Hallmarks of the ageing lung: 10 years later

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Abstract

Ageing is a crucial factor in the development of chronic lung diseases, including COPD, idiopathic pulmonary fibrosis, and lung cancer. Marking the 10th anniversary of the original "Hallmarks of the ageing lung" published in this journal, we present an updated review highlighting key cellular and molecular features of ageing that drive the onset and progression of these conditions. Ageing stands as the most significant risk factor for chronic lung diseases, which are characterised by structural and functional changes such as reduced elasticity, persistent inflammation, and impaired repair capacity. Recent evidence confirms that nearly all recognised hallmarks of ageing play a role in the pathogenesis of these diseases. Notably, extracellular matrix dysregulation, first proposed as a lung ageing hallmark in 2015, has become an integral aspect of ageing in lung disease. Environmental exposures, such as cigarette or wildfire smoke, accelerate age-related changes by increasing oxidative stress, promoting cellular senescence, and disrupting tissue homeostasis. In lung cancer, ageing contributes to genomic alterations, epigenetic dysregulation, immune evasion and therapeutic resistance. Additionally, the roles of extracellular vesicles and microbiome changes in shaping these ageing phenotypes are emerging areas of research. Early clinical studies are now targeting specific ageing hallmarks, such as cellular senescence, with the goal of reducing age-related pathology and improving outcomes. Overall, integrating ageing biology into lung disease research paves the way for innovative diagnostic and therapeutic strategies that address common molecular mechanisms across multiple chronic lung conditions.

Introduction: 10 years of lung ageing

The world's population is gradually ageing, and the World Health Organization predicts that the global population aged >60 years will double from 12% to 22% between 2015 and 2050 [1]. Ageing is a complex biological process characterised by a progressive loss of function in various physiological systems. In a seminal paper published in 2004, López-Otín *et al.* [2] initially proposed nine hallmarks of ageing based on three criteria: 1) they increase in an age-dependent manner; 2) their experimental amplification leads to an acceleration of ageing; and 3) conversely, their therapeutic manipulation leads to a delay in ageing. Over the past decade, extensive ageing research has uncovered additional hallmarks, which are described in a recently updated review [3], leading overall to 13 hallmarks up to date (figures 1 and 2). Here we revisit our first review from 2015 and provide an updated overview of the extended ageing features and their impact on chronic lung disease. We initially proposed "dysregulation of the extracellular matrix (ECM)" as an additional hallmark of ageing 10 years ago [4] and discuss additional studies further

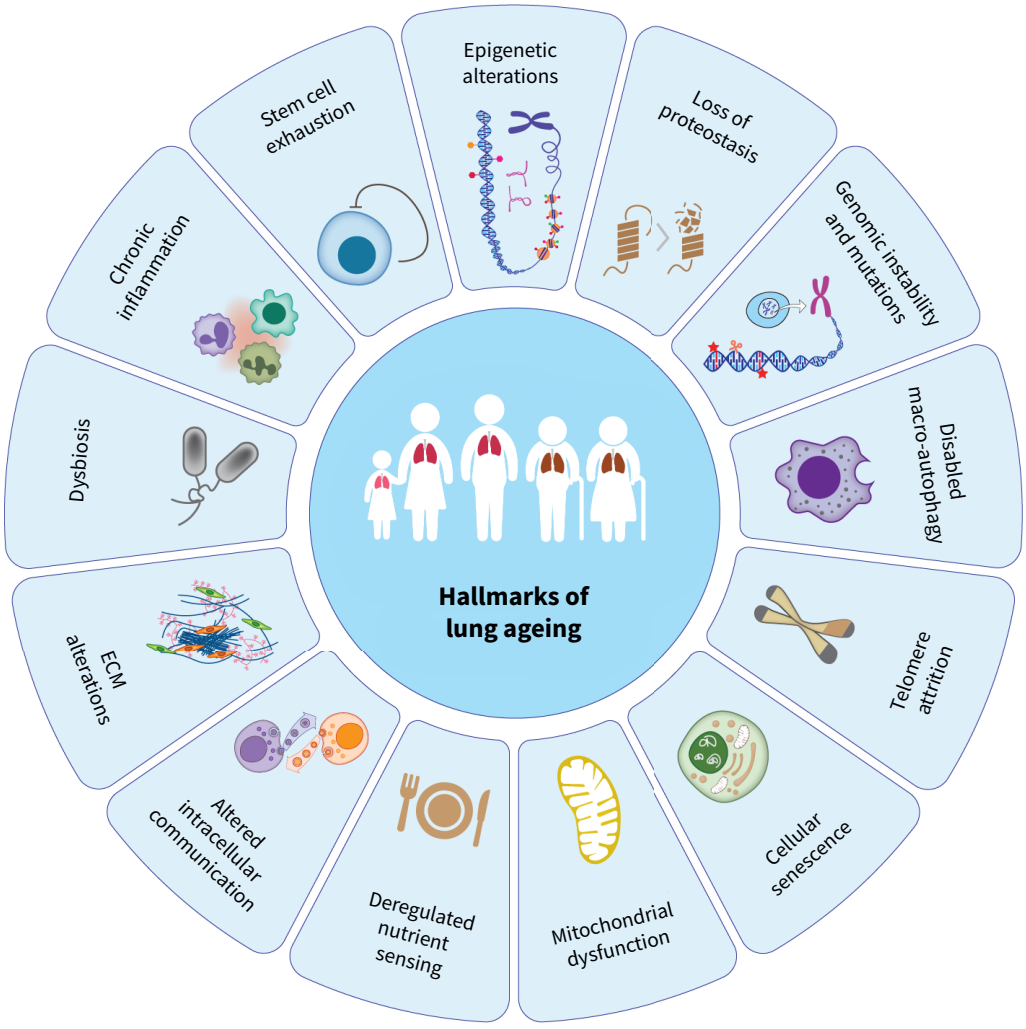


FIGURE 1 The 13 hallmarks of the ageing lung. This schematic depicts the nine original hallmarks of lung ageing and is updated to include the latest three additional hallmarks along with our previously proposed additional hallmark of the ageing lung: alterations of the extracellular matrix (ECM).

corroborating this concept. Since our first review published in the *European Respiratory Journal* in 2015, there have been >16 000 articles published in PubMed on this topic. While we cannot cover this exhaustive bibliography completely, we discuss findings for which descriptive or genetic evidence from multiple clinical cohorts or at least two different laboratories; and/or support exists from genetic mouse models or pharmacological targeting approaches in diseased animal models. Notably, now we have evidence that chronic lung diseases are affected by basically all hallmarks of ageing, suggesting that indeed this is a common underlying process. In this article, we begin to delineate the individual contribution and hierarchy among hallmarks. In addition, we discuss the development of potential anti-ageing therapies, which have gained significant interest over the past decade to potentially combat chronic lung disease.

Lung ageing

The lungs are constantly exposed to environmental and cellular stress factors such as (household) air pollution, particulate matter pollution and tobacco smoke [4]. Biological ageing of the lung, unlike chronological ageing, reflects the cumulative impact of genetic and epigenetic predisposition, environmental exposures, lifestyle factors and early-life injuries, all of which shape individual lung ageing trajectories and disease susceptibility (figure 3). As we age, the lungs undergo structural and physiological changes that result in increased airspace size, loss of elasticity, decreased ventilatory control, decreased chest wall compliance, and loss of respiratory muscle strength, all of which impair lung function [5–8]. Ageing is the single biggest risk factor for chronic lung disease. In 2017, >500 million people worldwide

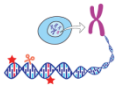
	The 13 hallmarks of lung ageing	Definition
	**Genomic instability**	The increased tendency of the genome to acquire mutations due to exposure to endogenous and exogenous agents leading to increased acquisition of genomic mutations which may drive age-related changes
	**Telomere attrition**	The gradual or accelerated shortening of telomeres due to cellular replication, DNA damage or reduced expression of telomere maintenance machinery which accelerates cell cycle arrest during ageing
	**Epigentic alterations**	An increase in hereditable and environmental driven changes in gene expression that occur without altering the DNA sequence itself, which accumulate during ageing and may be accelerated in disease
	**Loss of proteostasis**	Impaired regulation and maintenance of intracellular protein synthesis, folding, transport and degradation
	**Disabled macroautophagy**	Increased damage/loss of function of the mitochondria, leading to reduced ATP production and/or increased reactive oxygen species
	**Deregulated nutrient sensing**	The cellular process by which cells detect and respond to the availability of nutrients, enabling regulation of metabolism, growth and survival
	**Mitochondrial dysfunction**	Increased damage/loss of function of the mitochondria, leading to reduced ATP production and/or increased reactive oxygen species
	**Cellular senescence**	The accumulation of cells that are in a state of stable, irreversible cell cycle arrest, which remain metabolically active and release low graded chronic inflammation impeding tissue repair and immune response
	**Stem cell exhaustion**	Acceleration in the decline in function or number of stem cells, resulting in decreased or dysfunctional tissue repair capacity
	**Altered intercellular communications**	Changes in how cells signal or respond to one another, leading to changes in cellular response and a potential for a dysregulated immunological response
	**ECM alterations**	Increased deposition, altered composition or increased degradation of the ECM, inducing alterations in tissue structure
	**Dysbiosis**	An imbalance/change in the microbiome
	**Chronic inflammation**	Long-lasting, low-grade inflammation that is persistent over a long period of time

FIGURE 2 Description of the 13 hallmarks of ageing. Characteristics of all current hallmarks are described. ECM: extracellular matrix.

lived with a chronic lung disease, which is the third leading cause of death [9]. Most chronic respiratory disease-attributable deaths were due to COPD, which is strongly associated with ageing. Patients aged >65 years have a five-fold increased risk of developing COPD compared with patients aged <40 years [10].

Hallmarks of ageing in COPD

COPD is considered a disease of accelerated ageing, with Fletcher and Peto [11] demonstrating an accelerated decline in lung function of COPD patients (forced expiratory volume in 1 s 50–100 mL per year) compared to age-matched healthy individuals (~20 mL per year). The incidence of COPD increases with age and there is a strong correlation between the hallmarks of ageing and COPD. However, while genome-wide association studies (GWAS) have identified specific gene loci that are associated with ageing

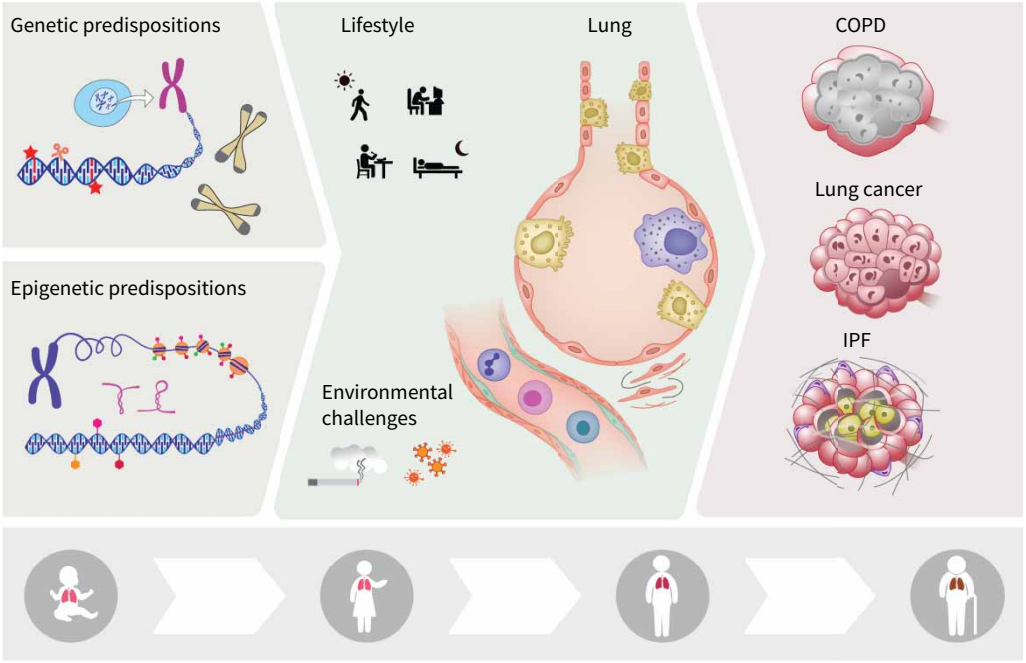


FIGURE 3 The hallmarks of lung ageing evolve throughout life. Genetic and epigenetic predispositions established early in life, combined with lifestyle factors and environmental exposures during childhood and adulthood, contribute to the development and acceleration of lung ageing, thereby increasing the risk of age-related chronic lung diseases, including COPD, idiopathic pulmonary fibrosis (IPF) and lung cancer.

hallmarks, overall evidence for genetic changes in the hallmarks of ageing in COPD is limited. It is debated whether the expression of the hallmarks is a consequence of the disease rather than causative [8]. However, COPD patients display all the hallmarks of ageing and over the past decade data have emerged characterising these hallmarks in COPD samples and models implicating them in disease pathogenesis.

Genomic instability in COPD

Accumulation of genetic damage caused by genomic instability and defective DNA repair is a hallmark of ageing, with cigarette smoke-induced DNA damage as a proposed link to COPD. Previously, elevated DNA damage markers in COPD patients were identified, driven by oxidative stress [12, 13]. Recent work has shown dysfunction of DNA repair pathways in COPD, with alterations in 15 genes associated with DNA repair and damage tolerance detected [14]. Micro (mi)RNAs may regulate DNA repair in COPD, with miR-24-3p being downregulated and no longer able to inhibit BRAC1, priming the DNA damage response (DDR) and inducing apoptosis [15]. miR-126-3p is also elevated, increasing the DDR protein, ataxia telangiectasia mutated, which may overactivate DNA repair [16]. In addition, clonal haematopoiesis of indeterminate potential (CHIP) is an age-related phenomenon in which somatic mutations in clonal blood populations induce aberrant inflammatory responses. COPD subjects display increased evidence of CHIP, and this may drive elevated chronic inflammation [17, 18]. The increase in DNA damage and loss of DNA repair in the COPD lung may lead to increased susceptibility to cigarette smoke and accelerate COPD pathogenesis.

Telomere attrition in COPD

Telomeres are short, repetitive DNA sequences located at the end of chromosomes that protect DNA from mutations during normal cell division. Telomeres shorten during normal cell division, leading to replicative senescence and this can be accelerated, due to oxidative stress-mediated DNA damage [19]. The causal relationship between telomere length and COPD remains unclear. However, a prospective study examining telomere length in COPD patients at two time points 10 years apart showed that those with accelerated telomere shortening had progressively poorer lung function over time [20]. Telomeres in airway epithelial cells from COPD subjects display telomere-associated DNA damage foci without observing significant telomere shortening, leading to senescence [21]. Disruption of the shelterin/telosome complex, a telomere protective protein complex, is disrupted in COPD, with loss of telomere protection protein 1 [22]. Overall,

telomeres appear to be shorter and damaged in COPD patients, but it remains unclear whether this is the cause or a consequence of disease.

Epigenetic alterations in COPD

Epigenetic changes contribute to ageing, with alterations in DNA methylation, structural changes in chromatin, post-translational modifications of histones, and changed expression and function of non-coding RNAs all associated. Over the past 10 years, technologies for studying epigenetics have improved significantly, leading to a better understanding of how these may influence disease pathogenesis. COPD has potential developmental origins [23], with changes in the epigenome a suggested mechanism. Genome-wide methylation profiling of both fetal and adult lung tissue examined whether epigenetic modifications due to *in utero* smoke (IUS) exposure led to an increased risk of COPD. Co-methylation network analysis showed shared methylation pattern changes in the fetal samples which had been exposed to IUS as the adult COPD samples, suggesting *in utero* cigarette smoke exposure may increase COPD risk [24]. Integration of the methylation status of COPD lung tissue and GWAS data is now being used to try to identify genes which may be modulated by both environmental and genetic factors, highlighting pathways not previously explored [25]. Assay for transposase-accessible chromatin using sequencing performed on primary lung cells from COPD subjects and overlapped with COPD GWAS data identified 250 single nucleotide polymorphisms (SNPs) directly overlapping with accessible chromatin [26]. Functional studies are emerging to try and understand whether these epigenetic changes can alter COPD pathogenies. Examining epigenetic modifiers have emerged over the past 10 years. Protein arginine methyltransferase 7 (PRMT7) regulates histone methylation and is elevated in COPD subjects. Loss of PRMT7 leads to reduced emphysema in mice due to decreased monocyte recruitment and inflammation [27].

miRNAs are dysregulated in COPD and have the potential to influence disease pathology [28]. miRNA alterations may induce cellular senescence in COPD, with miR-34a and miR-570 both increased in COPD leading to senescence induction through the downregulation of sirtuin-1 [29, 30]. miR-320d is downregulated in COPD, but reversed in patients are treated with inhaled corticoid steroids, *via* suppression of NF-κB [31]. Decreased histone deacetylase (HDAC)2 in COPD is thought to promote steroid insensitivity [32], and its loss may be driven in part by miR-223 [33]. Overall, dysregulated miRNA expression in COPD is now well characterised and may be an age-associated mechanism driving the pathophysiology of the disease.

Loss of proteostasis in COPD

Proteostasis is the process by which a cell regulates the maintenance of functional proteins. Disruption of proteostasis leads to accumulation of incorrectly translated misfolded or incomplete proteins. Age-related changes in proteostasis are primarily driven by stress in the endoplasmic reticulum (ER), which triggers the unfolded protein response (UPR) [34]. In COPD, there are examples of changes in proteasome function and increased ER stress [35], whereby both hereditary and disease-related changes in proteostasis contribute to the pathogenesis of COPD.

α_1-antitrypsin deficiency is the only known genetic disorder that causes COPD. Mutations in α_1-antitrypsin not only lead to reduced functional α_1-antitrypsin protein, but also accumulation of misfolded α_1-antitrypsin driving ER stress and inflammation [36]. In sporadic COPD, exposure to cigarette smoke induces ER stress in macrophages, reducing their ability for efferocytosis [37]. Cigarette-smoke-exposed mice and cells show changes in the stability of the 20S and 26S proteasome complex, altering proteostasis [38]. Proteostasis also regulates antigen presentation, with the immunoproteasome being a specialised type of proteasome which improves major histocompatibility complex (MHC) class 1-mediated antigen presentation [38]. In COPD bronchoalveolar lavage cells and lung tissue, the immunoproteasome is compromised, recapitulated by cigarette smoke exposure, reducing MHC class 1 presentation, and thereby hampering the adaptive immune response [39]. In peripheral blood mononuclear cells from severe COPD subjects, the opposite overactivation of the immunoproteasome occurs, driving pro-inflammatory cytokine release [40]. Altered proteostasis as seen in COPD subjects may thus lead to chronic inflammation and altered immune response.

Disabled macroautophagy in COPD

Macroautophagy (hereafter autophagy) is the degradation and recycling of organelles and cell components *via* the lysosome. Autophagy occurs through the labelling of damaged organelles and their inclusion in double-membrane vesicles, the autophagosomes. Autophagosomes fuse with the lysosome leading to enzyme-mediated degradation of organelles. Autophagy is crucial for the maintenance of cellular homeostasis and a protective mechanism upon stress; however, it can lead to excessive degradation and cell death. The role of autophagy in COPD remains controversial and may be cell-type-specific or

dependent on chronic *versus* acute cigarette exposure [41, 42]. Inhibition of autophagy in cigarette-exposed mice resulted in decreased muc5ac expression, suggesting autophagy to drive mucus production [43]. Activation of autophagy also led to a reduction in bronchial inflammation [44]. Conversely, elevated levels of p62, LC3, and aggresomes are found in COPD lung tissue, suggesting incomplete autophagy [45, 46]. Moreover, cigarette smoke exposure can drive cellular senescence through impaired mitophagy, the process in which damaged or dysfunctional mitochondria are degraded [47]. Mitophagy is activated in epithelial cells exposed to cigarette smoke, increasing mitochondrial dysfunction, promoting cell death by necroptosis and emphysema [48]. Alterations in autophagy, although not fully resolved, appear to drive COPD pathogenesis.

Deregulated nutrient sensing in COPD

The mammalian target of rapamycin (mTOR) pathway is central to nutrient sensing, with both mTORC1 and mTORC2 being able to respond to nutrients and stressors regulating cellular growth and metabolism [3]. mTOR inhibition extends lifespan in yeast, worms and mice and is therefore believed to be a major regulator of cellular ageing [49–51]. mTOR activity is increased in COPD and can drive cellular senescence in COPD smooth muscle and endothelial cells [52, 53]. mTOR inhibition in mice exposed to cigarette smoke exhibited reduced lung damage, suggesting a protective effect [54]. Participants in the COPDGene study who received metformin, a diabetes drug which activates AMP-activated protein kinase (AMPK) and inhibits mTOR, had slower progression of emphysema [54]. Other nutrient pathways are affected as well, such as insulin-like growth factor (IGF) signalling, with IGF1 being reduced in COPD lung tissue [55]. Deletion of the senescence marker p16 restored IGF1 levels in mice exposed to cigarette smoke [55]. Overall, changes in the nutrient sensor network are observed in COPD that may be targeted therapeutically.

Mitochondrial dysfunction in COPD

Mitochondria, the powerhouse of the cell, provide the energy a cell needs to function. Mitochondria release reactive oxygen species (ROS) that if not handled correctly induce cellular damage, modulate cell death, and can promote inflammation through mitochondrial (mt)DNA release [56]. In COPD, mitochondria are fragmented, elongated and swollen, have high mitochondrial superoxide formation, and increased levels of mtDNA damage are observed [57]. Adenine nucleotide translocase (ANT)2, a mitochondrial ATP–ADP transporter, which regulates mitochondrial function, is downregulated in COPD causing dysregulated mitochondrial function and ciliary motility [58]. The airway smooth muscle of COPD patients exhibits reduced mitochondrial membrane potential and increased mitochondrial ROS (mROS) [59]. COPD macrophages have impaired ability to phagocytose bacteria, with altered mitochondrial function implied [60]. The COPD lung is also overloaded with iron, and much of this iron resides in the mitochondria, with chelation of iron after cigarette smoke exposure in mice reducing lung inflammation and immune cell infiltrates [61]. Dysregulated mitochondrial function appears to be a universal feature of cells from COPD patients and alters both inflammation and the ability to fight off invading pathogens.

Cellular senescence in COPD

Cellular senescence occurs in response to numerous stressors and triggers, including DNA damage, telomere dysfunction, and oncogene activation [62]. Senescent cells undergo cell cycle arrest, but remain metabolically active and release inflammatory cytokines, chemokines, and proteases (the senescence-associated secretory phenotype (SASP)) [63]. The number of senescent cells is increased in COPD patients with increased numbers of senescent alveolar type 2 (AT2) cells [55, 64], small airway epithelial cells [30], endothelial cells [53, 65], smooth muscle cells of the pulmonary artery [65, 66], and parenchymal and small airway fibroblasts [67, 68]. An increase in these senescent cells in the lung is associated with the chronic inflammation observed in COPD patients, with the SASP of senescent cells appearing to reflect the chronic inflammation of COPD. Oxidative stress from cigarette smoke is proposed as a major trigger of senescence in COPD, potentially leading to DNA damage and cell cycle arrest [69], particularly due to decreased expression of DNA repair genes [14]. Cigarette smoke exposure *in vitro* induces cellular senescence activating both the ATM-p53-p21 and p16-Rb signalling pathways [47], induces telomere shortening and damage [21] as well as mitochondrial and DNA damage [70], all suggesting that cigarette smoke can induce senescence. The current data suggest that senescent cells are increased in COPD lungs and that the accumulation of these cells may cause reduced lung repair capacity and chronic inflammation associated with the disease.

Stem cell exhaustion in COPD

Impairment of the endogenous regenerative capacity of the lung has evolved as another paradigm in COPD, with lung stem cell exhaustion, including basal cells in the airways and alveolar type II cells in the distal lung [71]. Consequently, the COPD lung may become unable to respond to damage and repair.

Airway basal cells appear to be depleted in COPD, showing a reduced capacity for repair and differentiation [72]. COPD basal cells also exhibit disease stage-specific gene alterations that impair their ability to differentiate into ciliated cells, potentially impacting the cellular composition of the lung [73]. Recently, a unique population of secretory cells were found in respiratory bronchioles of the lung named respiratory airway secretory cells (RASCs). These cells are in a transcriptionally intermediate state between secretory cells and AT2 cells. The RASC-to-AT2 cell trajectory is altered in COPD and may lead to an altered ability to repair the lung alveolus [74]. An emphysema-specific form of AT2 cell has been identified and suggested to originate from both club cells and RASC, displaying reduced regenerative capacity and associated with a senescence and mitochondrial dysfunction phenotype [75]. Two additional AT2 cell populations have been identified in COPD patients, with AT2B cells exhibiting altered bioenergetics and impaired cellular stress tolerance [76, 77], while AT2i shows an increased inflammatory phenotype [78]. Overall, there appears to be a loss of fully functioning stem cell populations in the COPD lung, impeding repair capacity.

Altered intercellular communication in COPD

Altered intercellular communication is a central hallmark of many diseases, with low grade chronic inflammation termed "inflammaging" a key feature of the COPD lung environment [79], as well as increased numbers of senescent immune cells (immunosenescence) being observed [80]. Here, we focus on the role of extracellular vesicles in COPD. Extracellular vesicles are small membrane-bound vesicles that are released from cells into the extracellular space and are critical for intercellular communication. Increased numbers of extracellular vesicles are seen in COPD patients [81] and extracellular vesicles may promote emphysema and emphysema-like features in mice, with extracellular vesicles containing neutrophil elastases and matrix metalloproteinase (MMP)12 [82]. Extracellular vesicles from COPD patients may also propagate senescence; miR-34a is elevated in extracellular vesicles from COPD patients and downregulates sirtuin-1 and drives cellular senescence [83]. Extracellular vesicles may communicate intercellularly, with exosomal miR-21 being released from epithelial cells to alter fibroblast function [84]. Extracellular vesicles may therefore be key intercellular messengers in the lung, driving disease pathobiology.

ECM alterations in COPD

ECM alterations in COPD are driven by a well-described protease/antiprotease imbalance, including dysregulated MMP function [85]. Clinical studies have highlighted ECM and ECM-associated proteins as potential biomarkers in COPD, showing the importance of disease pathology [57, 86–88]. These ECM changes in COPD have been connected to ageing with several ECM genes being differentially expressed and associated with age and COPD [89]. In patients with severe, early-onset COPD, fibroblasts with dysregulated ECM proteins exhibited a higher degree of senescence compared to controls [90]. Furthermore, elastin peptides have been found to drive inflammaging [91]. Pronounced alterations in the ECM of COPD patients and in mouse models have been described and may explain airway remodelling in disease [92, 93]. These data demonstrate intrinsically altered properties of the ECM in COPD.

Dysbiosis in COPD

Dysbiosis, the imbalance of microbiota characterised by an abnormal occurrence of pathogenic bacteria and a loss of diversity, has been associated with COPD. Low abundance of certain bacterial genera such as *Prevotella* and *Veillonella* and higher abundance of *Moraxella* have been associated with higher severity and more severe symptoms [94]. In COPD patients treated with inhaled corticosteroids, these changes in the microbiota were associated with pro-inflammatory gene expression [94–96]. Studying COPD sputum revealed that dysbiosis is associated with an increased exacerbations severity in COPD and that the microbiome is distinct if exacerbations are associated with bacteria or eosinophil inflammation [97, 98]. The variation in α- and β-diversity is significantly reduced during frequent exacerbations [92, 98]. Beyond the local microbiome changes in the respiratory tract in COPD, increasing evidence points to a mechanistic role of the gut microbiota driving lung inflammation and COPD [99–102]. Short-chain fatty acids (SCFA), produced by the gut microbiota and known to modulate lung inflammation, are significantly reduced following cigarette smoke exposure, with decreased faecal SCFA levels in mice and lower plasma SCFA concentrations in human smokers [103]. Alterations in the microbiota are seen in COPD subjects, but mechanistic understanding of how alterations in the microbiome cause disease pathology is still needed.

Chronic inflammation in COPD

Chronic inflammation is a key feature of COPD and has been extensively reviewed elsewhere [104, 105]. COPD-related alterations in the innate and adaptive immune system are driven or at least accompanied by age-related changes in the immune system. As with age, the number of activated neutrophils in the sputum and bronchoalveolar lavage fluid (BALF) of COPD patients is increased and is positively related to disease severity [106, 107]. Adaptive immune cells, including $CD8^+$ and $CD4^+$ T-cells such as type 1 (Th1) and

17 (Th17) T-helper cells, are enriched in the lung parenchyma and airways of COPD patients, as highlighted in prior reviews [105, 108]. Single-cell studies reveal diverse T-cell states with exhausted $CD8^+$ and effector/memory $CD4^+$ subsets [109, 110], while functional analyses show altered Th1/Th17 balance associated with disease severity [111, 112] and expansion of cytotoxic $CD8^+$ terminal effector memory T-cells and tissue resident memory cells contributing to local inflammation [113, 114]. In addition, B-cells increase in the peripheral airways and lung parenchyma in lymphoid follicles in patients with COPD and are associated with disease severity [115, 116]. Moreover, an ageing T-cell repertoire has been observed in ageing [117] and found to predominantly consist of naive T-cells expressing late differentiation, senescence or exhaustion markers [118]. COPD innate cells are impeded in their ability to phagocytose bacterial pathogens, response to viral infections, or migrate/ perform chemotaxis [119, 120].

Conclusion

Over the past 10 years there has been an emergence of data showing in both COPD models and patient derived samples elevated markers of the hallmarks of ageing. Key hallmarks which have been predominantly examined and changed our understanding of the disease include cellular senescence, stem cell exhaustion, loss of proteostasis and chronic inflammation (figure 4).

Hallmarks of ageing in lung cancer

Ageing and cancer are intricately linked by common biological and environmental factors, with ageing as the primary risk factor. Cancer incidence increases steadily with age, peaking between 85 and 90 years before declining due to competing health risks [3]. This suggests that ageing both promotes and later may suppress cancer. Older individuals face increased cancer risk due to comorbidities and age-related diseases, reflecting a strong connection between systemic ageing and cancer susceptibility [121].

Genomic instability in lung cancer

Ageing promotes genomic instability in the lung through cumulative DNA damage from ROS, telomere shortening and environmental carcinogens, alongside declining DNA repair mechanisms like homologous recombination and mismatch repair [122]. Genomic instability-related genes have prognostic value in lung adenocarcinoma (LUAD); a signature including *ANLN*, *RHOV*, *KRT6A*, *SIGLEC6* and *KLRG2* was linked to favourable outcomes through effects on immune infiltration [123]. Whole-exome sequencing also identified *NLRP3* and *PBX1* mutations in a rare cancer, hepatoid lung adenocarcinoma [124]. Lung cancer occurs in patients with DNA repair disorders like Werner syndrome, where *WRN* mutations affect tumour profiles [125]. Cigarette smoke further impairs WRN protein, promoting senescence in lung cells [126]. SNPs in DNA repair genes influence lung cancer progression as well, and certain SNPs affect therapy response in both squamous cell carcinoma and adenocarcinoma [127]. In nonsmall cell lung cancer (NSCLC), aneuploidy is linked to nuclear envelope collapse and defective DNA repair from laminopathies [128]. Lamin expression varies by subtype: *LMNB1* knockdown suppresses lung adenocarcinoma cell growth by triggering DNA damage-driven senescence [129]; whereas Lamin B2 consistently correlates with advanced NSCLC [130]. Additionally, depletion of Lamin A/C enhances R-loop accumulation, increasing genomic instability, and reducing survival in small cell lung cancer (SCLC) [131]. Ageing- and exposure-related DNA damage, declining repair and nuclear-envelope defects drive genomic instability in lung cancer, while repair-associated variants predict prognosis and therapy response.

Telomere attrition in lung cancer

Telomere shortening during ageing plays a dual role in lung cancer. Telomere dysfunction correlates with tumour progression and metastasis [132], and reduced telomere length is associated with a poor prognosis [133]. In 79 patients, telomere shortening, high telomerase levels, and altered shelterin expression were associated with shorter survival and poor response to immunotherapy [134]. In a cohort of older adults, lung cancer cases showed increased short-telomere burden *versus* controls [135]. In NSCLC, overexpression of *TERT* is associated with decreased survival, decreased $CD8^+$ T-cell infiltration, and an increase in myeloid-derived suppressor cells, which promote progression. 6-Thio-dG treatment leads to telomere dysfunction, which decreases tumour growth and promotes DNA damage and cell arrest [136]. Telomerase inhibition with 6TdG shows promising results in inhibiting tumour growth in SCLC [137], highlighting the targeted use of telomerases as a therapeutic approach.

Epigenetic alterations in lung cancer

Tumour-suppressive mechanisms in adulthood, such as restricting pluripotency and growth, may later drive ageing phenotypes, with epigenetic changes central to this process [138]. DNA methylation and chromatin alterations can repress stemness and invasion, while age-related hypomethylation may have evolved to limit proliferation and plasticity, thereby reducing cancer risk [139]. In lung cancer, aberrant CpG island methylation of tumour-suppressor genes such as *p16INK4A* and *MGMT* and tumour-associated genes such

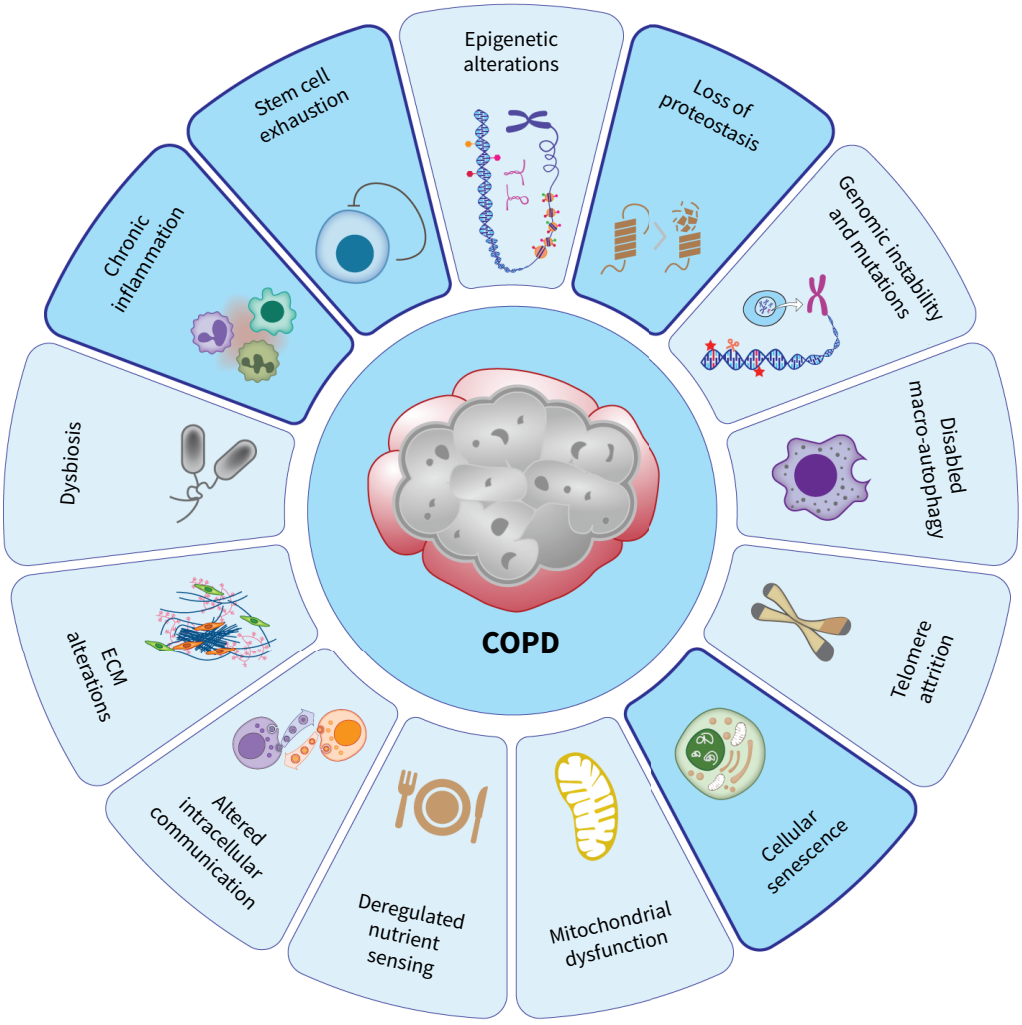


FIGURE 4 The hallmarks of the ageing lung in COPD. All 13 hallmarks of lung ageing are identified in COPD subjects, implicating them in pathogenesis. The prominence and weight of each hallmark in the disease may be different compared to other chronic lung diseases and the expression of some hallmarks may be a consequence rather than driver of the disease. However, over the past 10 years, numerous publications exploring the role each hallmark of ageing plays in the disease have been published. The predominant hallmarks and those most specific to the disease pathobiology of COPD are highlighted and include chronic inflammation, stem cell exhaustion, loss of proteostasis and cellular senescence. ECM: extracellular matrix.

as PTTG1IP participate in the development and progression of the disease [140–142]. Recent evidence links mSWI/SNF-dependent chromatin regulation to oncogene control and therapy response, where epidermal growth factor receptor (EGFR) signalling epigenetically plays a role [143]. Additionally, miRNA dysregulation drives proliferation, metastasis, angiogenesis and resistance to apoptosis [144]. Interestingly, a miR-SNP association study identified a prognostic variant in early-stage NSCLC, where it probably improves survival by modulating *FZD4* expression [145]. Long noncoding (lnc)RNAs also regulate gene expression; for instance, the LINC00973-centred ceRNA network (competing endogenous RNA) associates with poor NSCLC prognosis and highlights targets such as *BMP2*, *LOXL2* and *RTKN2* [146]. Other lncRNAs, including *MALAT1* (in NSCLC), *HOTAIR* (in LUAD) and *H19* (in NSCLC), are overexpressed, promote progression, and represent promising therapeutic targets [147–149].

Loss of proteostasis in lung cancer

Loss of proteostasis destabilises homeostasis and fosters malignant transformation. In contrast, tumour cells exploit proteostasis pathways to survive metabolic stress, hypoxia and pH changes, often hijacking mechanisms like the UPR and ER stress signalling [150]. In *KRAS*-mutant cancers, *KRAS* inhibitors

(*KRAS*i) often face resistance through inositol-requiring enzyme (IRE)1α reactivation, which restores proteostasis, making IRE1α a potential therapeutic target [151]. ER stress has dual roles in lung cancer: it can activate UPR for damage control or promote tumour survival when persistent. While ER stress may trigger apoptosis *via* interferon-γ or cisplatin, it also supports progression through *PIMT* downregulation, and eIF2α phosphorylation (aiding hypoxic survival) [152, 153]. Interestingly, circular ATF6 is shown to perturb ER proteostasis and boost EGFR-tyrosine kinase inhibitor response in NSCLC [154]. Thus, ER stress significantly influences metabolism, gene expression and drug resistance in LUAD. Overall, targeting ER proteostasis and UPR signalling may offer tractable vulnerabilities to overcome lung cancer progression and therapy resistance.

Disabled macroautophagy in lung cancer

In lung cancer, macroautophagy has dual, context-dependent roles in tumourigenesis, progression, metastasis, and therapy resistance [155]. Impaired autophagy, due to mutations in Beclin-1 or ATG, increases tumourigenic potential [156, 157]. Inhibition of autophagy in NSCLC by silencing *ATG5* leads to increased ROS and DNA damage, which accelerates tumour progression [155]. Conversely, autophagy in established tumours promotes cancer progression by helping tumour cells adapt to stress, resist apoptosis, and survive under hypoxic conditions [158]. In lung cancer cells, disruption of autophagy by deletion of *ATG7* leads to increased mitochondrial mutations and dramatic drop in total nucleotide pools, eventually affecting cell metabolism [159]. Autophagy affects the tumour microenvironment, with tumour-associated macrophages promoting epithelial–mesenchymal transition in lung adenocarcinoma cells *via* pathways such as *FUT4*/p-ezrin [160]. Autophagy can also drive resistance to NSCLC therapies, and while inhibitors such as chloroquine block autophagic degradation, variable efficacy underscores the need for biomarkers, supported by evidence that combining chloroquine with alpelisib enhances apoptosis and suppresses tumour cell growth and invasiveness compared with alpelisib alone [161]. Overall, autophagy is a context-dependent regulator of lung cancer metabolism, microenvironmental cross-talk, and treatment response, making it a biomarker-guided therapeutic target.

Deregulated nutrient sensing in lung cancer

Impaired nutrient sensing, particularly *via* the protein kinase B (AKT)/mTOR pathway, is a hallmark of cancer and ageing that sustains tumour cell proliferation [3]. The mTOR pathway, which is often overactivated in lung cancer, promotes tumour growth, while the AMPK pathway, which normally inhibits growth under energy-deficient conditions, is suppressed, allowing the cancer to proliferate despite energy deficits [162]. In addition, the hexosamine biosynthesis pathway (HBP) supports lung cancer progression by enhancing protein glycosylation and chemoresistance. HBP activity, driven by *KRAS* and LKB1 mutations, maintains cell survival and promotes invasion in NSCLC. Targeting HBP enzymes such as GFPT has shown promise in reducing tumour growth [163]. Conversely, in *KRAS*-mutant lung adenocarcinoma with *STK11*/*KEAP1* loss, tumours shift to a pro-survival lipid/redox metabolism (high *SCD1* and *SLC7A11*) linked to poor outcomes, and blocking *SCD1* can trigger ferroptotic cell death and shrink tumours, making this axis a clear biomarker and drug target [164]. Additionally, studies showed that tumour cells evade destruction by depriving activated T-cells of nutrients to suppress antitumour immunity [165]. Other strategies, such as miR-495-3p reprogramming, focus on disrupting nutrient pathways to target cancer stem cells, which are critical for tumour development and recurrence [166]. Understanding these pathways could guide therapies to block lung cancer metabolism.

Mitochondrial dysfunction in lung cancer

Ageing is linked to mitochondrial dysfunction, including mtDNA mutations, reduced mitophagy, and ROS buildup. Moreover, loss of antioxidants such as *SOD2* increases oxidative stress and SASP biomarkers tied to mortality, although effects on lifespan can be nonlinear and context-dependent [167]. Interestingly, a recent study showed that cancer cells can transmit mtDNA-mutant, mitophagy-resistant mitochondria (shielded by mitophagy-inhibitory factors) into tumour-infiltrating lymphocytes, replacing native mitochondria and driving T-cell metabolic dysfunction and senescence [168]. In the same vein, extracellular vesicles from activated cancer-associated fibroblasts (CAFs) can transfer mtDNA to tumour cells, restoring mitochondrial function, and enhancing metastasis [169]. Additionally, the E3 ligase *UBR4* appears to be tumour-promoting in LUAD by sustaining mitochondrial quality control, and cell-cycle progression, whereas *UBR4* loss triggers mitochondrial stress-linked senescence and markedly slows tumour growth [170]. Conversely, cancer cells favour glycolysis (Warburg effect), but they still rely on mitochondrial metabolism for biosynthesis. Against this backdrop, glycolysis-related gene signature is also shown to predict prognosis in LUAD [171], underscoring the clinical value of metabolic reprogramming. Overall, these findings position mitochondria as central players linking ageing biology to lung cancer.

Cellular senescence in lung cancer

Senescence in stromal cells promotes tumourigenesis by SASP-driven paracrine signalling, immune modulation and tumour stimulation, while tumour cell senescence suppresses growth through arrest and immune activation [172]. Cigarette smoke and other stressors induce SASP factors that reshape the microenvironment, promote tumour growth, and suppress immunity. For instance, cigarette-smoke-induced downregulation of *YTHDC2* promotes macrophage senescence, fostering a tumour-supportive microenvironment in lung cancer [173]. As a promising anticancer agent, dexmedetomidine is shown to suppress lung cancer cell growth by triggering ROS-driven DNA damage and premature senescence by activating the p53/p16 signalling [174]. Interestingly, senescent idiopathic pulmonary fibrosis (IPF) fibroblasts can fuel NSCLC growth and epithelial–mesenchymal transition by secreting exosomes enriched in SASP factors, especially *MMP1*, which signals through *PAR1* to activate the phosphoinositide-3-kinase (PI3K)/AKT/mTOR axis, highlighting an actionable stromal driver in IPF-associated lung cancer [175]. Small interfering RNA-mediated suppression of the splicing factor SRSF3 induces senescence and inhibits proliferation across diverse NSCLC cell lines regardless of *TP53* mutation status, supporting SRSF3 as a universally applicable therapeutic target [176]. Chemotherapies such as alkylating agents, platinum compounds, topoisomerase inhibitors and microtubule disruptors can also induce senescence through DNA damage or mitotic arrest [177, 178]. Therapy-induced senescent cells may be cleared by innate and adaptive immunity, supporting combinations with immunotherapies, including CAR T-cells [179]. Thus, senescence represents both a tumour-suppressive mechanism and a source of pro-tumour inflammation, making senescence-based strategies promising lung cancer therapy.

Stem cell exhaustion in lung cancer

Stem cell depletion may act as a tumour suppressor, possibly explaining the decline in lung cancer incidence after the age of 75 years [180, 181]. Conversely, the conversion of progenitor cells into cancer stem cells with dysregulated self-renewal contributes to carcinogenesis. Cancer stem cells identified serve as potential target to immunotherapy, such CAR T-cell, and tumour vaccines [182]. AT2 cells, stem cells of alveolar epithelia, can undergo senescence from telomere attrition, genetic factors, or cigarette smoke, creating a pro-cancerous niche [183]. Age-associated decline in mesenchymal stromal cell function was previously reported to compromise alveolar epithelial stem cell self-organisation through *Nox4*, one of the reactive oxygen species [184]. A recent study showed that mesenchymal stem-like cells promote lung cancer tumourigenicity and metastasis by triggering epithelial–mesenchymal transition and stem-like reprogramming [185]. Novel strategies, including basal airway stem cell therapy to restore tissue integrity [186], and patient-derived NSCLC organoids [187, 188], offer precision approaches to overcome stem cell exhaustion in lung cancer.

Intercellular communication in lung cancer

Intercellular communication plays a key role in lung cancer progression, metastasis and therapy response. Extracellular vesicles, particularly exosomes, mediate communication within tumour microenvironment by transferring proteins, lipids and RNAs, thereby influencing tumour growth and metastasis [189]. Exosomal noncoding RNAs play a significant role in signal transduction between tumour and immune cells and influence proliferation, invasion, immune evasion and resistance to therapy [190]. Given that, in the IPF microenvironment, senescent myofibroblast-like lung fibroblasts release extracellular vesicles enriched with miR-19a that promote NSCLC proliferation, suggesting extracellular vesicle cargo as a targetable driver in IPF-associated lung cancer [191]. CAF-derived extracellular vesicles also carry a cocktail of various molecules, but their release and proteomic cargo remain largely unchanged after ionising radiation [192]. Additionally, A549-derived extracellular vesicles can be efficiently electroporated to carry glucose oxidase and then deliver this enzymatic starvation cargo to lung cancer cells, causing marked cytotoxicity and supporting extracellular vesicles as Trojan-horse drug delivery vehicles [193]. Understanding these mechanisms reveals potential therapeutic strategies targeting intercellular communication in lung cancer.

ECM alterations in lung cancer

ECM dysregulation is a key driver of lung cancer progression, promoting transformation, angiogenesis, inflammation, metastasis and therapy resistance. This remodelling is actively shaped by stromal and immune cells, and ECM proteomic signatures are emerging as tools for patient stratification and personalised therapy [194]. Mechanistically, cathepsin V upregulation in LUAD promotes metastasis by cleaving fibronectin and cadherins while dampening T-cell-associated immunity [195]. ECM-centred drivers also extend to ageing and high-risk tissue states: age-related elastin degradation releases elastin-derived peptides that enhance proliferative/stress programmes in lung cancer cells [196], and multi-omics analyses define an ECM-enriched tumour subtype in squamous cell carcinoma that predicts pre-malignant progression, resembles IPF-like remodelling, and marks poor prognosis through

matrix-linked resistance programmes [197]. Together, these findings position ECM remodelling as both a mechanistic engine of progression and a tractable axis for biomarker-guided intervention.

Dysbiosis in lung cancer

The lower airway microbiota differs between SCLC and NSCLC. In severe lung cancer, the microbiota is more like oral mucosa samples. Supraglottic predominant taxa, including *Veillonella*, are enriched in severe NSCLC, linked to *p53* mutations, inflammatory pathways and poorer survival [198]. *Streptococcus* and *Veillonella* further activate extracellular signal-regulated kinase and PI3K signalling [199], suggesting a direct role of microbiota in promoting tumour signalling. Meanwhile, *Veillonella parvula* induced dysbiosis, inflammation and weight loss in murine models [198]. BALF from mice with lung adenoma/adenocarcinoma showed higher bacterial load, reduced diversity, cytokine induction and γδ-T17 activation [200]. NSCLC patients also display gut dysbiosis, with reduced Actinobacteria/Proteobacteria and increased *Prevotella*, alongside altered metabolites and serum proteins affecting interleukin (IL)-8 and NF-κB signalling. Faecal microbiota transplantation from NSCLC patients triggered inflammation in mice, reversible with acid supplementation, highlighting the gut–lung axis in NSCLC-related inflammation [201]. Together, lung cancer-associated airway and gut dysbiosis tracks oncogenic inflammation, and disease severity, supporting the microbiome as a biomarker and therapeutic target.

Chronic inflammation in lung cancer

Chronic inflammation is central to lung cancer pathogenesis and ageing [202]. Transcriptomic analyses and mouse models indicate that ageing creates an inflammatory lung microenvironment that promotes lung tumour outgrowth through activated tumour necrosis factor-α-signalling, which can be partially attenuated by anti-inflammatory α_1-antitrypsin [203]. In another study, a distinct subset of tumour-associated aged neutrophils ($CXCR4^{+}CD62L^{low}$) is shown to be accumulated in the lung pre-metastatic niche, and releases mitochondria-dependent neutrophil extracellular trap formation [204]. In the same vein, in *KRAS*-driven lung tumourigenesis, an early-arising *p16^INK4a*$^{+}$*Cxcr1*$^{+}$ senescent alveolar macrophage subset suppresses cytotoxic T-cells and promotes adenoma progression and eventually stimulates the recruitment of inflammatory cells [205]. Age-related markers such as IL-6 and C-reactive protein increase lung cancer risk [206]. Inflammatory status also influences therapy outcomes: elevated markers predict poor response to immunotherapies like nivolumab [207]. With ageing, $CD8^{+}$ T-cell activity and memory formation decline, weakening antitumour immunity in elderly patients [208]. Interestingly, a recent study showed that in elderly patients with lung squamous cell carcinoma, SOAT2-^{high} regulatory T-cells rewire cholesterol metabolism to enhance immunosuppression, reduce $CD8^{+}$ T-cell-mediated antitumour immunity [110]. Overall, ageing-driven chronic inflammation and immune remodelling create a tumour-promoting, immunosuppressed lung microenvironment that accelerates NSCLC progression.

Conclusion

Ageing hallmarks drive lung cancer across the continuum from early tumour initiation to late progression in a context-dependent tumour-suppressive and tumour-promoting effects (figure 5). This framework underscores opportunities for earlier detection and hallmark-targeted interventions. Over the past 10 years key hallmarks that have been predominantly examined and changed our understanding of the disease include loss of proteostasis, mitochondrial dysfunction, deregulated nutrient sensing and altered intracellular communication (figure 6).

Hallmarks of ageing in IPF

Genetic evidence, particularly telomere shortening, links ageing hallmarks to idiopathic pulmonary fibrosis (IPF), while environmental stressors like cigarette smoke accelerate these processes. Patients display elevated markers across all ageing hallmarks, and recent evidence underscores their significant role in IPF.

Genomic instability in IPF

Rare cases of pulmonary fibrosis occur in individuals with DNA repair disorders such as dyskeratosis congenita and ataxia telangiectasia, as well as in families with unidentified DNA repair defects [209–211]. However, fibrosis is not a common feature of hereditary DNA repair syndromes, and while loss of heterozygosity and microsatellite instability are detected in IPF, they do not indicate a classical replication error phenotype [212–214]. Treatment with bleomycin, a DNA-damaging agent, can lead to the development of pulmonary fibrosis [215]. Mosaic loss of the Y chromosome (LOY), a common age-related somatic mutation in men, is associated with increased risk for IPF [216]. LOY occurs primarily in immune cells and is linked to age and telomere dysfunction; however, Mendelian randomisation studies have not confirmed a causal role in IPF [217, 218]. Clonal haematopoiesis of indeterminate potential, characterised by somatic mutations in hematopoietic stem cells, increases with age and is associated with chronic lung disease, although its exact role in IPF remains unclear [219].

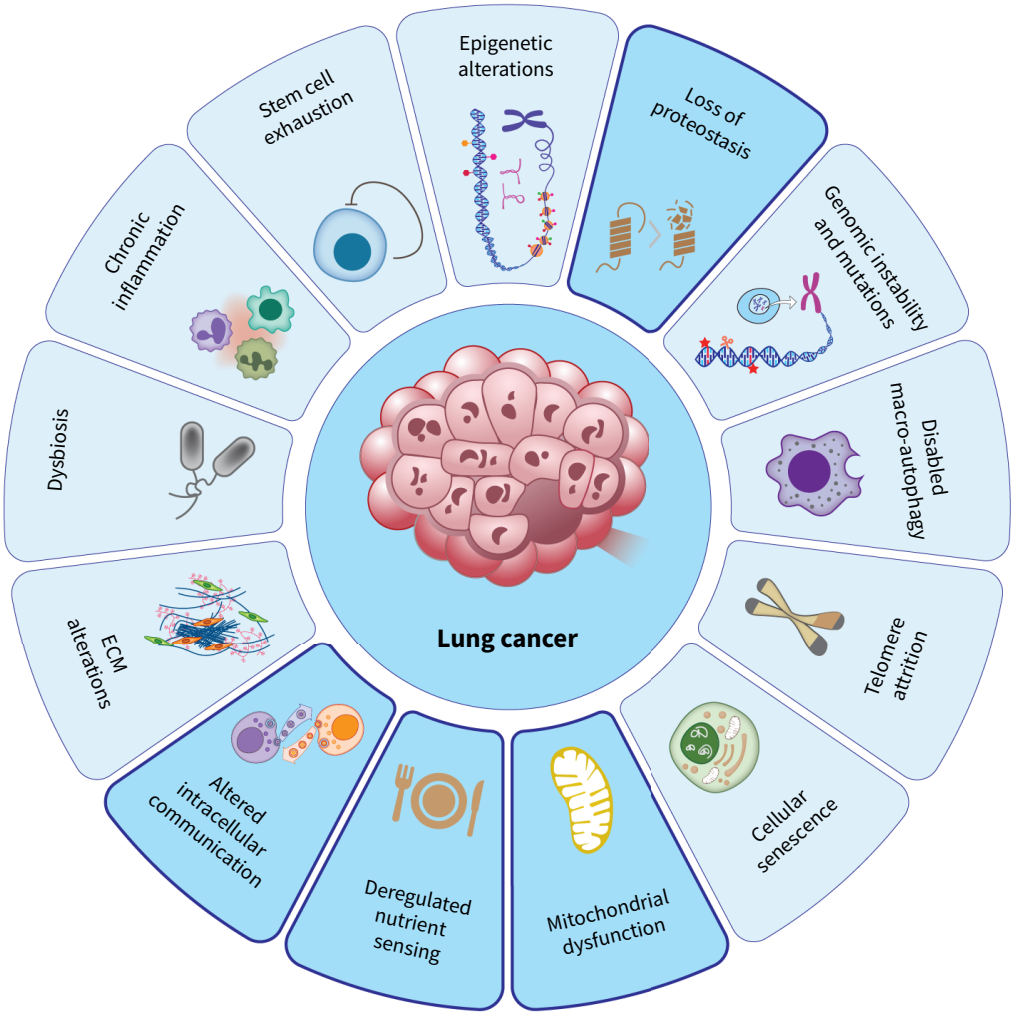


FIGURE 5 The hallmarks of the ageing lung in lung cancer. All 13 hallmarks of lung ageing are identified in lung cancer subjects, implicating them in disease initiation and progression. The relative contribution and hierarchy of each hallmark may differ from other chronic lung diseases, and some may reflect secondary changes rather than primary drivers. Nonetheless, extensive research over the past decade has elucidated how each hallmark contributes to lung cancer pathogenesis. Among these, the most prominent and lung cancer-specific hallmarks are highlighted and include loss of proteostasis, mitochondrial dysfunction, deregulated nutrient sensing, and altered intracellular communication. ECM: extracellular matrix.

Telomere attrition in IPF

Telomere shortening is intricately linked to IPF pathogenesis and a promising biomarker for diagnosis, disease progression and mortality risk [220–223]. Mutations in genes involved in telomere maintenance, such as *TERT*, *TERC*, the TERT complex-associated *DYSKERIN1* and *RTEL1*, result in shortened telomeres and are found in families with hereditary IPF [224–226]. In addition, patients exhibit extrapulmonary manifestations, which is associated with a lower survival rate [227]. Most IPF patients, including those without familial predisposition or identified mutations, have short telomeres regardless of their chronological age [220, 223] and acute exacerbations are associated with shorter telomeres than stable IPF patients [228]. Fibrotic lesions have significantly shortened telomeres compared to nondiseased tissue [229], which is associated with disease severity and survival [230]. Telomere shortening leads to chromosomal instability, aneuploidy, and activation of the cGAS-STING pathway, which amplifies inflammation and fibrosis [231]. Similarly, physiological ageing in mice induces lung fibrosis with telomere shortening, while telomerase gene therapy prevents fibrosis in telomere-deficient or bleomycin-injured mice [232, 233].

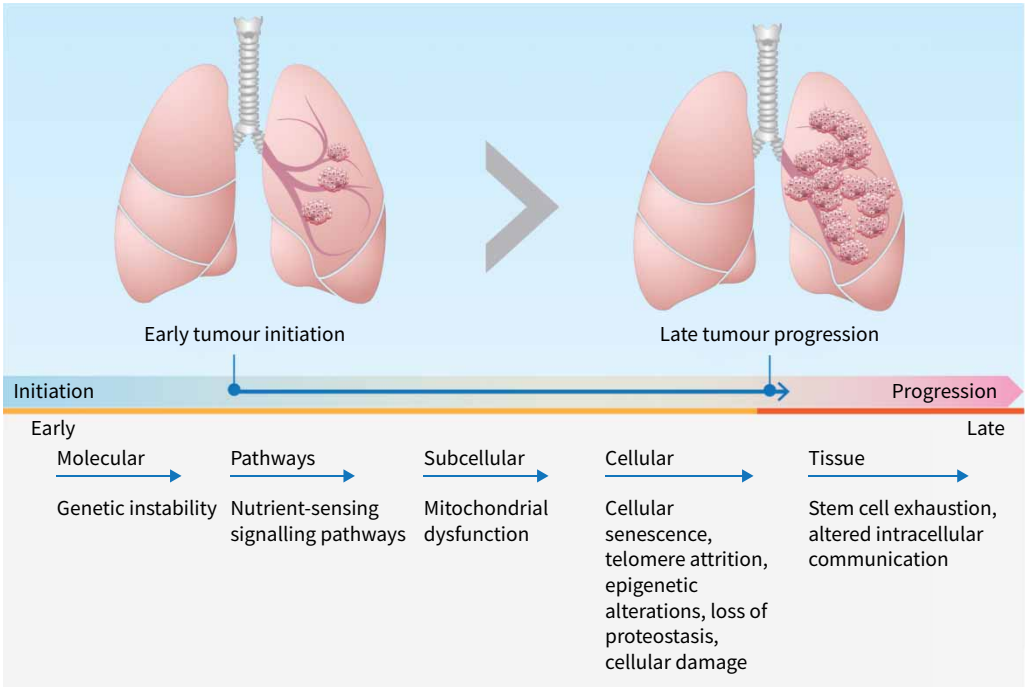


FIGURE 6 Schematic representation of ageing-related hallmarks driving lung cancer initiation and progression. The figure illustrates how distinct hallmarks of ageing, ranging from molecular damage (*e.g.* genomic instability) to tissue-level dysfunction (*e.g.* stem cell exhaustion), contribute to lung cancer development. During early tumour initiation, molecular and cellular hallmarks are predominant. As the tumour progresses, alterations in signalling pathways, mitochondrial dysfunction and impaired intercellular communication become increasingly relevant. The timeline suggests a dynamic interplay, with specific hallmarks becoming more prominent at different stages of tumour evolution, from early transformation to advanced malignancy.

Epigenetic alterations in IPF

In IPF, histone acetylation and DNA hypermethylation disrupt normal gene regulation correlating with altered gene expression [234–237]. Epigenome analyses revealed hundreds of differentially methylated CpG islands in IPF lungs, affecting genes involved in apoptosis, morphogenesis, and biosynthesis [238]. In airway macrophages, epigenetic profiling revealed high heterogeneity, but no evidence of accelerated ageing based on epigenetic clocks [239]. Moreover, epigenetic reprogramming of lipid and glucose metabolism in airway macrophages is linked to disease severity [240]. Histone modifications, particularly HDAC-mediated changes, influence fibrotic gene expression [241, 242]. IPF patients exhibit dysregulated expression of multiple miRNAs, and experimental modulation of specific miRNAs (including, but not limited to, let7, miRNA21, 29 and 101) induces other ageing hallmarks and fibrotic changes in mice [243–248]. Along this line, recent studies highlighted miRNA33 overexpression in airway macrophages of IPF patients contributing to mitochondrial dysfunction and fibrosis [249].

Loss of proteostasis in IPF

Rare familial IPF cases with heterozygous mutations in *SFTPC* or *SFTPA2* genes result in abnormal protein folding, and activation of the UPR, often leading to apoptosis [250–256]. Induced pluripotent stem cell-derived AT2 cells modelling these mutations confirm impaired progenitor capacity. Viral infections can exacerbate this stress, especially in aged lungs, where they trigger fibrosis [257, 258]. UPR activation is observed in AT2 cells in sporadic IPF [259–262]. Pharmacological and genetic models show that chronic UPR dysregulation promotes inflammation, epithelial senescence and fibrosis [260, 263–265]. ER chaperone Grp78 (BiP) is critical in this context; its deficiency exacerbates fibrosis and epithelial ageing [266, 267]. Heat shock proteins (HSPs), particularly HSP70, are reduced in IPF, impairing stress responses. HSP70 polymorphisms may be protective, whereas anti-HSP70 autoantibodies are associated with poor prognosis [268–271]. is disrupted in IPF, with increased 26S proteasome activity contributing to myofibroblast differentiation and senescence [272]. The immunoproteasome is elevated in aberrant epithelial cells of IPF patients, in physiologically and prematurely aged mice which is associated with $CD8^+$ T-cell activation [39, 273–276]. The integrated stress response (ISR) is persistently activated in IPF.

Its inhibition with ISRIB promotes AT2-to-AT1 differentiation, epithelial repair, and limits monocyte-driven fibrosis in young and aged models [277–279].

Disabled macroautophagy in IPF

Autophagy activity is reduced in IPF lungs, and its inhibition experimentally induces epithelial and myofibroblast senescence as well as ECM production [280, 281]. Transforming growth factor (TGF)-β1 suppresses autophagy *via* mTORC1 [280, 282]. In bleomycin models, autophagy protects against fibrosis, but declines with age. Reduced PARK2 impairs mitophagy, activates platelet-derived growth factor receptor (PDGFR)/PI3K/AKT signalling, drives myofibroblast proliferation, and can be reversed by PDGFR inhibition [283]. In IPF, PINK1 and PARK2 are reduced in BAL cells, while ROS and Akt1-driven mitophagy in macrophages increase, promoting TGF-β1 production and apoptosis resistance [284, 285]. Downregulation of autophagy-related proteins such as EI24, PLAC8 and ATG4B exacerbates fibrosis in animal models, whereas their overexpression mitigates it [286–288]. Deletion of Atg7, Atg5 in myeloid cells leads to spontaneous lung inflammation and fibrosis *via* inflammatory activation [289]. mTOR overactivation, as seen in Tsc1-deficient mice, worsens fibrosis, while rapamycin-induced autophagy improves outcomes [290]. USP13 loss with ageing impairs autophagy and promotes fibrosis, with downregulation in IPF patients and aged fibrotic mice [291].

Dysregulated nutrient sensing in IPF

Impaired nutrient sensing is increasingly recognised as a key contributor to IPF pathogenesis. IGF-1 is upregulated in IPF and signals *via* PI3K/AKT, with context-dependent effects on ATII cells and fibroblasts [292–296]. Its activity, modulated by altered IGF-binding proteins in IPF, suggests spatiotemporal regulation [293, 297]. AMPK, often downregulated in IPF under CBX5 control, promotes fibroblast activation and ECM accumulation, while also regulating epithelial fate and ATII differentiation [298, 299]. Metformin, an AMPK activator, reduces fibrosis in pre-clinical models [300–302], although clinical evidence is inconclusive [303, 304]. In contrast, mTOR signalling is upregulated, driving fibroblast proliferation, collagen synthesis, and suppressing autophagy [305–308]. Targeting mTOR has shown promise in pre-clinical models [309–311], and target engagement in IPF lungs in a proof-of-mechanism study [312]. However, dysregulation of the AKT/mTOR axis is intertwined with mesenchymal–epithelial interactions, as loss of the AKT-inhibitor phosphatase and tensin homologue promotes fibroproliferation and affects epithelial integrity [313–317]. The hypoxic and lactate-rich IPF microenvironment activates hypoxia-inducible factor (HIF)-1α, shifting metabolism toward glycolysis, suppressing oxidative phosphorylation, and promoting matrix accumulation [318]. Elevated HIF-1α levels under normoxic conditions suggest a pseudohypoxic state, reflecting impaired nutrient sensing.

Mitochondrial dysfunction in IPF

In IPF lungs, mitochondrial dysfunction is evident in AT2 cells, fibroblasts and macrophages [249, 319, 320]. Fibrotic lungs show a decrease in glycolysis, β-oxidation, and TCA cycle, with alveolar macrophages in fibrotic lungs increase fatty acid oxidation to compensate for the glycolytic shift [239, 321]. Ageing fibroblasts and IPF lung myofibroblasts exhibit increased mitochondrial uncoupling protein 2, leading to oxidative stress and senescence [322]. In AT2 cells, mitochondrial impairment is associated with ER stress, defective mitophagy, and the release of mtDNA [323, 324]. IPF patients show elevated mtDNA in plasma and BALF, with BALF levels further increased during acute exacerbation [325, 326]. Mitochondrial ROS production involves pro-fibrotic TGF-β signalling and NOX4 activation in the fibrotic lung [327–329]. Deficiency of the complex I subunit NDUFS2 contributes to AT2-AT1 transition cell accumulation, senescence and ISR activation exacerbating fibrosis [277]. Mitochondrial fatty acid oxidation adds to the regulation of lung progenitor cell repair responses, and deficiency impairs lung repair [330]. In addition, decreased expression of the mitochondrial ANT1 in IPF alveolar epithelial cells promotes cellular senescence [331].

Cellular senescence in IPF

Senescent cells are consistently found in IPF AT2, airway epithelial and fibroblast cells [332, 333]. Notably, AT2 cells have been recently described to demonstrate the greatest transcriptional changes in healthy aged lungs [334]. AT2 cells show impaired proliferation and abnormal senescence signalling, reflected in deficient alveolosphere formation [335]. Senescent fibroblasts similarly fail to support alveolospheres and resist apoptosis, contributing to persistent ECM production [336]. Single-cell RNA-sequencing has identified epithelial populations co-expressing AT1 and AT2 markers along with senescence-associated genes [337–339]. Senescent cells activate pathways including cGAS/STING and p53-Mdm2, linked to DNA damage responses and apoptosis. They upregulate MHC class I antigen presentation activating CD8T-cells [340] and release SASP factors that disrupt tissue repair [332]. In IPF, elevated levels of SASP markers (*e.g.* IL–8, TGF–β, MMP–1/7/9, GDF15) are detected in BALF, sputum,

serum, and lung tissue and rise during acute exacerbations [341–347]. Animal studies confirm that senescent AT2 cells promote fibrogenesis [332, 333, 348–350]. Accordingly, therapies promoting their clearance are emerging as promising strategies for IPF treatment [351, 352].

Stem cell exhaustion in IPF

Stem cell dysfunction is a key driver of IPF. AT2 cells show senescence and exhaustion due to telomere shortening, mitochondrial dysfunction, and ER stress [333, 350, 353, 354]. With age and injury, bronchiolar progenitors including BASCs and club cells expand, while AT2 cells decline, a shift driven by H3K9me2 [355, 356]. Dysregulated Hippo-YAP/TAZ–β-catenin–Myc signalling gives rise to supercompetitive BASCs that displace AT2 cells [357]. Novel intermediate cells like AT0 and TRB-SC, augmented in fibrotic regions, contribute to aberrant repair [358, 359]. Aberrant basaloid epithelial cells in IPF, display senescence and activate Wnt, TGF-β, and Notch signalling, disrupting repair [337, 360, 361]. Spatial transcriptomics reveal fibrotic niches dominated by basaloid cells and myofibroblasts [362, 363], with epithelial and vascular loss preceding fibrosis [364]. IPF endothelial and mesenchymal cells show stress- and age-associated phenotypes, including hypoxia, YAP/TAZ activation, and accumulation of transitional states [357, 365–367].

Altered intercellular communication in IPF

Altered intracellular communication is a prominent feature of IPF on many levels, including establishment of an inflamm-aged environment and the occurrence of an immunosenescent milieu [332, 368, 369]. Here, we focus on extracellular vesicles as emerging and important mediators of intercellular communication. Various cell types secrete extracellular vesicles, including epithelial cells, macrophages and fibroblasts, and IPF patients show an increase in extracellular vesicles in their BALF [370–372]. Among these, fibroblast-derived extracellular vesicles play a key role by exacerbating fibrosis through the transfer of pathogenic molecules including SFRP1, SASP components, and pro-fibrotic miRNAs [371, 373–375]. These extracellular vesicles affect multiple cell types and amplify the fibrotic response. IPF-specific extracellular vesicles can be detected in various body fluids, including plasma, sputum, and urine, indicating the potential for cross-organ signalling [376–379].

ECM alterations in IPF

Increased ECM deposition is a fibrotic hallmark correlating with age [380–383]. Klotho, an ageing-associated protein, has been demonstrated to act as a master regulator of TGF-β, ECM and cell migration in experimental fibrosis [382], while MDM4, a stiffness-regulated p53 inhibitor, attenuates fibrosis when inhibited in aged mice [384]. In IPF, a major driver of ECM remodelling is activated fibroblasts showing persistent pro-fibrotic signalling and senescence [276, 301, 367]. ECM secreted by lung fibroblasts from older animals can drive myofibroblast differentiation [385, 386]. Recent evidence suggests that other structural cells, including alveolar epithelial cells, which are senescent in IPF, contribute to ECM [387–389]. In line with this, MMP14 is elevated in IPF lung epithelium; its deletion in mice worsens fibrosis, while deficiency increases epithelial senescence [390]. It is likely that these cells change their ECM production profile with age, similar to fibroblasts [391] and as has been shown in other organs, such as renal fibrosis [392]. Notably, senolytics reduce SASP alongside ECM markers in alveolar epithelial cells [333].

Dysbiosis in IPF

IPF progression has been linked to dysbiosis and higher bacterial load, which is associated with increased mortality [393, 394], and patients with high bacterial load and low α-diversity have a higher risk of acute exacerbation and death, consistent with reductions in microbial diversity observed in IPF patients [395, 396]. Corisin, a peptide from *Staphylococcus nepalensis*, is elevated during IPF exacerbations and exacerbates fibrosis in hTGFβ1 transgenic mice [397]. In bleomycin-induced lung injury in mice, dysbiosis occurs before peak tissue damage, and germ-free mice are protected from mortality, highlighting the pathogenic role of the microbiome [398]. In bleomycin-treated mice, *Candida albicans* overgrowth worsens fibrosis through Th17 responses [399]. Microbial metabolites like sodium butyrate reduce inflammation and lung fibrosis [400]. Quercetin treatment in rats attenuates fibrosis, reduces cellular senescence, and alters gut microbiota [401]. These findings highlight the relevance of microbial dysbiosis in IPF pathogenesis and support future translational studies linking human observations with experimental models.

Chronic inflammation in IPF

Both innate and adaptive immunity contribute to IPF. Elevated neutrophils, eosinophils, macrophages, and cytokines such as IL-8, TGF-β, IGFBP-2, and MMP-7 are found in patient sputum and BALF [341, 402, 403]. Following epithelial injury, alarmins (TSLP, IL-25, IL-33) drive type 2 immunity promoting fibrosis [404–407]. Macrophages amplify fibrotic signalling through cytokine and growth factor secretion, L-arginine metabolism, and matrix remodelling [408–410].

Tertiary lymphoid structures in IPF lungs harbour dendritic, T-, and B-cells [411, 412]. B-cells expand in IPF, producing autoantibodies and promoting fibrosis, while IgA^+ and $MZB1^+$ plasma cells correlate with lung function decline [413–415]. CD8T-cell–macrophage interactions impair alveolar regeneration after viral pneumonia [416], and IL-17A-producing $CD4^+$ T-cells promote fibrosis in murine models [417]. A recent preprint shows that in aged mice, exhausted granzyme K^+ T-cells induce ATII cell senescence, contributing to nonresolving fibrosis [418].

Conclusion

Recent work shows that many more cell populations in IPF exhibit pronounced ageing phenotypes than previously appreciated, including AT2 cells, macrophages and mesenchymal cells, but also endothelial cells, spanning both cell-autonomous and intercellular changes as well as ECM dysregulation. Key hallmarks, including cellular senescence, telomere shortening, loss of proteostasis and mitochondrial dysfunction are mechanistically linked to pathology (figure 7) and are being targeted by emerging (pre-) clinical therapies.

Therapies to target ageing

One area of the ageing field that has expanded greatly over the past 10 years is the identification and development of new anti-ageing strategies to support the management of chronic age-related disease (table 1). Chronic lung diseases have been at the forefront of clinical trials for senomorphic and senolytic therapy (table 2). An important area of development is senotherapy, in which senescent cells are targeted. This strategy hopes to restore tissue homeostasis and prevent the harmful effects of senescent cells by targeting them. This area is divided into two principal areas: senolytics and senomorphics (figure 8).

Senolytics are drugs that selectively kill and remove senescent cells by taking advantage of changes in anti-apoptotic mechanisms in senescent cells; they reactivate apoptotic pathways in senescent cells and selectively kill them before they are removed by the immune system. The concept of eliminating senescent cells and extending lifespan stems from groundbreaking work in which senescent cells were genetically removed in old mice extending the lifespan and healthspan of mice [419]. First-generation senolytics were developed to exploit anti-apoptosis mechanisms, while second-generation senolytics exploit surface markers and specific phenotypes of senescent cells. Many pre-clinical studies and even first feasibility studies clinical trials with senolytics in humans were then conducted in IPF patients [351, 352], while less pre-clinical evidence is present in other CLD. Senomorphic strategies target central signalling hubs of senescent cells including mTOR or Janus kinase (JAK)/signal transducer and activator of transcription proteins (STAT) or sirtuins, not to deplete, but to reprogramme senescent cells to neutralise or rejuvenate them. Alternative strategies to reduce the age-related number of senescent cells and the chronic diseases they cause include modulating the immune system and (re)activating immune cells to eliminate senescent. Most of the current therapeutic interventions targeting the hallmarks of ageing have focused on either the immune system or senescent cells, but there is also initial pre-clinical work investigating the effects of targeting the other hallmarks of ageing (table 1). Furthermore, some ageing-targeting therapies have already entered clinical trials for the treatment of chronic lung diseases (table 2), further highlighting the enormous potential these hold for a paradigm-shifting therapeutic approach. However, these therapies should be used cautiously and with a clear understanding of the senescence mechanisms specific to each disease. As noted by Lemay *et al*. [420], senotherapeutic agents can have beneficial or harmful effects depending on whether they are given early or late in disease progression. Senolytics are intended for short-term use, while senomorphics require continuous treatment due to persistent SASP production. Early senescence may be protective through antiproliferative effects, especially in cancer, whereas persistent senescence contributes to vascular and tissue remodelling in COPD and IPF. Because senescence is heterogeneous across cell types, therapies must be tailored to disease stage and cellular context. Future single-cell studies will help refine these approaches by identifying disease- and stage-specific senescent cell populations.

Conclusion

The past decade has seen a tremendous expansion on research and refinement of definitions of the hallmarks of ageing. Although to a different degree, we now have evidence for all (extended) hallmarks of ageing in major chronic lung disease, corroborating that ageing is a main driver (and risk factor) for chronic lung disease. ECM dysregulation, which we postulated as a hallmark of lung ageing in 2015, is now being suggested as more generalisable integrative hallmark of ageing [421]. It has been shown that ageing is affecting the composition and organisation of the ECM, leading to reduced viscoelasticity [422]. Hyaluronic acid synthase, a crucial glycosaminoglycan in the extracellular matrix, extends the healthspan and lifespan of naked mole rats and leads to improved musculoskeletal function and reduced inflammaging in ageing mice [423]. Alteration in ECM can be driven by other hallmarks and, in turn, can impact specific

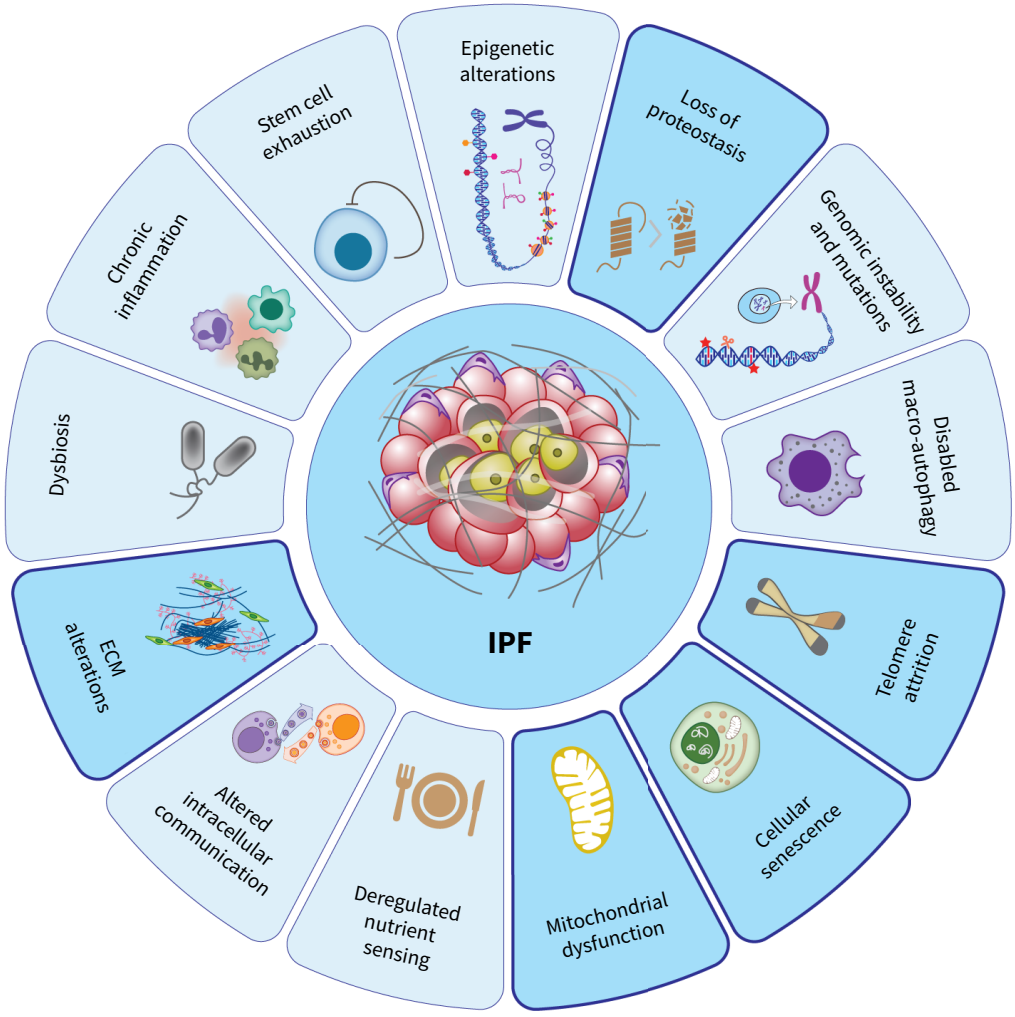


FIGURE 7 Hallmarks of the ageing lung in idiopathic pulmonary fibrosis (IPF). All 13 hallmarks of lung ageing are identified in IPF subjects, implicating them in disease initiation and progression. The relative contribution and hierarchy of each hallmark may differ from other chronic lung diseases, and some may reflect secondary changes rather than primary drivers. Nonetheless, extensive research over the past decade has elucidated how each hallmark contributes to IPF pathogenesis. Among these, the most prominent and IPF-specific hallmarks are highlighted and include extracellular matrix (ECM) alterations, telomere attrition, loss of proteostasis, cellular senescence, and mitochondrial dysfunction.

hallmark mechanisms such as inflammation, cellular senescence, mitochondrial homeostasis, and stem cell exhaustion. However, ECM alteration can activate other hallmarks, such as senescence and mitochondrial dysfunction. It has been shown that reduced ECM integrity facilitates TGF-β mediated mitochondrial fission and unfolded protein [424]. Overall, many of the recent studies have begun to investigate the connection and potential hierarchy of hallmarks and how this leads to age-driven maladaptation and failure of central lung maintenance and repair processes (figure 9). Overall, cellular ageing hallmarks reflect cellular stress response pathways, which are critical resilience mechanisms. Failure of these responses represents the Achilles' heel of premature ageing. This has been highlighted in studies in centenarians, long-lived animals, and other model organisms in which central stress and maintenance pathways such as DNA damage control, hypoxia sensing, and the UPR promote longevity [425]. These pathways transiently halt proliferation and macromolecule synthesis to allow repair, but depending on stress type, intensity, and cellular context, they can lead to either recovery, senescence or controlled cell death. The outcomes likely impact innate immune activation, ranging from SASP-driven inflammation to type I interferon responses, extracellular vesicle release, or inflammatory cell death, further demonstrating the interconnectivity of ageing hallmarks. Notably, centenarians maintain low but functional innate immune function, ensuring adequate stress sensing while avoiding chronic inflammation [425]. Thus, the quality of stress responses

TABLE 1 Pre-clinical data on therapeutic targets against the hallmarks of ageing: current and future potential therapeutic interventions developed to target the hallmarks of ageing and their evidence for use in age associated lung disease

Class of senotherapeutic therapy	Molecule	Mechanism of action	References to supportive *in vitro*/*in vivo* studies		
			IPF	COPD	Lung cancer
First generation of senolytics					
Inhibitor of senescent cell anti-apoptotic pathways	Dasatinib+quercetin	Tyrosine kinase inhibitor and a natural flavonoid with antioxidant properties	[332, 333, 352]	[427]	[428, 429]
	Navitoclax (ABT-263)	A potent inhibitor of Bcl-xL, Bcl-2 and Bcl-w which induces mitochondrial pathway apoptosis	[430, 431]	[432]	[433]
	Venetoclax (ABT-737)	BH3 mimetic inhibitor of Bcl-xL, Bcl-2 and Bcl-w, which induces mitochondrial pathway apoptosis; poor bioavailability	No studies	[434]	[435]
	FOXO4-Dri	Senolytic peptide which disrupts the interaction between FOXO4 and p53 in the nucleus, allowing translocation of p53 to the mitochondria and induction of apoptosis	[436]	[437]	[438]
	UBX1325	A BCL-xL inhibitor	No studies in the lung, but evidence in other organs/model [439, 440]		
	Fisetin	Antioxidant flavonoid that has senolytic effect in some cell types	[441]	[442]	[443]
Second generation of senolytics					
CAR-T therapy	uPAR CAR T-cells	CAR T-cells generated to target cell surface marker uPAR, which is upregulated on senescent cells	No studies	No studies	[444]
	NKG2D CAR T-cells	CAR T-cells generated to target cell natural killer group 2 member D ligands (NKG2DLs)		[445]	
Cardiac glycosides	Ouabain/digoxin	Inhibitor of Na^+/K^+-ATPase	[446]	[45]	[447]
Galacto-conjugates	Navitoclax-galactosidase	A galactose-derived prodrug of navitoclax that is activated by b-galactosidase	No studies	No studies	[448]
Targeting senescence cell Iron overload	TRX-CBI	Fe(II)-activatable prodrugs have been designed to selectively kill iron overload senescent cells		[449]	
Glutamine synthesis	CB839	Senescent cells display increased glutaminolysis and inhibition of glutaminase-1 enzyme induces apoptosis of senescent cells		[450]	
Senostatics					
mTOR inhibitors	Rapamycin, everolimus, AZD8055	Inhibitors of mTOR	[310, 451]	[53]	[452–454]
AMPK activators	AICAR, metformin	Activators of AMPK leading to mTOR inhibition	[300, 310]	[54]	[455]
Sirtuin-activating compounds	Resveratrol, SRT-2172, SRT1720 NAD^+ boosters	Activators of the sirtuin family of age associated deacetylases	[456]	[457–459]	[460]
Mitochondrial targeting therapies	mitoQ, mitoTEMPO, SkQ1, SS-31,	Therapeutic directly targeting the mitochondrial, especially mROS	[461]	[59, 462]	[463]
JAK/STAT inhibitors	Ruxolitinib, JSI-124, STA-21	Inhibitors of the JAK/STAT pathway	[464]	[65]	[465, 466]
cGAS-STING	H-151 PF-06928215, C-176	Inhibitors of the cGAS-STING pathway	[467]	[468]	[469, 470]
Alternative therapeutic strategies to target the hallmarks of ageing					
Targeting lung dysbiosis/ gut–lung axis	Targeting of antibiotics/ probiotics, faecal transfer	Targeting of bacterial metabolites, antibiotics/ probiotics, faecal transfer		[99, 471]	
Resetting of the epigenetic clocks	Cell based therapies/ iPSCs	Epigenetic reprogramming			
Vaccination	CD153 vaccine	CD153 vaccine which targets senescent T-cells		[472, 473]	

IPF: idiopathic pulmonary fibrosis; CAR: chimeric antigen receptor; mTOR: mammalian target of rapamycin; AMPK: AMP-activated protein kinase; JAK: Janus kinase; STAT: signal transducer and activator of transcription proteins: cGAS-STING: cyclic GMP–AMP synthase stimulator of interferon genes; BCL: B-cell lymphoma; FOX: forkhead box; uPAR: urokinase-type plasminogen activator receptor; CAR-T: CAR T-cell therapy; Na: sodium; K: potassium; Fe: iron; mROS: mitochondrial reactive oxygen species; iPSCs: induced pluripotent stem cells.

TABLE 2 Clinical trials evaluating senotherapeutic agents in chronic lung diseases: clinical trials investigating the potential benefits of reducing senescent cell burden or modulating senescence-associated effects in COPD, idiopathic pulmonary fibrosis (IPF) and lung cancer.

	Treatment	Therapeutic class/target	Phase	Clinicaltrials.gov identifier and reference
COPD exacerbations	Metformin	mTOR pathway	IV	NCT01247870 [474, 475]
COPD	Metformin	mTOR pathway	II	NCT03651895 [476]
COPD	NAD^+ precursor nicotinamide riboside	Loss of NAD^+	NA	NCT04990869 [458]
IPF	Dasatinib+quercetin	Tyrosine kinase+flavonoid	I	NCT02874989 [351, 352]
IPF	Setanaxib, GKT137831	NOX1/4	II	NCT03865927 [477–479]
IPF	Rentosertib, INS018_055	Kinase TNIK	IIa	NCT05938920 [480] (China) and NCT05975983 [481, 482] (USA)
Lung cancer (KRAS or NRAS mutations)	Trametinib and navitoclax	BCL-xL inhibitor and tyrosine kinase	I/II	NCT02079740 [483]

mTOR: mammalian target of rapamycin; NA: not applicable; NOX: NADPH oxidase; TNIK: TRAF2- and NCK-interacting kinase; BCL: B-cell lymphoma.

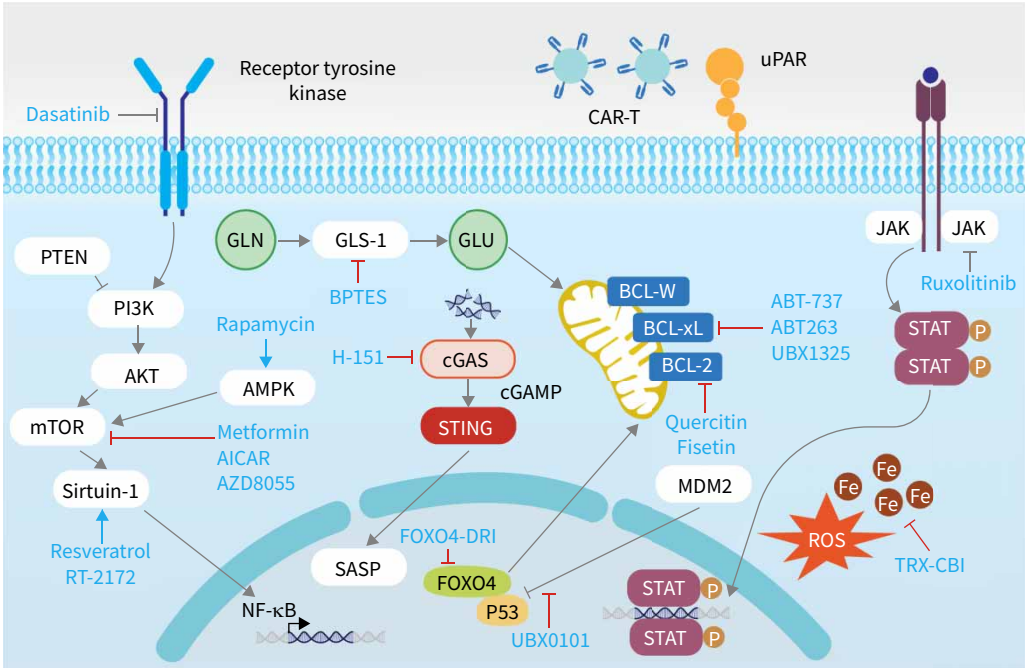


FIGURE 8 Senotherapeutic strategies for treating chronic lung diseases. First-generation senolytics and senomorphics targeted pathways and receptors which regulate a senescent cell ability to be resist the induction of apoptosis or drive senescence-associated secretory phenotype (SASP) release. This included targeting the phosphoinositide-3-kinase (PI3k)–protein kinase B (Akt)–mammalian target of rapamycin (mTOR) pathway, receptor tyrosine kinases, the sirtuins, and anti-apoptotic mitochondrial proteins. Through the use of high-throughput drug screens, identification of senescent cell-specific surface markers and senescent cell phenotypical changes, new second-generation senolytics are emerging. These utilise novel technologies such as chimeric antigen receptor T-cell therapy (CAR-T) to target surface markers, target metabolic changes in senescent cells such as glutaminase (GLS)-1, target the increased levels of iron found within senescent cells as well as activation of pathways such as the cyclic GMP-AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway or interactions between p53 and forkhead box family O transcription factors (FOXO)4. All these therapeutics try to either kill the senescent cell or target the SASP leading to reduce chronic inflammation and allow regeneration of tissue. AMPK: AMP-activated kinase; BCL: B-cell lymphoma; DRI: D-retro-inverso; Fe: iron; Gln: glutamine; Glu: glutamate; MDM2: Mouse double minute 2 homolog; p53: tumour protein p53; PTEN: phosphatase and tensin homologue; ROS: reactive oxygen species; uPAR: urokinase-type plasminogen activator receptor. Table 1 presents a more comprehensive list of current therapeutic targets.

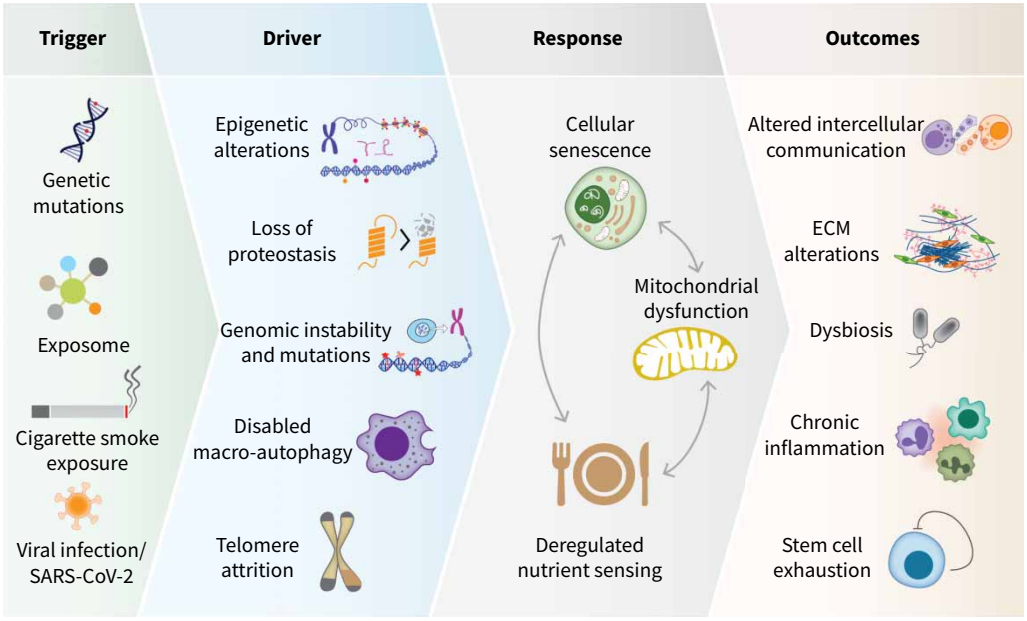


FIGURE 9 The interconnection and potential hierarchy of ageing hallmarks. Lung ageing is driven by internal and external triggers, which may induce specific hallmarks that subsequently lead to cellular responses and affect major biological functions related to lung diseases. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; ECM: extracellular matrix.

critically determines health trajectories, and a more fine-tuned approach to preserve these pathways is required to sustain lung health and resilience across ageing. Only recently, studies focusing on cell types and mechanisms relevant to healthy ageing have been conducted [334, 426]. It will be essential for future studies in this field to expand research to better understand disease- and cell-specific ageing processes and specifically gain insight into the temporal and hierarchical connection of hallmarks in early or even pre-disease states. This could lead to the identification of resilience mechanisms that are central to adapt to molecular damage and keep lung maintenance and repair intact. Importantly, the past decade saw the first studies that target hallmarks of ageing in lung disease, from pre-clinical investigation to ongoing clinical studies, thus providing valuable proof-of-concept for ageing as a viable therapeutic target. While these studies have laid important groundwork, they are focused largely on single hallmarks, and the focus of novel disease-tailored therapeutics that target interconnected ageing processes is important for future progress in the development of therapeutics for lung diseases.

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