions are a critical structure in restricting trans-epithelial permeability. Microbial signals, from the metabolite indole, for example, promote the strength of the epithelial barrier through up-regulation of tight junctions and associated cytoskeletal proteins (Bansal et al., 2010). The microbiota supports the high immune tolerance in the lungs, which is further maintained by alveolar macrophages and dendritic cells, which induce regulatory T cells (Tregs) and

the release of **PGE2**, **TGF-β** and **IL-10** (Hussell & Bell, 2014). Pattern recognition receptors, such as **Toll-like receptors** (TLRs), sense microbial signals during infection and elicit a protective immune response. However, ligands for pattern recognition receptors are also produced by commensal microbiota during healthy colonisation, and here, they enable an immune response that is thought to regulate commensal microbes by preventing over growth, thus maintaining tissue integrity (Rakoff-Nahoum et al., 2004).

When a pathogen is detected and local immune responses require systemic reinforcement, neutrophils respond swiftly to pathogen- and damage-associated molecular pattern molecules (PAMPs and DAMPs), chemokines, cytokines and lipid mediators and are recruited to sites of inflammation, alongside monocytes and other trafficking inflammatory cells. Neutrophils are effective phagocytes, but their granular contents have the ability to cause immense local damage. Figure 1 contains a non-exhaustive overview of the contents of neutrophil granules and their substrates, as examples of the tissue damaging potential of these cells. This is more fully reviewed elsewhere (Hughes et al., 2019).

All of the immune facets described above are impacted by host ageing (termed immunosenescence), impairing the ability to respond as effectively to pathogens and also to tolerate benign inhalants. This has been reviewed in detail elsewhere (Hughes et al., 2019), but three examples are given, below.

The lung microbiota is known to change in composition with age. Lower microbiome diversity and the presence of specific microbial taxa are associated with ageing and decreased lung function in pathogenic disease states. Ageing is associated with a reduction in the relative abundance of *Prevotella*, *Veillonella* and *Leptotrichia* and an increase in *Rothia* and *Lactobacillus*, compared with healthy young adults. In the same study, bacterial density was increased in healthy older adults compared with healthy young adults. During pneumonic events, these differences were exaggerated, with even greater dysbiosis in older patients with CAP (de Steenhuijsen Piters et al., 2016). The results mirror those of studies of the gut microbiome (more easily accessible via stool samples compared with lung washings), where in older, frail adults, a decline in overall microbiome function was noted, with a significant loss in diversity (Rampelli et al., 2013). There are known associations of microbiome dysbiosis and ill-health, including a loss of tolerance, decreased resistance to and reduced containment of potential pathogens, leading to infections such as pneumonia.

While the production of anti-microbial peptides appears to be preserved with age (such as **cathelicidin** and **β-defensin**-2) (Castañeda-Delgado et al., 2013), many facets of the innate immune cell response are altered with ageing. This has been reviewed elsewhere in depth, but in brief, studies have shown that a dysfunction in neutrophils, including inaccurate migration (Sapey et al., 2014, 2017,

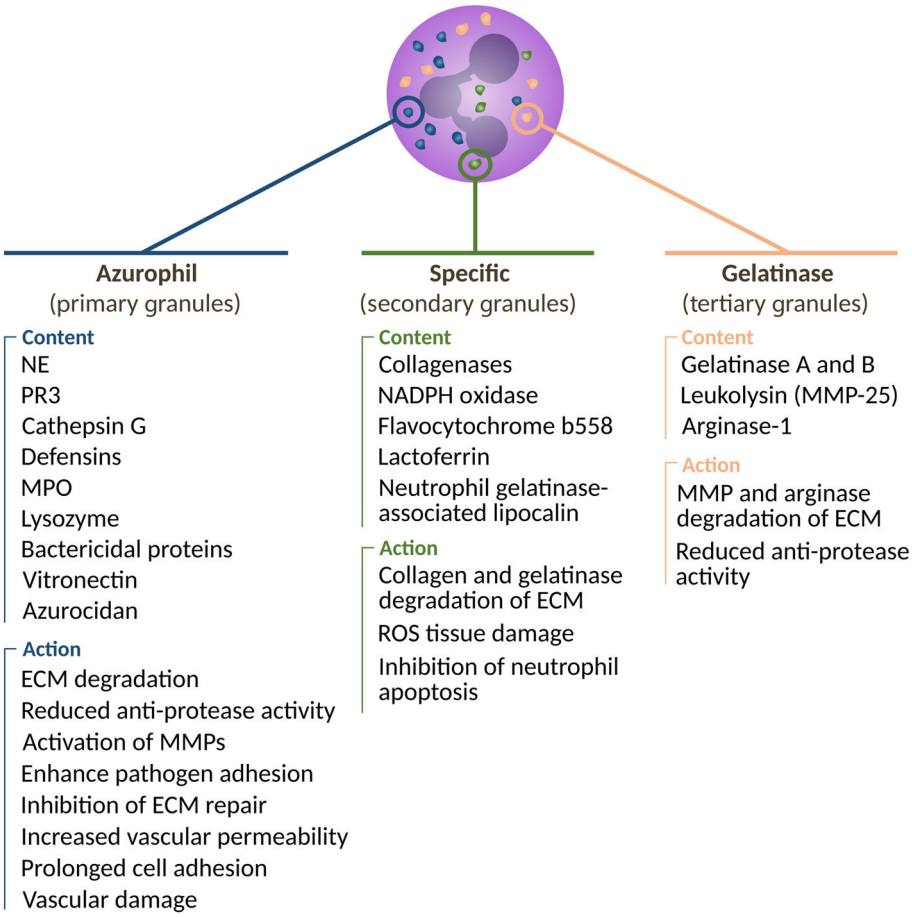

FIGURE 1 Neutrophilic contents and activity. Neutrophils have primary (azurophilic), secondary (specific) and tertiary (gelatinase) granules. The granular contents highlighted are aimed at antimicrobial activity but can cause tissue damage (shown as actions), when released extracellularly. This can lead to excessive inflammation if uncontrolled. ECM, extracellular matrix; MPO, myeloperoxidase; NE, neutrophil elastase; PR3, proteinase 3

2019), reduced phagocytosis of bacteria and impairment in release of neutrophil extracellular traps (NETs) with no reduction and potentially even increased unstimulated ROS release (Hazeldine et al., 2014) in elderly individuals. This dysfunction is again exaggerated in patients with pulmonary infections and appears sustained, lasting at least 6 weeks after the insult (Sapey et al., 2017, 2019). The altered effector functions contribute to excessive inflammation and degranulation, leading to bystander extracellular matrix (ECM) and cellular damage, tissue remodelling and worsening pathology. This damage is especially problematic in the lungs. The elastin and collagen fibre structure of the lung are vital for lung compliance. The elastic fibre is a complex structure that contains at least two morphologically distinguishable components: amorphous elastin and microfibrils. Previous studies have conclusively shown that elastin degradation by leukocyte proteinases is a key and irreversible step in the pathogenesis of COPD. Lung cells cannot repair elastic fibres damaged by elastin degradation (Shifren & Mecham, 2006), and this leads to permanently compromised lung function as elastic tissue is replaced with non-elastic, scar formation.

The adaptive immune system is also compromised in ageing. The relative number of CD8+ T cells decreases with age without a corresponding change in CD4+ T cells; there is also a very pronounced age-dependent loss of CD45RA+ naïve T cells and dysregulation of T-cell/B-cell interactions (Lazuardi et al., 2005). This supports the hypothesis that older people are less able to respond to new pathogens or mount an effective response to pathogens faced before. Further, regulatory T cell function may be impaired in the elderly, reducing immune tolerance and impairing the containment of inflammation.

5 | WHY DO THE LUNGS AGE AND WHAT IS THE EVIDENCE FOR THE HALLMARKS OF AGEING IN LUNG DISEASE?

Certain changes characterise tissue ageing, and these are referred to as the hallmarks of ageing. They include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence (discussed above in brief), stem cell exhaustion and altered intercellular communication (López-Otín et al., 2013). A 10th extrinsic hallmark, dysregulation of ECM, has also been described in lung ageing due to the impact of the inability to replace damaged elastin fibres (Meiners et al., 2015). These hallmarks, though distinct, are interconnected and arise over time as a result of exposure to sources of damage that ultimately result in loss of cellular function and dysregulated tissue homeostasis (Figure 2). Although an emerging field, there is evidence of most of these processes in lung diseases, which most commonly affect the elderly.

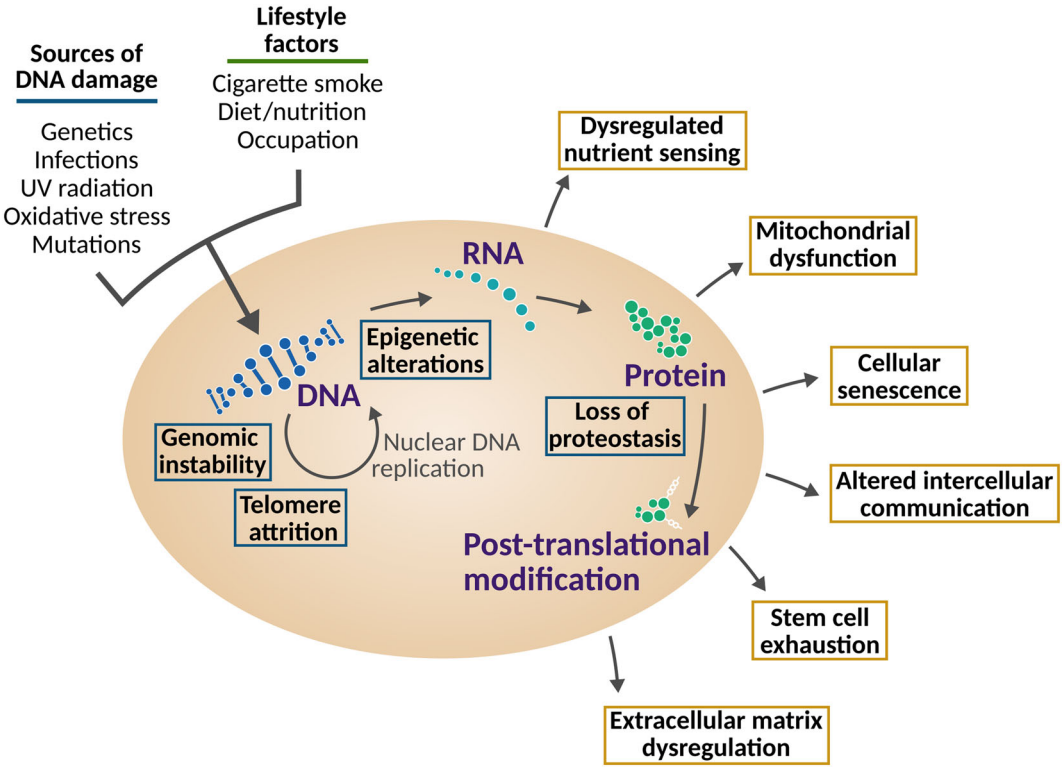

FIGURE 2 The inter-related hallmarks of ageing. Diagrammatic representation of the connection between the hallmarks of ageing that starts with damage to the DNA that can translate to intracellular modifications that affect DNA replication and transcription as well as RNA translation and post-translation modification of proteins. Cellular damage results in dysfunction and altered phenotype, which is represented by the hallmarks outside the cell

1. Genomic instability

Genomic instability is defined as decline in the DNA repair process in response to DNA damage. In murine and human lung tissue, DNA damage accumulates with age (Birch et al., 2015; Lee et al., 1999), indicating that genomic instability is an important feature of normal lung ageing. DNA damage affects both nuclear and mitochondrial DNA, as well as the nuclear architecture (López-Otín et al., 2013).

DNA damage occurs through external stimuli such as infections and environmental pollutants or endogenously through replication errors, ROS-associated damage and spontaneous mutations (López-Otín et al., 2013; Thannickal et al., 2015). For example, *Streptococcus pneumoniae* and influenza virus (both acute respiratory pathogens) have been shown to induce DNA damage in epithelial cells both in vitro and, indirectly, in vivo as determined by increases in γ histone 2AX (γH2AX), a marker of DNA damage (Li et al., 2015).

The mitophagy pathway, phosphatase and tensin homologue (PTEN)-induced kinase 1 (PINK1)–parkin (PARK2), is important in the removal of damaged mitochondrial DNA. Using murine, ex vivo and lung cancer cell line models, deletion of *PARK2* increased chromosomal instability, inflammation and tumour growth, suggesting that genome instability is linked to chronic inflammation and lung cancer (Lee et al., 2016). The E3 ubiquitin ligase, PARK2, is also implicated in COPD, with reduced level shown in COPD lungs and an increase in ROS-induced mitochondrial DNA damage seen in primary human bronchial epithelial cells with reduced expression of PARK2 (Ito et al., 2015).

Patients with non-small cell lung cancer (NSCLC) are also known to have a high rate of DNA damage due to the limitation of their DNA repair processes (Orlow et al., 2008). Transcriptomic analysis shows that genes involved in DNA replication, cell cycle, mismatch repair and p53 signalling pathway are up-regulated in lung cancer and other lung diseases suggesting an overlap of DNA-associated cellular dysfunction across the spectrum of lung disease (Otálora-Otálora et al., 2019).

2. Telomere attrition

Telomeres, through telomerase activity, protect the ends of linear chromosomes thereby ensuring genomic stability and integrity. Telomere attrition is the reduction in the length and function of telomeres through sustained stress created by excessive DNA damage and replication. Most somatic cells do not express telomerase and are therefore susceptible to telomere shortening or damage (López-Otín et al., 2013).

With increasing age, and repeated chromosome replication, telomere length is naturally shortened (Daniali et al., 2013). Advanced age is associated with a higher frequency of cellular proliferative events, and once telomeres have reached a critical length, p53-dependent cell cycle arrest occurs (Saretzki et al., 1999). Telomere length varies from tissue to tissue, with less proliferative tissues such as muscle and fat having longer telomeres while highly proliferative tissues such as skin cells having shorter telomeres (Daniali et al., 2013). In the lung, environmental factors such as cigarette smoke, pollution and repeated infections can increase oxidative stress and inflammation, which accelerates telomere shortening due to increased cellular proliferation and DNA replication in response to damage (Daniali et al., 2013). Indeed, in a recent systematic review of 19 articles assessing pollution and telomere length in adults, both long-term and short-term exposure to PM2.5 showed an inverse association with telomere length, demonstrating the importance of air quality on lung senescence (Miri et al., 2019).

In COPD, telomere shortening appears to be tissue dependent. There are inconsistent reports of telomere shortening in homogenised lung tissue (Birch et al., 2015; Everaerts et al., 2018), but telomeres do appear shortened in circulating leukocytes of COPD patients compared with healthy controls (Rutten et al., 2016; Savale et al., 2009). There is an association between telomere length and declining lung function (Rutten et al., 2016).

Short telomere length is also a feature of IPF, and while it is more common in patients with genetic mutations in the telomerase genes *TERT* and *TERC*, as seen in familial IPF, it can also occur sporadically in individuals without mutations (Courtwright & El-Chemaly, 2019). Alveolar epithelial type II cells (AECIIs) from non-fibrotic areas of patients with sporadic IPF have been shown to have longer telomere compared with fibrotic areas emphasising the association of telomere attrition with fibrosis and the need to assess hallmarks of ageing in specific tissue locations where damage is present (Snetselaar et al., 2017).

3. Epigenetic alterations

Epigenetic alterations are changes in DNA modification processes—DNA methylation, histone modification and chromatin remodelling—that in turn alter DNA function (López-Otín et al., 2013). Normal epigenetic modifications are important for the translational and transcriptional function of DNA. When alterations in the epigenetic process occur, it manifests as transcriptional noise, impairment in DNA repair, irregularity in RNA processing and chromosomal instability (López-Otín et al., 2013). Signals that induce DNA damage such as oxidative stress, infection and cigarette smoke can be a trigger for epigenetic alterations in the lungs.

In COPD, evidence suggests that alteration in the DNA methylation process is a contributing factor to disease pathology. DNA methylation genes in COPD are differentially expressed compared with patients without COPD (Vucic et al., 2014). **Nuclear factor-E2-related factor 2** (Nrf2) drives the expression of numerous cytoprotective genes involved in xenobiotic metabolism, antioxidant responses and anti-inflammatory responses. In COPD, alterations in DNA methylation of genes involved in the Nrf2-mediated oxidative stress response pathway compromise the function of this pathway, enabling a more sustained inflammatory response to ROS, thereby exposing COPD airways to greater ROS-associated damage (Vucic et al., 2014).

Underlying genetic factors such as α-1 antitrypsin deficiency (AATD), which predisposes to COPD but at a younger age and with less/no cigarette smoke exposure, also contribute to epigenetic alterations. AATD patients can be heterogeneous in the age of onset, rate

of decline and clinical manifestation of COPD despite a similar underlying genetic mutation of the *SERPINA1* gene and similar AAT levels present (Sapey, 2020). Heterogeneity of CpG methylation between individuals with AATD may contribute to the varied clinical manifestations of AATD, highlighting the role of epigenetics in disease progression (Wang, Marek, et al., 2019).

Emerging evidence points to histone modification playing a role in the pathophysiology of IPF. Histone acetylation reduces the binding of histone to DNA, which expands chromatin and promotes transcription. Cell free nucleosomes associated with histone modification, HMGB1, mH2A1.1, H3K9Ac and H3K27Ac were significantly lower in IPF patients compared with healthy controls (Guiot et al., 2017).

4. Loss of proteostasis

Misfolded or unfolded proteins are normally refolded through chaperone-mediated pathways or degraded in a process known as proteostasis (López-Otín et al., 2013). Loss of proteostasis is the accumulation of misfolded proteins, often occurring as a result of tissue stress, and is a major contributor to age-related lung disease seen with age (López-Otín et al., 2013).

AATD causes a genetically driven loss of proteostasis with an accumulation of misfolded AAT in hepatocytes and macrophages, leading to low levels of functional AAT and cellular damage (Belchamber et al., 2020) due to endoplasmic reticulum (ER) stress responses. Patients with cystic fibrosis (CF) have a genetic dysfunction in the **cystic fibrosis transmembrane regulator** (CFTR) protein, leading to a decline in lung health, an increased susceptibility to infection, pancreatic dysfunction and infertility (Gibson et al., 2003). Protein misfolding of the **cystic fibrosis transmembrane regulator** results in a build-up of intracellular chloride ions, which is thought to draw in sodium ions and water down electrochemical and osmotic gradients, thickening secretions (Gibson et al., 2003). Environmental stress causing loss of proteostasis can be due to heat shock, ER stress or oxidative stress (López-Otín et al., 2013), all of which can cause acute lung injury by interfering with activity of heat shock proteins and the unfolded protein response (UPR) (Yang et al., 2021). Impaired activity of the UPR to restore homeostasis has been seen in IPF, and this response is a possible target for development of therapies aimed at reducing ER stress (Burman et al., 2018). For example, binding immunoglobulin protein (BiP) keeps the ER proteins of the UPR pathway, protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK), activating transcription factor 6 (ATF6) and inositol requiring enzyme 1α (IRE1α) inactive, but there is evidence of increased expression of binding immunoglobulin protein, a marker of ER stress, in AECII of IPF patients (Burman et al., 2018), suggesting activation of UPR pathway due to ER stress. Crucially, ER stress in AECII appears to contribute to development of fibrosis after lung injury (Burman et al., 2018).

5. Deregulated nutrient-sensing

Nutritional regulation of cell growth, metabolism and proliferation is a central part of normal tissue function. Deregulated nutrient sensing is seen in the elderly and can manifest in the form of altered metabolism and/or increased inflammation.

The insulin and **insulin-like growth factor 1** (IGF-1) pathway, when deregulated, can signal overexpression of **mammalian target of rapamycin** (mTOR) through the PI3K–**Akt** pathway, which in turn can accelerate the ageing of cells (López-Otín et al., 2013). Dietary restriction has been shown to increase life span in several models with this mechanism also evolutionarily conserved (Lang et al., 2019). In murine models of lung disease, mice on restricted calorie diet were recently shown to be protected from pulmonary injury and inflammation when exposed to particulate matter (Li, Chen, et al., 2020). Targeting the nutrient sensing **mTOR** pathway has been shown to reduce pulmonary fibrosis in mice with evidence of a reduction in lung collagen (characteristic of fibrosis) (Korfhagen et al., 2009), and in vitro a reduction in senescence-associated, pro-inflammatory markers in primary endothelial and smooth muscle cells taken from COPD patients (Houssaini et al., 2018).

The IGF/mTOR ageing pathway is linked to other pathways in lung diseases. In COPD, increased ROS leads to hypermetabolism with increased mTOR activation and reduced autophagy, via **Akt** inhibition of **forkhead box** O3A (FOXO3A), further exacerbating senescence and age-related disease progression (Mercado et al., 2015). The heightened metabolism increases the demand for more energy further exacerbating the ROS production and creating oxidative stress. The activity of mTOR also plays a role in maintaining protein homeostasis, perhaps through interaction with the UPR (discussed above) or regulation of autophagy via **forkhead box** O3A. Crucially, mTOR is involved in both pro-inflammatory and anti-inflammatory pathways. Activation by IGF via PI3K/Akt activates the nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) via mTOR resulting in release of pro-inflammatory cytokines. Conversely, **metformin** is believed to exert its anti-inflammatory properties via mTOR perhaps through AMP-activated protein kinase (AMPK) (Mercado et al., 2015). This evidence shows mTOR as a central regulator of metabolism, with importance in maintaining energy and protein homeostasis and regulation of inflammation, confirming why it is a target of novel therapeutics as discussed below.

6. Mitochondrial dysfunction

Mitochondrial dysfunction is the loss of mitochondrial homeostasis that alters the energy creating activity of this organelle. The bioenergetic function of mitochondria can reduce with age due to an accumulation of mutations in mitochondrial DNA, defective mitophagy, electron transport destabilisation and reduced mitochondria replenishment (López-Otín et al., 2013).

In response to ER stress and age, mitochondria in AECIIs were shown to have altered respiration and bioenergetics and impaired fission and fusion using murine and cellular models, with AECIIs from IPF lungs also demonstrating an accumulation of dysfunctional mitochondria (Bueno et al., 2015). Reduced expression of the PINK1, a regulator of mitophagy and mitochondrial homeostasis, was observed in IPF lungs and ER stressed mice with PINK

deficiency showed a pro-fibrotic phenotype (Bueno et al., 2015). Broadly, dysfunction in mitochondria can drive changes in metabolism of lipids, glucose and other nutrients that can promote a fibrotic phenotype in the lung (Bueno et al., 2020). Increased inflammation as a result of mitochondrial response to increased ROS, impaired mitophagy and reduced mitochondrial bioenergetics have all been associated with other lung diseases such as COPD, viral pneumonia and lung cancer (Ahmad et al., 2015; Belchamber et al., 2019; Lupfer et al., 2013).

Mitochondria also play an important role in antioxidant defence against ROS. Despite being a major source of ROS, mitochondria possess antioxidant defence mechanism that helps in maintaining oxidative balance. Reviewed elsewhere (Białas et al., 2016), manganese SOD is the main mitochondria antioxidant enzyme, and peroxide produced by this enzyme from ROS is degraded by catalase. Together with the **GSH** system, manganese SOD and catalase are important in maintaining lung oxidative homeostasis. Oxidative imbalance as a result of mitochondria dysfunction contributes to the pathogenesis of COPD (Białas et al., 2016).

7. Cellular senescence

Immunosenescence has been outlined previously. Cellular senescence refers to the ageing of cells resulting in a deterioration and loss of function. Measurement of senescence is complex and can be difficult to study in vivo, especially in the lungs (Hamsanathan et al., 2019). However, several markers have been used to assess senescence, which generally include senescence-associated β-galactosidase, inflammatory cytokines in the senescence-associated secretory phenotype (SASP) and regulators of cell cycle, cyclin-dependent kinase inhibitors p16 and p21 (Hamsanathan et al., 2019; López-Otín et al., 2013).

Senescent markers have been reported in human lung fibroblasts from IPF patients (Álvarez et al., 2017), while Serpine-1 was shown to increase senescence in AECII (Jiang et al., 2017). Cellular senescence in lung fibroblasts, epithelial and endothelial cells by cigarette smoke is known to contribute to COPD and COPD co-morbidities (Ahmad et al., 2015) and cigarette smoke induces expression of p16 and p21 in a murine model of COPD (Rashid et al., 2018). In aged mice, high lung expression of p16 increases adhesion of bacterial ligands and increases susceptibility to pneumococcal pneumonia (Shivshankar et al., 2011). Logically, the higher population of senescent cells in older people may be a contributing factor to the increased susceptibility to the SARS-Cov-2.

8. Stem cell exhaustion

Stem cell exhaustion refers to depletion of the stem cell reserve due to excessive proliferation and differentiation. In health, the adult lung is relatively quiescent with a slow cell turnover. However, after insult, injury or infection, the lung can rapidly respond, replenishing damaged tissue using tissue-specific lung stem/progenitor cells with self-renewal and differentiation potential (Volckaert & De Langhe, 2014). Studies have shown that the differentiation potential of lung basal stem cells decreases with ageing in human patients (Wang, Lu, et al., 2019).

The **FGF** FGF10–FGFR2B signalling pathway has been shown to help maintain basal cells and can promote differentiation of basal cells to AECIIs, which is important for epithelial regeneration (Yuan et al., 2019). In COPD, airway basal progenitor cells are depleted, have reduced self-renewal and multipotentiality and mostly differentiated to basal and mucus epithelial cells and less to ciliated cells when compared with progenitor cells from non-COPD patients (Ghosh et al., 2018). A lack of ciliated cells can impair mucociliary escalator function in these patients, contributing to mucus retention and airway plugging. Further, evidence from COPD patients describe that airway progenitor variant clones contribute to the squamous and goblet cell metaplasia seen in patients (Rao et al., 2020).

9. Altered intercellular communication

Disruption in immune and metabolic cell signalling pathways is a hallmark of ageing that can result in inflammation, senescence and neuroendocrine dysfunction (López-Otín et al., 2013). It has been recently demonstrated that inhibition of PI3K/Akt can reduce bacterial numbers and pro-inflammatory cytokines in secondary bacterial pneumonia after an initial viral challenge in mice (Yang et al., 2019). Activation of this pathway in COPD peripheral blood mononuclear cells (PBMCs) has also been demonstrated where it contributes to corticosteroid resistance (To et al., 2010). While PI3K inhibition has no effect on phagocytosis of macrophages from COPD patients (Bewley et al., 2016), up-regulation of PI3K, which negatively correlates with phosphatase and tensin homologue (PTEN), increases the release of pro-inflammatory cytokines (Yanagisawa et al., 2017), suggesting that targeting this altered pathway is a potential target for treating age-related lung disease. Interestingly, inhibition of mTOR in PBMCs from COPD patients has shown promise in restoration of corticosteroid sensitivity (Mitani et al., 2016). The NF-κB pathway is also a site of altered cellular communication in lung disease that can lead to increased inflammation.

10. ECM dysregulation

This hallmark of ageing has been proposed specifically for the lungs. The ECM provides support to help maintain lung integrity and biomechanics. Growing evidence suggests that ECM dysregulation is an important hallmark of lung ageing, mostly as a result of proteinase/anti-proteinase imbalance (Meiners et al., 2015). This is exemplified in AATD, where ECM degradation is a hallmark of the disease (Crossley et al., 2019). ECM degradation is closely associated with proteinases, and although neutrophil serine proteinases are the quintessential proteinase for ECM degradation (Butler et al., 2018), others are implicated. For example, the MMP inducer, **CD147**, is elevated in serum of patients with COPD (Berg et al., 2018) and metalloproteinase ECM degradation is seen in COPD with ECM fragments increased in COPD lung (Bihlet et al., 2017).

In IPF, high levels of circulating MMPs and tissue inhibitor of MMPs (TIMPs) suggest high ECM turnover in these patients (Todd et al., 2020). MMPs enhance the development of IPF through dysregulation of ECM homeostasis (Craig et al., 2015). Ongoing advances in the study of ECM in vitro such as the use of decellularized or acellular lung scaffolds could provide valuable avenue towards use of ECM components to reengineer and remodel damaged lung tissue clinically (Wagner et al., 2014).

6 | THERAPEUTICS THAT TARGET THE AGEING PROCESS FOR THE TREATMENT OF LUNG DISEASE

Many therapies in lung diseases treat symptoms, by enhancing bronchodilation or enabling more effective mucus clearance. Some conditions, such as asthma and IPF, have disease-modifying drugs, but these remain limited in scope and available to only a subset of patients.

There has been increasing interest in the concept of multiceuticals or using one treatment to target a central driver of pathology that might be present across a number of disease processes. Drugs that target the hallmarks of ageing might form such a therapeutic strategy for lung disease and could be used across any lung (or other organ) pathology, where they are present. There are a number of approaches under investigation, with three areas described to provide key examples, below.

6.1 | Senolytics and drugs impacting on epigenetic changes

Targeting the senescence pathway in age-related disease is of significant interest and the subject of ongoing therapeutic investigations. Senolytics are drugs that target senescent cells. Ex vivo treatment of fibrotic primary mouse AECIIs with the senolytic drugs **dasatinib** plus **quercetin** (DQ) resulted in a reduction in expression of senescent marker *P16*, an increase in apoptosis and reduction in expression of SASP markers *Mmp12*, *Serpine1* and *Spp1* (Lehmann et al., 2017). An open-label pilot study in 14 IPF patients showed DQ improved physical performance, but this needs to be confirmed in larger randomised control clinical trials (Justice et al., 2019). However, it is promising that DQ has been proven to be effective in reducing senescence burden in a bleomycin mice model of IPF. This landmark study showed that secretome of senescent fibroblasts, which were selectively killed by DQ, was fibrogenic and that DQ-mediated removal of senescent cells improved pulmonary function and physical health, although lung fibrosis was visibly unaltered (Schafer et al., 2017). Findings from a recent open-label trial in patients with diabetic and chronic kidney disease further demonstrate the promise of this drug combination, as it demonstrated a reduction in senescence-associated markers and cells after treatment with DQ (Hickson et al., 2019). Metformin, a drug used for decades to improve diabetes control, has also been shown to inhibit the SASP by interfering with inhibitor of NF-κB kinase (IKK)/NF-κB activation (Moiseeva et al., 2013) and has been shown to exert antifibrotic effects in the lung by inhibiting **TGFβ1** action, suppressing collagen formation and activating PPARγ signalling in lung fibroblasts derived from IPF patients (Kheirollahi et al., 2019).

Targeting underlying epigenetic modifications can help reduce senescence. In a murine bleomycin model of IPF, the inhibition of histone deacetylase using **suberoylanilide hydroxamic acid** (SAHA) (which has been approved for clinical use in cancer) induced apoptosis of IPF-promoting myofibroblasts, an effect that was mediated, at least in part, by up-regulation of the pro-apoptotic gene *Bak* and down-regulation of the anti-apoptotic gene *Bcl-xL* (Sanders et al., 2014). In the same study, **suberoylanilide hydroxamic acid** (SAHA)-treated mice displayed increased lung function compared with the bleomycin-only group (Sanders et al., 2014). Further evidence of epigenetic drugs as novel therapeutics for lung disease has been extensively reviewed (Comer et al., 2015). For instance, the expression of the miRNA miR-17–92 cluster, important in homeostasis of lung epithelial cells, is reduced in IPF lung tissue and fibroblasts with a corresponding increase in expression of DNA methyl transferase 1 (DNMT-1) (Dakhlallah et al., 2013). Treatment with **5′-aza-2′-deoxycytidine**, a demethylating agent, in murine bleomycin IPF model reduced fibrosis and resulted in increased expression of miR-17–92 demonstrating therapeutic potential (Dakhlallah et al., 2013).

In addition, **histone deacytelases** (HDAC) are dysregulated in COPD and the use of quercetin and **theophylline** to up-regulate HDAC has shown some success in both murine and clinical models (Comer et al., 2015). In particular, it was demonstrated that corticosteroid resistance, which can limit the use of steroids as an anti-inflammatory, in COPD patients was ameliorated by treatment with low-dose theophylline by up-regulating HDAC2 activity via inhibition of PI3K δ (To et al., 2010). This suggests that targeting HDAC2 up-regulation can be a useful strategy for COPD patients, especially in patients with steroid resistance where long-term use can be detrimental through physical weight gain and excessive suppression of the immune system.

6.2 | Metabolism and inflammation

Therapies targeting metabolism focus on the mTOR pathway due to its central role in metabolism. Evidence from studies in mice and clinical trials has demonstrated that use of rapamycin, an inhibitor of mTOR, can alleviate the progression of pulmonary fibrosis and the severity of pneumonia (Houssaini et al., 2018; Korfhagen et al., 2009). The use of rapamycin as an adjuvant therapy with corticosteroids significantly improved PaO_2/FiO_2 and lessened the requirement for ventilator support in patients with influenza virus-induced severe pneumonia and acute respiratory failure (Wang et al., 2014). Similar results were obtained in mice showing a reduction in lung injury and viral titres as well as reduced NLRP3 inflammasome activation via inhibition of the mTOR pathway in mice receiving adjuvant therapy with rapamycin and antiviral drugs (Jia et al., 2018). Upstream of mTOR, inhibition of PI3K can improve neutrophil migration in elderly

patients (Sapey et al., 2014). Large randomised clinical trials targeting this pathway in treatment of age-related lung disease would be very useful in providing definitive evidence of their efficacy.

Both steroids and non-steroids anti-inflammatory drugs are used to reduce lung inflammation. Notably, **dexamethasone** was the first drug proven effective at reducing mortality of severe COVID-19 (Horby et al., 2021), with other drugs targeting inflammation now proven to be effective (such as **tocilizumab** and **remdesivir**) and many more under investigation. Our recent study of elderly patients with CAP and sepsis demonstrated that using **simvastatin** as adjuvant therapy improved neutrophil function (chemotaxis and NETosis) and reduced neutrophil elastase in circulation while improving clinical endpoints such as hospital free mortality and SOFA scores (Greenwood et al., 2014; Sapey et al., 2019).

Adjuvant therapy of steroids with PI3K δ inhibitors may also be a useful strategy in treatment of COPD as discussed earlier (To et al., 2010). PBMCs from COPD patients have also been demonstrated to show improved sensitivity to dexamethasone after treatment with rapamycin (Mitani et al., 2016). The use of steroids with adjuvant therapy may prove useful in the elderly as steroid use in this patient group requires caution due to side effects such as delirium, confusion, agitation and the presence of other co-morbidities.

6.3 | Stem cells

Advanced therapies such as stem cells targeting regeneration and tissue repair remain a subject of increasing research. In particular, in a preclinical model of acute respiratory distress syndrome, mesenchymal stem cells (MSCs) have been shown to reduce inflammation and increase expression of alternate macrophage markers (Morrison et al., 2017) that function in tissue repair and homeostasis. Sun et al. (2018) reviewed mesenchymal stem cells in COPD, with some evidence of efficacy in reducing inflammation in preclinical models of COPD; however, clinical trials are yet to show similar efficacy, although they have been proven safe in clinical studies. Mesenchymal cell therapy is expensive, has limited availability and may not form a treatment that can be provided at scale to many individuals with a chronic illness on a repeated basis. However, if the application of stem cells can reverse organ damage or stop further damage following a single or limited number of cycles of therapy, there is great potential for its use.

7 | CONCLUDING REMARKS

Our population is ageing and there is a pressing need to ensure old age is associated with good health, not only for the individual but also for society, to support economies and ensure healthcare and social care services are sustainable and resilient. Age is associated with multi-morbidity and many of these conditions are driven by the hallmarks of ageing. The lungs appear particularly prone to age-associated tissue damage leading to dysfunction, and lung diseases are common with advancing age. Traditional management of chronic lung diseases aim for symptom management with a small number of disease-modifying drugs for which there is limited access for specific groups of individuals. Treatments for acute lung infections, such as antibiotics, are not always effective in the elderly. More therapeutic options are urgently needed to reduce both mortality and morbidity and preserve lung function.

A new way of tackling these conditions may be to focus on shared underlying mechanisms. Here, one therapy might address a number of pathological outputs potentially within the same disease, the same organ and maybe across damaged organs within the host. The hallmarks of ageing have been described in many age-related illnesses including lung diseases. These result in immunesenescence, dysfunctional metabolism and excessive inflammation, all of which have been linked to lung damage. There is already some evidence that targeting ageing can impact positively on aspects of lung disease, with preclinical and early phase clinical studies demonstrating clinical benefit. There are a suite of clinical therapies (both novel and repurposed) being investigated within this field. Should these be successful, it is likely that drugs targeting ageing will improve multi-morbidity and increase the percentage of people who experience healthy ageing. With lung disease increasing globally, targeting ageing pathways to reduce the burden of age-related lung disease may offer therapeutic hope.

7.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22 (Alexander, Christopoulos, et al., 2021; Alexander, Cidlowski, et al., 2021; Alexander, Fabbro, et al., 2021a, 2021b; Alexander, Kelly, et al., 2021; Alexander, Mathie, et al., 2021).

ACKNOWLEDGEMENTS

AAF is funded by the Medical Research Council (MRC; MR/S002782/1), MJH is funded by the Wellcome Trust, AS is funded by the National Institute for Health Research (NIHR) and British Lung Foundation, KBRB is funded by the Alpha-1 Foundation and ES is funded by the NIHR, Alpha 1 Foundation, MRC and Health Data Research UK (HDR UK).

CONFLICT OF INTEREST

The authors declare no relevant conflicts in reference to this article.

AUTHOR CONTRIBUTIONS

AAF, MJH, AS, KBR and ES all wrote the manuscript. ES finalised the manuscript and edited prior to submission.

ORCID

Aduragbemi A. Faniyi https://orcid.org/0000-0003-1670-1680
Elizabeth Sapey https://orcid.org/0000-0003-3454-5482

REFERENCES

Ahmad, T., Sundar, I. K., Lerner, C. A., Gerloff, J., Tormos, A. M., Yao, H., & Rahman, I. (2015). Impaired mitophagy leads to cigarette smoke stress-induced cellular senescence: Implications for chronic obstructive pulmonary disease. *The FASEB Journal*, *29*(7), 2912–2929.

Alexander, S. P. H., Christopoulos, A., Davenport, A. P., Kelly, E., Mathie, A., Peters, J. A., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., & Pawson, A. J. (2021). THE CONCISE GUIDE TO PHARMACOLOGY 2021/22: G protein-coupled receptors. *British Journal of Pharmacology*, *178*(S1), S27–S156.

Alexander, S. P. H., Cidlowski, J. A., Kelly, E., Mathie, A., Peters, J. A., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., Pawson, A. J., & Southan, C. (2021). THE CONCISE GUIDE TO PHARMACOLOGY 2021/22: Nuclear hormone receptors. *British Journal of Pharmacology*, *178*(S1), S246–S263.

Alexander, S. P. H., Fabbro, D., Kelly, E., Mathie, A., Peters, J. A., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., Pawson, A. J., & Southan, C. (2021a). THE CONCISE GUIDE TO PHARMACOLOGY 2021/22: Catalytic receptors. *British Journal of Pharmacology*, *178*(S1), S264–S312.

Alexander, S. P. H., Fabbro, D., Kelly, E., Mathie, A., Peters, J. A., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., Pawson, A. J., & Southan, C. (2021b). THE CONCISE GUIDE TO PHARMACOLOGY 2021/22: Enzymes. *British Journal of Pharmacology*, *178*(S1), S313–S411.

Alexander, S. P. H., Kelly, E., Mathie, A., Peters, J. A., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., Pawson, A. J., Southan, C., & Buneman, O. P. (2021). THE CONCISE GUIDE TO PHARMACOLOGY 2021/22: Introduction and other protein targets. *British Journal of Pharmacology*, *178*(S1), S1–S26.

Alexander, S. P. H., Mathie, A., Peters, J. A., Veale, E. L., Striessnig, J., Kelly, E., Armstrong, J. F., Faccenda, E., Harding, S. D., Pawson, A. J., & Southan, C. (2021). THE CONCISE GUIDE TO PHARMACOLOGY 2021/22: Ion channels. *British Journal of Pharmacology*, *178*(S1), S157–S245.

Álvarez, D., Cárdenes, N., Sellarés, J., Bueno, M., Corey, C., Hanumanthu, V. S., Peng, Y., D'Cunha, H., Sembrat, J., Nouraie, M., & Shanker, S. (2017). IPF lung fibroblasts have a senescent phenotype. *American Journal of Physiology. Lung Cellular and Molecular Physiology*, *313*(6), L1164–l73.

Amitani, R., Wilson, R., Rutman, A., Read, R., Ward, C., Burnett, D., Stockley, R. A., & Cole, P. J. (1991). Effects of human neutrophil elastase and *Pseudomonas aeruginosa* proteinases on human respiratory epithelium. *American Journal of Respiratory Cell and Molecular Biology*, *4*(1), 26–32.

Atsou, K., Chouaid, C., & Hejblum, G. (2011). Variability of the chronic obstructive pulmonary disease key epidemiological data in Europe: Systematic review. *BMC Medicine*, *9*, 7–10.

Bansal, T., Alaniz, R. C., Wood, T. K., & Jayaraman, A. (2010). The bacterial signal indole increases epithelial-cell tight-junction resistance and attenuates indicators of inflammation. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(1), 228–233.

Becklake, M. R., & Kauffmann, F. (1999). Gender differences in airway behaviour over the human life span. *Thorax*, *54*(12), 1119–1138.

Belchamber, K. B. R., & Donnelly, L. E. (2020). Targeting defective pulmonary innate immunity - a new therapeutic option? *Pharmacology & Therapeutics*, *209*, 107500.

Belchamber, K. B. R., Singh, R., Batista, C. M., Whyte, M. K., Dockrell, D. H., Kilty, I., Robinson, M. J., Wedzicha, J. A., Barnes, P. J., & Donnelly, L. E. (2019). Defective bacterial phagocytosis is associated with dysfunctional mitochondria in COPD macrophages. *The European Respiratory Journal*, *54*(4), 1802244. https://doi.org/10.1183/13993003.02244-2018

Belchamber, K. B. R., Walker, E. M., Stockley, R. A., & Sapey, E. (2020). Monocytes and macrophages in alpha-1 antitrypsin deficiency. *International Journal of Chronic Obstructive Pulmonary Disease*, *15*, 3183–3192. https://doi.org/10.2147/COPD.S276792

Berg, J., Halvorsen, A. R., Bengtson, M. B., Taskén, K. A., Mælandsmo, G. M., Yndestad, A., Halvorsen, B., Brustugun, O. T., Aukrust, P., Ueland, T., & Helland, Å. (2018). Levels and prognostic impact of circulating markers of inflammation, endothelial activation and extracellular matrix remodelling in patients with lung cancer and chronic obstructive pulmonary disease. *BMC Cancer*, *18*(1), 739–743.

Bewley, M. A., Belchamber, K. B., Chana, K. K., Budd, R. C., Donaldson, G., Wedzicha, J. A., Brightling, C. E., Kilty, I., Donnelly, L. E., Barnes, P. J., & Singh, D. (2016). Differential effects of p38, MAPK, PI3K or rho kinase inhibitors on bacterial phagocytosis and efferocytosis by macrophages in COPD. *PLoS ONE*, *11*(9), e0163139.

Białas, A. J., Sitarek, P., Miłkowska-Dymanowska, J., Piotrowski, W. J., & Górski, P. (2016). The role of mitochondria and oxidative/antioxidative imbalance in pathobiology of chronic obstructive pulmonary disease. *Oxidative Medicine and Cellular Longevity*, *2016*, 7808576.

Bihlet, A. R., Karsdal, M. A., Sand, J. M., Leeming, D. J., Roberts, M., White, W., & Bowler, R. (2017). Biomarkers of extracellular matrix turnover are associated with emphysema and eosinophilic-bronchitis in COPD. *Respiratory Research*, *18*(1), 22–33.

Birch, J., Anderson, R. K., Correia-Melo, C., Jurk, D., Hewitt, G., Marques, F. M., Green, N. J., Moisey, E., Birrell, M. A., Belvisi, M. G., & Black, F. (2015). DNA damage response at telomeres contributes to lung aging and chronic obstructive pulmonary disease. *American Journal of Physiology. Lung Cellular and Molecular Physiology*, *309*(10), L1124–L1137.

British Lung Foundation. (2020). Idiopathic pulmonary fibrosis (IPF) 2019 [August 6, 2020]. Available from: https://www.blf.org.uk/support-for-you/idiopathic-pulmonary-fibrosis-ipf/causes

Budinger, G. R. S., Kohanski, R. A., Gan, W., Kobor, M. S., Amaral, L. A., Armanios, M., Kelsey, K. T., Pardo, A., Tuder, R., Macian, F., Chandel, N., Vaughan, D., Rojas, M., Mora, A. L., Kovacs, E., Duncan, S. R., Finkel, T., Choi, A., Eickelberg, O., … Thannickal, V. J. (2017). The intersection of aging biology and the pathobiology of lung diseases: A joint NHLBI/NIA workshop. *The Journals of Gerontology. Series a, Biological Sciences and Medical Sciences*, *72*(11), 1492–1500.

Bueno, M., Calyeca, J., Rojas, M., & Mora, A. L. (2020). Mitochondria dysfunction and metabolic reprogramming as drivers of idiopathic pulmonary fibrosis. *Redox Biology*, *33*, 101509. https://doi.org/10.1016/j.redox.2020.101509

Bueno, M., Lai, Y. C., Romero, Y., Brands, J., St Croix, C. M., Kamga, C., Corey, C., Herazo-Maya, J. D., Sembrat, J., Lee, J. S., & Duncan, S. R. (2015). PINK1 deficiency impairs mitochondrial homeostasis and promotes lung fibrosis. *The Journal of Clinical Investigation*, *125*(2), 521–538.

Burman, A., Tanjore, H., & Blackwell, T. S. (2018). Endoplasmic reticulum stress in pulmonary fibrosis. *Matrix Biology*, *68-69*, 355–365.

Butler, A., Walton, G. M., & Sapey, E. (2018). Neutrophilic inflammation in the pathogenesis of chronic obstructive pulmonary disease. *COPD*, *15*(4), 392–404.

Castañeda-Delgado, J. E., Miranda-Castro, N. Y., González-Amaro, R., González-Curiel, I., Montoya-Rosales, A., Rivas-Calderon, B., & Rivas-Santiago, B. (2013). Production of antimicrobial peptides is preserved in aging. *Clinical Immunology*, *148*(2), 198–205. https://doi.org/10.1016/j.clim.2013.05.015

Centre for Disease Control and Prevention. (2021a). Weekly Updates by Select Demographic and Geographic Characteristics 2021 [June 23, 2021]. Available from: https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm#AgeAndSex

Centre for Disease Control and Prevention. (2021b). COPD Costs 2018 [June 5 2021]. Available from: https://www.cdc.gov/copd/infographics/copd-costs.html

Choi, W. I., Dauti, S., Kim, H. J., Park, S. H., Park, J. S., & Lee, C. W. (2018). Risk factors for interstitial lung disease: A 9-year nationwide population-based study. *BMC Pulmonary Medicine*, *18*(1), 96–103.

Comer, B. S., Ba, M., Singer, C. A., & Gerthoffer, W. T. (2015). Epigenetic targets for novel therapies of lung diseases. *Pharmacology & Therapeutics*, *147*, 91–110. https://doi.org/10.1016/j.pharmthera.2014.11.006

Costa, C., Incio, J., & Soares, R. (2007). Angiogenesis and chronic inflammation: Cause or consequence? *Angiogenesis*, *10*(3), 149–166. https://doi.org/10.1007/s10456-007-9074-0

Courtwright, A. M., & El-Chemaly, S. (2019). Telomeres in interstitial lung disease: The short and the long of it. *Annals of the American Thoracic Society*, *16*(2), 175–181.

Craig, V. J., Zhang, L., Hagood, J. S., & Owen, C. A. (2015). Matrix metalloproteinases as therapeutic targets for idiopathic pulmonary fibrosis. *American Journal of Respiratory Cell and Molecular Biology*, *53*(5), 585–600.

Crossley, D., Stockley, R., & Sapey, E. A.-O. (2019). Alpha-1 antitrypsin deficiency and accelerated aging: A new model for an old disease? *Drugs & Aging*, *36* (1179–1969 [Electronic]), 823–840.

Dakhlallah, D., Batte, K., Wang, Y., Cantemir-Stone, C. Z., Yan, P., Nuovo, G., Mikhail, A., Hitchcock, C. L., Wright, V. P., Nana-Sinkam, S. P., Piper, M. G., & Marsh, C. B. (2013). Epigenetic regulation of miR-17∼92 contributes to the pathogenesis of pulmonary fibrosis. *American Journal of Respiratory and Critical Care Medicine*, *187*(4), 397–405. https://doi.org/10.1164/rccm.201205-0888OC

Daniali, L., Benetos, A., Susser, E., Kark, J. D., Labat, C., Kimura, M., Desai, K. K., Granick, M., & Aviv, A. (2013). Telomeres shorten at equivalent rates in somatic tissues of adults. *Nature Communications*, *4*, 1597–1603. https://doi.org/10.1038/ncomms2602

Daniel, P., Woodhead, M., Welham, S., McKeever, T. M., & Lim, W. S. (2016). Mortality reduction in adult community-acquired pneumonia in the UK (2009–2014): Results from the British Thoracic Society audit programme. *Thorax*, *71*(11), 1061–1063.

de Steenhuijsen Piters, W. A., Huijskens, E. G., Wyllie, A. L., Biesbroek, G., van den Bergh, M. R., Veenhoven, R. H., Wang, X., Trzciński, K., Bonten, M. J., Rossen, J. W., & Sanders, E. A. (2016). Dysbiosis of upper respiratory tract microbiota in elderly pneumonia patients. *The ISME Journal*, *10*(1), 97–108. https://doi.org/10.1038/ismej.2015.99

Diana, J., Moura, I. C., Vaugier, C., Gestin, A., Tissandie, E., Beaudoin, L., Corthésy, B., Hocini, H., Lehuen, A., & Monteiro, R. C. (2013). Secretory IgA induces tolerogenic dendritic cells through SIGNR1 dampening autoimmunity in mice. *Journal of Immunology*, *191*(5), 2335–2343. https://doi.org/10.4049/jimmunol.1300864

Dickson, R. P., Erb-Downward, J. R., Martinez, F. J., & Huffnagle, G. B. (2016). The microbiome and the respiratory tract. *Annual Review of Physiology*, *78*, 481–504.

Ebihara, S., Sekiya, H., Miyagi, M., Ebihara, T., & Okazaki, T. (2016). Dysphagia, dystussia, and aspiration pneumonia in elderly people. *Journal of Thoracic Disease*, *8*(3), 632–639.

Escher, M., Hall, M., Baillie, J. K., Baruch, J., Blumberg, L., Carson, G., Citarella, B. W., Dankwa, E. A., Docherty, A., Dryden, M., & Donnelly, C. A. (2021). ISARIC Clinical Data Report 10 February 2021. medRxiv. 2020.07.17.20155218.

European Centre for Disease Prevention and Control. (2021). ECDC COVID-19 surveillance report 2021 [June 4, 2021]. Available from: https://covid19-surveillance-report.ecdc.europa.eu/#3_Risk_groups_most_affected

Everaerts, S., Lammertyn, E. J., Martens, D. S., De Sadeleer, L. J., Maes, K., van Batenburg, A. A., Goldschmeding, R., van Moorsel, C. H., Dupont, L. J., Wuyts, W. A., & Vos, R. (2018). The aging lung: Tissue telomere shortening in health and disease. *Respiratory Research*, *19*(1), 95–105. https://doi.org/10.1186/s12931-018-0794-z

Ferguson, G. T., Maltais, F., Karpel, J., Bothner, U., Kloer, I., Trampisch, M., & Buhl, R. (2020). Long-term safety of tiotropium/olodaterol in older patients with moderate-to-very-severe COPD in the TONADO® studies. *NPJ Prim Care Respir Med.*, *30*(1), 53–62.

File, T. M. Jr., & Marrie, T. J. (2010). Burden of community-acquired pneumonia in North American adults. *Postgraduate Medicine*, *122*(2), 130–141.

Ghosh, M., Miller, Y. E., Nakachi, I., Kwon, J. B., Barón, A. E., Brantley, A. E., Merrick, D. T., Franklin, W. A., Keith, R. L., & Vandivier, R. W. (2018). Exhaustion of airway basal progenitor cells in early and established chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*, *197*(7), 885–896.

Gibson, G. J., Loddenkemper, R., Lundbäck, B., & Sibille, Y. (2013). Respiratory health and disease in Europe: The new European Lung White Book. 2013/09/04 ed2013 Sep. 559-63 p.

Gibson, R. L., Burns, J. L., & Ramsey, B. W. (2003). Pathophysiology and management of pulmonary infections in cystic fibrosis. *American Journal of Respiratory and Critical Care Medicine*, *168*(8), 918–951.

Global Initiative for Chronic Obstructive Lung Disease. (2020). Global strategy for the diagnosis, management, and prevention of Chronic Obstructive Pulmonary Disease. Available from: https://goldcopd.org/gold-reports/

Glynn, J. R., & Moss, P. A. H. (2020). Systematic analysis of infectious disease outcomes by age shows lowest severity in school-age children. *Sci Data.*, *7*(1), 329–342.

Greenwood, H., Patel, J., Mahida, R., Wang, Q., Parekh, D., Dancer, R. C., Khiroya, H., Sapey, E., & Thickett, D. R. (2014). Simvastatin to modify neutrophil function in older patients with septic pneumonia (SNOOPI): Study protocol for a randomised placebo-controlled trial. *Trials*, *15*, 332–338.

Grudzinska, F. S., Aldridge, K., Hughes, S., Nightingale, P., Parekh, D., Bangash, M., Dancer, R., Patel, J., Sapey, E., Thickett, D. R., & Dosanjh, D. P. (2019). Early identification of severe community-acquired pneumonia: A retrospective observational study. *BMJ Open Respiratory Research*, *6*(1), e000438.

Grudzinska, F. S., Brodlie, M., Scholefield, B. R., Jackson, T., Scott, A., Thickett, D. R., & Sapey, E. (2020). Neutrophils in community-acquired pneumonia: Parallels in dysfunction at the extremes of age. *Thorax*, *75*(2), 164–171.

Grudzinska, F. S., Dosanjh, D. P., Parekh, D., Dancer, R. C., Patel, J., Nightingale, P., Walton, G. M., Sapey, E., & Thickett, D. R. (2017). Statin therapy in patients with community-acquired pneumonia. *Clinical Medicine (London, England)*, *17*(5), 403–407.

Guiot, J., Struman, I., Chavez, V., Henket, M., Herzog, M., Scoubeau, K., Hardat, N., Bondue, B., Corhay, J. L., Moermans, C., & Louis, R. (2017). Altered epigenetic features in circulating nucleosomes in idiopathic pulmonary fibrosis. *Clinical Epigenetics*, *9*, 84–91.

Hamsanathan, S., Alder, J. K., Sellares, J., Rojas, M., Gurkar, A. U., & Mora, A. L. (2019). Cellular senescence: The trojan horse in chronic lung diseases. *American Journal of Respiratory Cell and Molecular Biology*, *61*(1), 21–30. https://doi.org/10.1165/rcmb.2018-0410TR

Hanania, N. A., Mannino, D. M., Criner, G. J., Dransfield, M. T., Han, M. K., Jones, C. E., Kilbride, S., Lomas, D. A., Martin, N., Martinez, F. J., & Singh, D. (2021). Effect of age on the efficacy and safety of once-daily single-inhaler triple-therapy fluticasone furoate/umeclidinium/vilanterol in patients with COPD: A post hoc analysis of the informing the pathway of COPD treatment trial. *Chest*, *159*(3), 985–995.

Hazeldine, J., Harris, P., Chapple, I. L., Grant, M., Greenwood, H., Livesey, A., Sapey, E., & Lord, J. M. (2014). Impaired neutrophil extracellular trap formation: A novel defect in the innate immune system of aged individuals. *Aging Cell*, *13*(4), 690–698.

Helander, A., Silvey, K. J., Mantis, N. J., Hutchings, A. B., Chandran, K., Lucas, W. T., Nibert, M. L., & Neutra, M. R. (2003). The viral σ1 protein and glycoconjugates containing α2-3-linked sialic acid are involved in type 1 reovirus adherence to M cell apical surfaces. *Journal of Virology*, *77*(14), 7964–7977.

Hickson, L. J., Langhi Prata, L. G. P., Bobart, S. A., Evans, T. K., Giorgadze, N., Hashmi, S. K., Herrmann, S. M., Jensen, M. D., Jia, Q., Jordan, K. L., & Kellogg, T. A. (2019). Senolytics decrease senescent cells in humans: Preliminary report from a clinical trial of Dasatinib plus Quercetin in individuals with diabetic kidney disease. *eBioMedicine*, *47*, 446–456.

Ho, J. C., Chan, K. N., Hu, W. H., Lam, W. K., Zheng, L., Tipoe, G. L., Sun, J., Leung, R., & Tsang, K. W. (2001). The effect of aging on nasal mucociliary clearance, beat frequency, and ultrastructure of respiratory cilia. *American Journal of Respiratory and Critical Care Medicine*, *163*(4), 983–988. https://doi.org/10.1164/ajrccm.163.4.9909121

Horby, P., Lim, W. S., Emberson, J. R., Mafham, M., Bell, J. L., Linsell, L., Staplin, N., Brightling, C., Ustianowski, A., Elmahi, E., Prudon, B., Green, C., Felton, T., Chadwick, D., Rege, K., Fegan, C., Chappell, L. C., Faust, S. N., Jaki, T., … Landray, M. J. (2021). Dexamethasone in hospitalized patients with Covid-19. *The New England Journal of Medicine*, *384*(8), 693–704. https://doi.org/10.1056/NEJMoa2021436

Houssaini, A., Breau, M., Kebe, K., Abid, S., Marcos, E., Lipskaia, L., Rideau, D., Parpaleix, A., Huang, J., Amsellem, V., Vienney, N., & Validire, P. (2018). mTOR pathway activation drives lung cell senescence and emphysema. *JCI Insight*, *3*(3), e903203–e903223.

Hoyer, N., Prior, T. S., Bendstrup, E., Wilcke, T., & Shaker, S. B. (2019). Risk factors for diagnostic delay in idiopathic pulmonary fibrosis. *Respiratory Research*, *20*(1), 103–112.

Hughes, M. J., Sapey, E., & Stockley, R. (2019). Neutrophil phenotypes in chronic lung disease. *Expert Review of Respiratory Medicine*, *13*(10), 951–967.

Hussell, T., & Bell, T. J. (2014). Alveolar macrophages: Plasticity in a tissue-specific context. *Nature Reviews. Immunology*, *14*(2), 81–93.

Ito, S., Araya, J., Kurita, Y., Kobayashi, K., Takasaka, N., Yoshida, M., Hara, H., Minagawa, S., Wakui, H., Fujii, S., Kojima, J., Shimizu, K., Numata, T., Kawaishi, M., Odaka, M., Morikawa, T., Harada, T., Nishimura, S. L., Kaneko, Y., … Kuwano, K. (2015). PARK2-mediated mitophagy is involved in regulation of HBEC senescence in COPD pathogenesis. *Autophagy*, *11*(3), 547–559. https://doi.org/10.1080/15548627.2015.1017190

James, G. D., Donaldson, G. C., Wedzicha, J. A., & Nazareth, I. (2014). Trends in management and outcomes of COPD patients in primary care, 2000–2009: A retrospective cohort study. *NPJ Prim Care Respir Med.*, *24*, 14015. https://doi.org/10.1038/npjpcrm.2014.15

Janssens, J. P., Pache, J. C., & Nicod, L. P. (1999). Physiological changes in respiratory function associated with ageing. *The European Respiratory Journal*, *13*(1), 197–205.

Jia, X., Liu, B., Bao, L., Lv, Q., Li, F., Li, H., An, Y., Zhang, X., Cao, B., & Wang, C. (2018). Delayed oseltamivir plus sirolimus treatment attenuates H1N1 virus-induced severe lung injury correlated with repressed NLRP3 inflammasome activation and inflammatory cell infiltration. *PLoS Pathogens*, *14*(11), e1007428.

Jiang, C., Liu, G., Luckhardt, T., Antony, V., Zhou, Y., Carter, A. B., Thannickal, V. J., & Liu, R. M. (2017). Serpine 1 induces alveolar type II cell senescence through activating p53-p21-Rb pathway in fibrotic lung disease. *Aging Cell*, *16*(5), 1114–1124.

Johnson, C. A., & Collis, S. J. (2016). Ciliogenesis and the DNA damage response: A stressful relationship. *Cilia*, *5*, 19–32.

Justice, J. N., Nambiar, A. M., Tchkonia, T., LeBrasseur, N. K., Pascual, R., Hashmi, S. K., Prata, L., Masternak, M. M., Kritchevsky, S. B., Musi, N., & Kirkland, J. L. (2019). Senolytics in idiopathic pulmonary fibrosis: Results from a first-in-human, open-label, pilot study. *eBioMedicine*, *40*, 554–563.

Kheirollahi, V., Wasnick, R. M., Biasin, V., Vazquez-Armendariz, A. I., Chu, X., Moiseenko, A., Weiss, A., Wilhelm, J., Zhang, J. S., Kwapiszewska, G., & Herold, S. (2019). Metformin induces lipogenic differentiation in myofibroblasts to reverse lung fibrosis. *Nature Communications*, *10*(1), 2987–3003.

Kim, J., Davenport, P., & Sapienza, C. (2009). Effect of expiratory muscle strength training on elderly cough function. *Archives of Gerontology and Geriatrics*, *48*(3), 361–366.

Korfhagen, T. R., Le Cras, T. D., Davidson, C. R., Schmidt, S. M., Ikegami, M., Whitsett, J. A., & Hardie, W. D. (2009). Rapamycin prevents transforming growth factor-α-induced pulmonary fibrosis. *American Journal of Respiratory Cell and Molecular Biology*, *41*(5), 562–572.

Lam, H. C., Cloonan, S. M., Bhashyam, A. R., Haspel, J. A., Singh, A., Sathirapongsasuti, J. F., Cervo, M., Yao, H., Chung, A. L., Mizumura, K., & An, C. H. (2013). Histone deacetylase 6-mediated selective autophagy regulates COPD-associated cilia dysfunction. *The Journal of Clinical Investigation*, *123*(12), 5212–5230.

Lang, S., Hilsabeck, T. A., Wilson, K. A., Sharma, A., Bose, N., Brackman, D. J., Beck, J. N., Chen, L., Watson, M. A., Killilea, D. W., & Ho, S. (2019). A conserved role of the insulin-like signaling pathway in diet-dependent uric acid pathologies in *Drosophila melanogaster*. *PLoS Genetics*, *15*(8), e1008318.

Lazuardi, L., Jenewein, B., Wolf, A. M., Pfister, G., Tzankov, A., & Grubeck-Loebenstein, B. (2005). Age-related loss of naïve T cells and dysregulation of T-cell/B-cell interactions in human lymph nodes. *Immunology*, *114*(1), 37–43.

Lee, H. C., Lim, M. L., Lu, C. Y., Liu, V. W., Fahn, H. J., Zhang, C., Nagley, P., & Wei, Y. H. (1999). Concurrent increase of oxidative DNA damage and lipid peroxidation together with mitochondrial DNA mutation in human lung tissues during aging—Smoking enhances oxidative stress on the aged tissues. *Archives of Biochemistry and Biophysics*, *362*(2), 309–316.

Lee, S., She, J., Deng, B., Kim, J., de Andrade, M., Na, J., Sun, Z., Wampfler, J. A., Cunningham, J. M., Wu, Y., & Limper, A. H. (2016). Multiple-level validation identifies PARK2 in the development of lung cancer and chronic obstructive pulmonary disease. *Oncotarget*, *7*(28), 44211–44223.

Lehmann, M., Korfei, M., Mutze, K., Klee, S., Skronska-Wasek, W., Alsafadi, H. N., Ota, C., Costa, R., Schiller, H. B., Lindner, M., & Wagner, D. E. (2017). Senolytic drugs target alveolar epithelial cell function and attenuate experimental lung fibrosis ex vivo. *The European Respiratory Journal*, *50*(2), 1602367–1602382.

Lewis, B. W., Patial, S., & Saini, Y. (2019). Immunopathology of airway surface liquid dehydration disease. *Journal of Immunology Research*, *2019*, 2180409.

Li, D., Chen, S., Li, Q., Chen, L., Zhang, H., Li, H., Yu, D., Zhang, R., Niu, Y., Lu, S., & Ye, L. (2020). Caloric restriction attenuates C57BL/6J mouse lung injury and extra-pulmonary toxicity induced by real ambient particulate matter exposure. *Particle and Fibre Toxicology*, *17*(1), 22–39.

Li, N., Parrish, M., Chan, T. K., Yin, L., Rai, P., Yoshiyuki, Y., Abolhassani, N., Tan, K. B., Kiraly, O., Chow, V. T., & Engelward, B. P. (2015). Influenza infection induces host DNA damage and dynamic DNA damage responses during tissue regeneration. *Cellular and Molecular Life Sciences*, *72*(15), 2973–2988.

Li, X., Cao, X., Guo, M., Xie, M., & Liu, X. (2020). Trends and risk factors of mortality and disability adjusted life years for chronic respiratory diseases from 1990 to 2017: Systematic analysis for the Global Burden of Disease Study 2017. *BMJ*, *368*, m234.

Look, D. C., Walter, M. J., Williamson, M. R., Pang, L., You, Y., Sreshta, J. N., Johnson, J. E., Zander, D. S., & Brody, S. L. (2001). Effects of paramyxoviral infection on airway epithelial cell Foxj1 expression, ciliogenesis, and mucociliary function. *The American Journal of Pathology*, *159*(6), 2055–2069.

López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M., & Kroemer, G. (2013). The hallmarks of aging. *Cell*, *153*(6), 1194–1217.

Lozano, R., Naghavi, M., Foreman, K., Lim, S., Shibuya, K., Aboyans, V., Abraham, J., Adair, T., Aggarwal, R., Ahn, S. Y., & AlMazroa, M. A. (2012). Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet*, *380*(9859), 2095–2128.

Lupfer, C., Thomas, P. G., Anand, P. K., Vogel, P., Milasta, S., Martinez, J., Huang, G., Green, M., Kundu, M., Chi, H., & Xavier, R. J. (2013). Receptor interacting protein kinase 2-mediated mitophagy regulates inflammasome activation during virus infection. *Nature Immunology*, *14*(5), 480–488.

Maeda, K., & Akagi, J. (2016). Sarcopenia is an independent risk factor of dysphagia in hospitalized older people. *Geriatrics & Gerontology International*, *16*(4), 515–521.

McClaran, S. R., Babcock, M. A., Pegelow, D. F., Reddan, W. G., & Dempsey, J. A. (1995). Longitudinal effects of aging on lung function at rest and exercise in healthy active fit elderly adults. *Journal of Applied Physiology*, *78*(5), 1957–1968.

Meiners, S., Eickelberg, O., & Königshoff, M. (2015). Hallmarks of the ageing lung. *The European Respiratory Journal*, *45*(3), 807–827. https://doi.org/10.1183/09031936.00186914

Mercado, N., Ito, K., & Barnes, P. J. (2015). Accelerated ageing of the lung in COPD: New concepts. *Thorax*, *70*(5), 482–489.

Miri, M., Nazarzadeh, M., Alahabadi, A., Ehrampoush, M. H., Rad, A., Lotfi, M. H., Sheikhha, M. H., Sakhvidi, M. J., Nawrot, T. S., & Dadvand, P. (2019). Air pollution and telomere length in adults: A systematic review and meta-analysis of observational studies. *Environmental Pollution*, *244*, 636–647.

Mitani, A., Ito, K., Vuppusetty, C., Barnes, P. J., & Mercado, N. (2016). Restoration of corticosteroid sensitivity in chronic obstructive pulmonary disease by inhibition of mammalian target of rapamycin. *American Journal of Respiratory and Critical Care Medicine*, *193*(2), 143–153.

Moiseeva, O., Deschênes-Simard, X., St-Germain, E., Igelmann, S., Huot, G., Cadar, A. E., Bourdeau, V., Pollak, M. N., & Ferbeyre, G. (2013). Metformin inhibits the senescence-associated secretory phenotype by interfering with IKK/NF-κB activation. *Aging Cell*, *12*(1474–9726 [Electronic]), 489–498.

Morrison, T. J., Jackson, M. V., Cunningham, E. K., Kissenpfennig, A., McAuley, D. F., O'Kane, C. M., & Krasnodembskaya, A. D. (2017). Mesenchymal stromal cells modulate macrophages in clinically relevant lung injury models by extracellular vesicle mitochondrial transfer. *American Journal of Respiratory and Critical Care Medicine*, *196*(10), 1275–1286.

National Institute for Health and Care Excellence. (2021). Pneumonia (community-acquired): Antimicrobial prescribing 2019 [June 23, 2021]. Available from: https://www.nice.org.uk/guidance/ng138

Orlow, I., Park, B. J., Mujumdar, U., Patel, H., Siu-Lau, P., Clas, B. A., Downey, R., Flores, R., Bains, M., Rizk, N., & Dominguez, G. (2008). DNA damage and repair capacity in patients with lung cancer: Prediction of multiple primary tumors. *Journal of Clinical Oncology*, *26*(21), 3560–3566.

Otálora-Otálora, B. A., Florez, M., López-Kleine, L., Canas Arboleda, A., Grajales Urrego, D. M., & Rojas, A. (2019). Joint transcriptomic analysis of lung cancer and other lung diseases. *Frontiers in Genetics*, *10*, 1260–1278. https://doi.org/10.3389/fgene.2019.01260

Pavia, D., Thomson, M. L., & Pocock, S. J. (1971). Evidence for temporary slowing of mucociliary clearance in the lung caused by tobacco smoking. *Nature*, *231*(5301), 325–326.

Pedersen, M. (1990). Ciliary activity and pollution. *Lung*, *168*(Suppl), 368–376.

Plaza, V., Serra-Batlles, J., Ferrer, M., & Morejón, E. (2000). Quality of life and economic features in elderly asthmatics. *Respiration*, *67*(1), 65–70.

Polkey, M. I., Harris, M. L., Hughes, P. D., Hamnegärd, C. H., Lyons, D., Green, M., & Moxham, J. (1997). The contractile properties of the elderly human diaphragm. *American Journal of Respiratory and Critical Care Medicine*, *155*(5), 1560–1564.

Principe, S., Benfante, A., Calzetta, L., Rogliani, P., & Scichilone, N. (2019). Age does not affect the efficacy of anti-IL-5/IL-5R in severe asthmatics. *World Allergy Organization Journal*, *12*(11), 100081. https://doi.org/10.1016/j.waojou.2019.100081

Proença de Oliveira-Maul, J., Barbosa de Carvalho, H., Goto, D. M., Maia, R. M., Fló, C., Barnabé, V., Franco, D. R., Benabou, S., Perracini, M. R., Jacob-Filho, W., & Saldiva, P. H. (2013). Aging, diabetes, and hypertension are associated with decreased nasal mucociliary clearance. *Chest*, *143*(4), 1091–1097.

Prussin, A. J. 2nd, Garcia, E. B., & Marr, L. C. (2015). Total virus and bacteria concentrations in indoor and outdoor air. *Environmental Science & Technology Letters*, *2*(4), 84–88.

Raghu, G., Weycker, D., Edelsberg, J., Bradford, W. Z., & Oster, G. (2006). Incidence and prevalence of idiopathic pulmonary fibrosis. *American Journal of Respiratory and Critical Care Medicine*, *174*(7), 810–816.

Rakoff-Nahoum, S., Paglino, J., Eslami-Varzaneh, F., Edberg, S., & Medzhitov, R. (2004). Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. *Cell*, *118*(2), 229–241. https://doi.org/10.1016/j.cell.2004.07.002

Ramirez, J. A., Wiemken, T. L., Peyrani, P., Arnold, F. W., Kelley, R., Mattingly, W. A., Nakamatsu, R., Pena, S., Guinn, B. E., Furmanek, S. P., & Persaud, A. K. (2017). Adults hospitalized with pneumonia in the United States: Incidence, epidemiology, and mortality. *Clinical Infectious Diseases*, *65*(11), 1806–1812.

Rampelli, S., Candela, M., Turroni, S., Biagi, E., Collino, S., Franceschi, C., O'Toole, P. W., & Brigidi, P. (2013). Functional metagenomic profiling of intestinal microbiome in extreme ageing. *Aging (Albany NY)*, *5*(12), 902–912.

Rao, W., Wang, S., Duleba, M., Niroula, S., Goller, K., Xie, J., Mahalingam, R., Neupane, R., Liew, A. A., Vincent, M., Okuda, K., O'Neal, W. K., Boucher, R. C., Dickey, B. F., Wechsler, M. E., Ibrahim, O., Engelhardt, J. F., Mertens, T. C. J., Wang, W., … Xian, W. (2020). Regenerative metaplastic clones in COPD lung drive inflammation and fibrosis. *Cell*, *181*(4), 848–64.e18. https://doi.org/10.1016/j.cell.2020.03.047

Rappaport, I., & Mayer, E. (1954). Emphysema and the senile lung. *Journal of the American Geriatrics Society*, *2*(9), 581–591.

Rashid, K., Sundar, I. K., Gerloff, J., Li, D., & Rahman, I. (2018). Lung cellular senescence is independent of aging in a mouse model of COPD/emphysema. *Scientific Reports*, *8*(1), 9023–9037. https://doi.org/10.1038/s41598-018-27209-3

Rutten, E. P., Gopal, P., Wouters, E. F., Franssen, F. M., Hageman, G. J., Vanfleteren, L. E., Spruit, M. A., & Reynaert, N. L. (2016). Various mechanistic pathways representing the aging process are altered in COPD. *Chest*, *149*(1), 53–61.

Sanders, Y. Y., Hagood, J. S., Liu, H., Zhang, W., Ambalavanan, N., & Thannickal, V. J. (2014). Histone deacetylase inhibition promotes fibroblast apoptosis and ameliorates pulmonary fibrosis in mice. *The European Respiratory Journal*, *43*(5), 1448–1458.

Sapey, E. (2020). Neutrophil modulation in alpha-1 antitrypsin deficiency. *Chronic Obstr Pulm Dis.*, *7*(3), 247–259. https://doi.org/10.15326/jcopdf.7.3.2019.0164

Sapey, E., Gallier, S., Mainey, C., Nightingale, P., McNulty, D., Crothers, H., Evison, F., Reeves, K., Pagano, D., Denniston, A. K., & Nirantharakumar, K. (2020). Ethnicity and risk of death in patients hospitalised for COVID-19 infection in the UK: An observational cohort study in an urban catchment area. *BMJ Open Respiratory Research*, *7*(1), e000644.

Sapey, E., Greenwood, H., Walton, G., Mann, E., Love, A., Aaronson, N., Insall, R. H., Stockley, R. A., & Lord, J. M. (2014). Phosphoinositide 3-kinase inhibition restores neutrophil accuracy in the elderly: Toward targeted treatments for immunosenescence. *Blood*, *123*(2), 239–248. https://doi.org/10.1182/blood-2013-08-519520

Sapey, E., Patel, J. M., Greenwood, H., Walton, G. M., Grudzinska, F., Parekh, D., Mahida, R. Y., Dancer, R. C., Lugg, S. T., Howells, P. A., & Hazeldine, J. (2019). Simvastatin improves neutrophil function and clinical outcomes in pneumonia. A pilot randomized controlled clinical trial. *American Journal of Respiratory and Critical Care Medicine*, *200*(10), 1282–1293.

Sapey, E., Patel, J. M., Greenwood, H. L., Walton, G. M., Hazeldine, J., Sadhra, C., Parekh, D., Dancer, R. C. A., Nightingale, P., Lord, J. M., & Thickett, D. R. (2017). Pulmonary infections in the elderly lead to impaired neutrophil targeting, which is improved by simvastatin. *American Journal of Respiratory and Critical Care Medicine*, *196*(10), 1325–1336. https://doi.org/10.1164/rccm.201704-0814OC

Saretzki, G., Sitte, N., Merkel, U., Wurm, R. E., & von Zglinicki, T. (1999). Telomere shortening triggers a p53-dependent cell cycle arrest via accumulation of G-rich single stranded DNA fragments. *Oncogene*, *18*(37), 5148–5158.

Savale, L., Chaouat, A., Bastuji-Garin, S., Marcos, E., Boyer, L., Maitre, B., Sarni, M., Housset, B., Weitzenblum, E., Matrat, M., le Corvoisier, P., Rideau, D., Boczkowski, J., Dubois-Randé, J. L., Chouaid, C., & Adnot, S. (2009). Shortened telomeres in circulating leukocytes of patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*, *179*(7), 566–571. https://doi.org/10.1164/rccm.200809-1398OC

Schafer, M. J., White, T. A., Iijima, K., Haak, A. J., Ligresti, G., Atkinson, E. J., Oberg, A. L., Birch, J., Salmonowicz, H., Zhu, Y. I., & Mazula, D. L. (2017). Cellular senescence mediates fibrotic pulmonary disease. *Nature Communications*, *8*, 14532.

Sharma, G., & Goodwin, J. (2006). Effect of aging on respiratory system physiology and immunology. *Clinical Interventions in Aging*, *1*(3), 253–260. https://doi.org/10.2147/ciia.2006.1.3.253

Shei, R. J., Peabody, J. E., & Rowe, S. M. (2018). Functional anatomic imaging of the airway surface. *Annals of the American Thoracic Society*, *15*-(Suppl 3), S177–s83. https://doi.org/10.1513/AnnalsATS.201806-407AW

Shifren, A., & Mecham, R. P. (2006). The stumbling block in lung repair of emphysema: Elastic fiber assembly. *Proceedings of the American Thoracic Society*, *3*(5), 428–433.

Shivshankar, P., Boyd, A. R., Le Saux, C. J., Yeh, I. T., & Orihuela, C. J. (2011). Cellular senescence increases expression of bacterial ligands in the lungs and is positively correlated with increased susceptibility to pneumococcal pneumonia. *Aging Cell*, *10*(5), 798–806.

Snetselaar, R., van Batenburg, A. A., van Oosterhout, M. F. M., Kazemier, K. M., Roothaan, S. M., Peeters, T., Van Der Vis, J. J., Goldschmeding, R., Grutters, J. C., & Van Moorsel, C. H. (2017). Short telomere length in IPF lung associates with fibrotic lesions and predicts survival. *PLoS ONE*, *12*(12), e0189467.

Stam, H., Hrachovina, V., Stijnen, T., & Versprille, A. (1994). Diffusing capacity dependent on lung volume and age in normal subjects. *Journal of Applied Physiology*, *76*(6), 2356–2363.

Strongman, H., Kausar, I., & Maher, T. M. (2018). Incidence, prevalence, and survival of patients with idiopathic pulmonary fibrosis in the UK. *Advances in Therapy*, *35*(5), 724–736.

Sun, Z., Li, F., Zhou, X., Chung, K. F., Wang, W., & Wang, J. (2018). Stem cell therapies for chronic obstructive pulmonary disease: Current status of pre-clinical studies and clinical trials. *Journal of Thoracic Disease*, *10*(2), 1084–1098.

Terada, K., Muro, S., Ohara, T., Kudo, M., Ogawa, E., Hoshino, Y., Hirai, T., Niimi, A., Chin, K., & Mishima, M. (2010). Abnormal swallowing reflex and COPD exacerbations. *Chest*, *137*(2), 326–332.

Thannickal, V. J., Murthy, M., Balch, W. E., Chandel, N. S., Meiners, S., Eickelberg, O., Selman, M., Pardo, A., White, E. S., Levy, B. D., & Busse, P. J. (2015). Blue journal conference. Aging and susceptibility to lung disease. *American Journal of Respiratory and Critical Care Medicine*, *191*(3), 261–269.

The National Institute for Health and Care Excellence. (2021). Pneumonia in adults 2016 [June 4, 2021]. Available from: https://www.nice.org.uk/guidance/qs110

Thomas, E. T., Guppy, M., Straus, S. E., Bell, K. J. L., & Glasziou, P. (2019). Rate of normal lung function decline in ageing adults: A systematic review of prospective cohort studies. *BMJ Open*, *9*(6), e028150. https://doi.org/10.1136/bmjopen-2018-028150

Tilley, A. E., Walters, M. S., Shaykhiev, R., & Crystal, R. G. (2015). Cilia dysfunction in lung disease. *Annual Review of Physiology*, *77*, 379–406.

To, Y., Ito, K., Kizawa, Y., Failla, M., Ito, M., Kusama, T., Elliott, W. M., Hogg, J. C., Adcock, I. M., & Barnes, P. J. (2010). Targeting phosphoinositide-3-kinase-δ with theophylline reverses corticosteroid insensitivity in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*, *182*(7), 897–904. https://doi.org/10.1164/rccm.200906-0937OC

Todd, J. L., Vinisko, R., Liu, Y., Neely, M. L., Overton, R., Flaherty, K. R., Noth, I., Newby, L. K., Lasky, J. A., Olman, M. A., & Hesslinger, C. (2020). Circulating matrix metalloproteinases and tissue metalloproteinase inhibitors in patients with idiopathic pulmonary fibrosis in the multicenter IPF-PRO Registry cohort. *BMC Pulmonary Medicine*, *20*(1), 64–76.

Torres, A., Peetermans, W. E., Viegi, G., & Blasi, F. (2013). Risk factors for community-acquired pneumonia in adults in Europe: A literature review. *Thorax*, *68*(11), 1057–1065.

Verin, E., Clavé, P., Bonsignore, M. R., Marie, J. P., Bertolus, C., Similowski, T., & Laveneziana, P. (2017). Oropharyngeal dysphagia: When swallowing disorders meet respiratory diseases. *The European Respiratory Journal*, *49*(4), 1602530. https://doi.org/10.1183/13993003.02530-2016

Volckaert, T., & De Langhe, S. (2014). Lung epithelial stem cells and their niches: Fgf10 takes center stage. *Fibrogenesis & Tissue Repair*, *7*, 8–23.

Vucic, E. A., Chari, R., Thu, K. L., Wilson, I. M., Cotton, A. M., Kennett, J. Y., Zhang, M., Lonergan, K. M., Steiling, K., Brown, C. J., & McWilliams, A. (2014). DNA methylation is globally disrupted and associated with expression changes in chronic obstructive pulmonary disease small airways. *American Journal of Respiratory Cell and Molecular Biology*, *50*(5), 912–922.

Wagner, D. E., Bonenfant, N. R., Parsons, C. S., Sokocevic, D., Brooks, E. M., Borg, Z. D., Lathrop, M. J., Wallis, J. D., Daly, A. B., Lam, Y. W., & Deng, B. (2014). Comparative decellularization and recellularization of normal versus emphysematous human lungs. *Biomaterials*, *35*(10), 3281–3297.

Wang, C. H., Chung, F. T., Lin, S. M., Huang, S. Y., Chou, C. L., Lee, K. Y., Lin, T. Y., & Kuo, H. P. (2014). Adjuvant treatment with a mammalian target of rapamycin inhibitor, sirolimus, and steroids improves outcomes in patients with severe H1N1 pneumonia and acute respiratory failure. *Critical Care Medicine*, *42*(2), 313–321.

Wang, L., Marek, G. W. 3rd, Hlady, R. A., Wagner, R. T., Zhao, X., Clark, V. C., Fan, A. X., Liu, C., Brantly, M., & Robertson, K. D. (2019). Alpha-1 antitrypsin deficiency liver disease, mutational homogeneity modulated by epigenetic heterogeneity with links to obesity. *Hepatology*, *70*(1), 51–66.

Wang, Y., Lu, Y., Wu, Y., Sun, Y., Zhou, Y., Ma, Q., Zheng, Y., Yu, Q., Cao, Y., Chen, G., & Zhang, T. (2019). Alveolar differentiation potency of human distal airway stem cells is associated with pulmonary pathological conditions. *Stem Cells International*, *2019*, 7123078.

Williams, O. W., Sharafkhaneh, A., Kim, V., Dickey, B. F., & Evans, C. M. (2006). Airway mucus: From production to secretion. *American Journal of Respiratory Cell and Molecular Biology*, *34*(5), 527–536.

Wilson, D., Drew, W., Jasper, A., Crisford, H., Nightingale, P., Newby, P., Jackson, T., Lord, J. M., & Sapey, E. (2020). Frailty is associated with neutrophil dysfunction which is correctable with phosphoinositol-3-kinase inhibitors. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *75*(12), 2320–2325.

World Health Organisation. (2021). WHO Coronavirus (COVID-19) Dashboard 2021 [October 4, 2021]. Available from: https://covid19.who.int/

Yanagisawa, S., Baker, J. R., Vuppusetty, C., Fenwick, P., Donnelly, L. E., Ito, K., & Barnes, P. J. (2017). Decreased phosphatase PTEN amplifies PI3K signaling and enhances proinflammatory cytokine release in COPD. *American Journal of Physiology. Lung Cellular and Molecular*

Physiology, *313*(2), L230–l9. https://doi.org/10.1152/ajplung.00382.2016

Yang, Y., Li, C., Liu, N., Wang, M., Zhou, X., Kim, I. H., & Wu, Z. (2021). Ursolic acid alleviates heat stress-induced lung injury by regulating endoplasmic reticulum stress signaling in mice. *The Journal of Nutritional Biochemistry*, *89*, 108557.

Yang, Z., Zou, X., Feng, P., Zhan, H., Xiong, D., & Lang, J. (2019). Inhibition of the PI3K/AKT signaling pathway or overexpression of beclin1 blocks reinfection of *Streptococcus pneumoniae* after infection of influenza A virus in severe community-acquired pneumonia. *Inflammation*, *42*(5), 1741–1753.

Yip, K. P., Stockley, R. A., & Sapey, E. (2021). Catching "early" COPD—The diagnostic conundrum. *International Journal of Chronic Obstructive Pulmonary Disease*, *16*, 957–968.

Yuan, T., Volckaert, T., Redente, E. F., Hopkins, S., Klinkhammer, K., Wasnick, R., Chao, C. M., Yuan, J., Zhang, J. S., Yao, C., & Majka, S. (2019). FGF10-FGFR2B signaling generates basal cells and drives alveolar epithelial regeneration by bronchial epithelial stem cells after lung injury. *Stem Cell Reports*, *12*(5), 1041–1055.

How to cite this article: Faniyi, A. A., Hughes, M. J., Scott, A., Belchamber, K. B. R., & Sapey, E. (2022). Inflammation, ageing and diseases of the lung: Potential therapeutic strategies from shared biological pathways. *British Journal of Pharmacology*, 1–18. https://doi.org/10.1111/bph.15759