Chronic lung diseases: prospects for regeneration and repair

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Treatment outcomes with COPD and IPF are suboptimal. Better understanding of the diseases, such as targetable repair mechanisms, may generate novel therapies, and earlier diagnosis and treatment is needed to stop or even reverse disease progression. https://bit.ly/2Ga8J1g

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ABSTRACT COPD and idiopathic pulmonary fibrosis (IPF) together represent a considerable unmet medical need, and advances in their treatment lag well behind those of other chronic conditions. Both diseases involve maladaptive repair mechanisms leading to progressive and irreversible damage. However, our understanding of the complex underlying disease mechanisms is incomplete; with current diagnostic approaches, COPD and IPF are often discovered at an advanced stage and existing definitions of COPD and IPF can be misleading. To halt or reverse disease progression and achieve lung regeneration, there is a need for earlier identification and treatment of these diseases. A precision medicine approach to treatment is also important, involving the recognition of disease subtypes, or endotypes, according to underlying disease mechanisms, rather than the current "one-size-fits-all" approach. This review is based on discussions at a meeting involving 38 leading global experts in chronic lung disease mechanisms, and describes advances in the understanding of the pathology and molecular mechanisms of COPD and IPF to identify potential targets for reversing disease degeneration and promoting tissue repair and lung regeneration. We also discuss limitations of existing disease measures, technical advances in understanding disease pathology, and novel methods for targeted drug delivery.

Introduction

COPD and idiopathic pulmonary fibrosis (IPF) both represent a substantial unmet clinical need. COPD has become the third leading cause of death globally [1], and IPF has a median survival of ∼3 years after diagnosis, with survival rates comparable to some aggressive cancers [2], and no observed improvement in survival from 2000 to 2012 [3].

In this article, we discuss the current limitations of treatment for COPD and IPF, and potential future strategies with a focus on disease subtypes and lung regeneration and repair. This article is based on discussions at a meeting organised by the authors on 28–29 November 2018 in Gothenburg, Sweden, and supported by AstraZeneca, involving leading global experts in obstructive lung disease who discussed the latest innovations and issues in chronic lung disease (the participants are listed in the Acknowledgements section).

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COPD

COPD is a largely preventable and treatable disease characterised by persistent airflow limitation and respiratory symptoms due to chronic inflammation, which causes structural changes, such as fibrosis of the small airways and alveolar wall destruction (emphysema) [1, 4]. Early pathological changes occur in the small airways, with associated inflammation, wall thickening, peribronchiolar fibrosis and loss of terminal and transitional bronchioles and associated vasculature, before the onset of emphysema [5–9]. These early and irreversible destructive events do not initially affect the lung function parameters usually used to define COPD (forced expiratory volume in 1 s (FEV_1)/forced vital capacity ratio), making early detection difficult [10]. Smoking is a key risk factor for COPD; however, nonsmokers can also develop COPD (especially in low- and middle-income countries) and many smokers do not develop COPD [11], indicating a role of genetic risk, epigenetics and other environmental factors in its development [12]. The most documented genetic risk factor for COPD is α_1-antitrypsin deficiency that represents a specific subtype of COPD (endotype), although different phenotypes exist within this subtype that appear to be caused by variations in other factors, such as tumour necrosis factor (TNF)-α [13]. Autoimmunity and aberrant immunity (suppression of host defence mechanisms and dysfunction of innate immunity) may also contribute to disease progression, especially as the disease advances [14–16].

IPF

IPF is commonly described as a specific form of chronic, progressive, fibrosing, interstitial pneumonia of unknown cause, usually occurring in the elderly [17]. IPF incidence appears to be increasing: the diagnosis of IPF in the UK has increased from approximately 20 per 100 000 patients in 2000 to nearly 40 per 100 000 patients in 2012 [3, 18]. IPF arises from repetitive micro-injuries to the bronchial and alveolar epithelium, which, along with immune system dysregulation [19, 20], results in progressive scarring and the destruction of lung structures [18, 21, 22]. The aetiology of IPF is unknown [3], but smoking is a risk factor and may influence IPF onset [23, 24]. Major genetic risk factors, such as the mucin 5B gene and defective telomerase, have been identified, pointing to future genetic stratification [25, 26]. Of note, pulmonary emphysema and IPF can co-exist in the same patient as a distinct entity termed combined pulmonary fibrosis and emphysema (CPFE) [27]. This condition is characterised by emphysema in the upper lobes and fibrosis in the lower lobes of the lungs [27, 28]. CPFE is estimated to occur in up to 35% of patients with IPF [29].

Limitations of current treatment approaches

Commonly used maintenance treatments in COPD include β_2-agonists, anticholinergics, theophylline and corticosteroids [1]. Such treatments are primarily for improving lung function, reducing symptoms and the risk of exacerbations, and improving exercise tolerance and health status. To date, no disease-modifying treatments are available [30]. This is in sharp contrast with other chronic inflammatory-based diseases. In rheumatoid arthritis, for example, scientific advances and early treatment with disease-modifying drugs have resulted in the prevention of disease progression in up to 90% of patients [31].

Treatment options for IPF are even more limited and represent a pressing unmet clinical need [32]. Currently, only two antifibrotic drugs are recommended; namely, pirfenidone and the tyrosine kinase inhibitor nintedanib [17]. However, a recent analysis revealed that 40% of patients with confirmed IPF did not receive antifibrotics, reflecting a possible lack of understanding around the diagnosis and management of the disease, and problems with treatment access [33]. Furthermore, although these treatments may be life-extending [34, 35], potential adverse events could negatively impact quality of life [17], such as gastro-intestinal effects and photosensitivity with pirfenidone, and diarrhoea with nintedanib [36, 37].

Future treatment strategies for COPD and IPF

The marked unmet needs in COPD and IPF therapy highlight the need for new treatment strategies that focus on underlying disease endotypes, regeneration and repair.

A change in mindset is required among pulmonologists, regulators and policymakers to redefine perceptions of COPD and IPF. Current treatments have a “magic bullet” approach, where a single drug is intended to treat all forms of disease. However, both COPD and IPF are heterogeneous diseases with several clinical phenotypes [38] that may reflect multiple but, as of yet, mostly unidentified endotypes (subtypes of disease defined functionally and pathologically by molecular mechanism or treatment response) [39–41]. A move to a “complex subtypes” approach, where precision medicine allows COPD or IPF subtype-specific treatment, could be possible with combinations of interventions. Future treatment strategies may target different aspects of these diseases chronologically, or target several disease mechanisms simultaneously, with subsequent treatment withdrawal upon improvement. For new treatment strategies that focus on underlying disease endotypes, it will be crucial to study COPD and IPF at an early stage before confounding factors, comorbidities and disease progression mask subtle differences.

In the same way, both diseases have been described as "irreversible" [4, 42, 43]. However, lung regeneration, disease reversal and even a cure for COPD and IPF are the ultimate goals in disease management; merely slowing disease progression is important but does not completely address the unmet clinical need [44, 45]. Regeneration efforts could focus on activating the endogenous repair capacity of the lungs, and/or adopting exogenous regeneration through tissue engineering, bio-artificial scaffolds or adding healthy progenitor or stem cells to the lungs [46]. Evidence from retinoic acid studies shows that lung regeneration is feasible, at least in rodent models [47, 48]; however, we need a clear understanding of how endogenous repair processes become dysfunctional in the diseased lungs to identify targets for potential treatment strategies.

New targets for lung regeneration are being identified, but many of these may not be druggable *via* conventional approaches using either small-molecule inhibitors/activators or systemic antibodies [49]. New modality treatments are being developed, such as approaches using proteolysis-targeting chimaera (PROTAC), inhaled antisense oligonucleotides, gene editing (CRISPR: clustered regular interspaced short palindromic repeats) or exosomes that will allow us to target all pathways of interest (table 1). Although direct delivery to the target organ, in this case the lungs, is possible with inhaled approaches, new methodologies for delivering treatments are also needed.

Several practical considerations must also be borne in mind. The age and frailty of patient populations with COPD and IPF are likely to be among the greatest challenges to lung regeneration, as well as the existence of comorbid diseases. To achieve significant lung regeneration, it is likely that COPD and IPF

TABLE 1 Examples of emerging techniques to deliver therapy in patients with COPD and idiopathic pulmonary fibrosis (IPF) and their limitations

Technique	Description	Uses and advances made with the technique	Current limitations
PROTAC	Proteolysis-targeting chimaera that uses the cell's ubiquitin–proteasome system to target-specific proteins for degradation	Could induce the degradation of proteins previously considered "undruggable" [50] Highly selective for the target protein, with rapid, effective and prolonged degradation of the target [51] Valuable for mechanisms requiring precise targeting for degradation	Can only target a protein for degradation, not for modification
CRISPR	Can manipulate gene function through gene deletion, correction or replacement; enhancement of gene expression; base editing	Huge potential for target-specific genetic medication for gene therapy in COPD and IPF to target dysregulated genes or pathways (*e.g.* epigenetic changes to genes implicated in mucus hypersecretion in COPD) [52]	Concerns exist around safety and off-target effects; these are under investigation [53]
Inhaled antisense oligonucleotides	Single-stranded DNA or RNA (20–21 base pairs) complementary to the target mRNA	Knocks down the expression of the target gene [54] Can modulate molecules that cannot be targeted using antibodies [54] Inhalation could minimise toxicities associated with systemic exposure of antisense oligonucleotides [54]	Currently in the investigational stage Intracellular delivery to the site of action is a challenge [54]
Exosomes as delivery systems	A potential delivery system for nucleic acid drugs	Potential use in delivering drugs such as antagomirs or miRNA molecules, thanks to their low antigenicity and toxicity [55] Could target particular cell types *In vitro* and *in vivo* studies have shown promise in successfully delivering molecules [56]	Currently in the investigational stage

PROTAC: proteolysis-targeting chimaera; CRISPR: clustered regularly interspaced short palindromic repeats.

treatment will need to be at an earlier stage and in younger patients compared with what currently occurs in clinical practice. This argument is supported by evidence suggesting that early treatment and early smoking cessation have a positive effect on longitudinal lung function and symptoms [57]. COPD is currently diagnosed using spirometry [1], but these changes detected by spirometry occur relatively late in disease progression and are a poor measurement of peripheral airway obstruction in early disease [10]. Redefining COPD based on abnormalities in small airway function, measured using techniques such as magnetic resonance imaging and impulse oscillometry [58, 59], may identify disease earlier than current practises [10, 60] (table 2). Population screening of smokers for COPD could also be a possibility, but screening for IPF less so as it is an uncommon disease and difficult to diagnose [33].

Biomarkers

Biomarkers are central in identifying patient subgroups, phenotypes and endotypes [8, 78, 79]. They are crucial in monitoring and predicting disease progression and predicting responders to treatment [8, 79]. COPD and IPF are highly complex and heterogeneous, and no single biomarker has been identified for clinical applications in either disease [80–82]. Dividing COPD and IPF into endotypes is critical for breaking the diseases down into molecular pathways and disease mechanisms, and for linking molecular mechanisms to clinical features. Treatment targets for specific endotypes could thus be identified and could provide precision treatment to those patients most likely to respond [40, 83]. In the management of cancer, it has long been recognised that genetic mutations can give rise to cancer subtypes that predict prognosis and response to treatment [84]. A similar rationale needs to be applied to COPD and IPF to identify subgroups with distinct disease mechanisms [40, 83].

The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) and the Genetic Epidemiology of COPD (COPDGene) studies have identified numerous putative biomarkers in COPD. These include protein, cellular and genetic biomarkers associated with COPD characteristics and morbidity (including airflow limitation, emphysema and exacerbation frequency) [85–87]. The analysis of six inflammatory biomarkers (white blood cell count, C-reactive protein, interleukin-6, C-X-C motif chemokine ligand 8, TNF-α and fibrinogen) from patients in ECLIPSE led to the identification of a new COPD phenotype [88].

In IPF, several biomarkers are associated with specific phenotypes [89]. Protein degradation biomarkers and serum biomarkers have been identified that can discriminate between healthy individuals, patients with stable IPF and those with progressive IPF [90]. Four serum proteins have been identified from the metaplastic epithelium that could predict disease progression and mortality; namely, surfactant protein D, matrix metalloproteinase-7, carbohydrate antigen 19–9 and cancer antigen-125 [91]. A gain-of-function variant of the promotor of the mucin 5B (MUC5B) gene is associated with the pathogenesis of IPF [25]; identifying this variation in patients with pre-clinical IPF and targeting MUC5B could enable early diagnosis and prevent the progression of IPF to a state where the lung remodelling is irreversible [25, 92].

Early detection

As we learn more about COPD and IPF endotypes and phenotypes, advances in technology are required to identify these in patients and to allow for the early detection of disease and to monitor disease progression. Reliable tests for small airway function and the ability to quantify disease progression and its links to biomarkers will be essential for advancing our knowledge and for the management of COPD and IPF. Advances in the "-omics" field (for example, genomics, transcriptomics, proteomics, lipidomics and metabolomics) have led to new discoveries and promises to provide insights into endotypes. For instance, it may be possible to use blood samples to detect genomic biomarkers [93], and bioinformatic analysis may identify the activation of particular molecular pathways that could be targeted [94]. Also, breathomics of exhaled breath may help identify COPD phenotypes and provide biomarkers for diagnosis and disease progression [77].

A potential barrier to early, preventative therapies may be that patients who do not feel unwell or who are not experiencing any impact on their quality of life may be reticent about taking medication with associated side-effects. Payers may also be resistant to paying for medication when the current classifications of disease categorise the patient as "at risk" rather than having measurable disease, although it is noteworthy that primary prevention measures do exist in other diseases; for example, the treatment of systemic hypertension and hypercholesterolaemia to prevent cardiovascular diseases [95].

Since late disease is associated with profound structural damage to the lung that is currently irreversible [4, 96], there is great interest in identifying potentially treatable processes much earlier in disease, especially those around regeneration and repair [97–101].

TABLE 2 Examples of new or emerging techniques for studying COPD and idiopathic pulmonary fibrosis (IPF)

Technique	Description	Uses and advances made with the technique	Current limitations
Micro-CT imaging	High-resolution CT imaging	Higher-resolution *versus* standard CT imaging [61] Can reveal structural changes associated with small airway disease [61] Reveals massive loss in number and area of terminal bronchioles in patients with centrilobular emphysematous COPD [6] When partnered with parametric response mapping as an imaging biomarker, micro-CT could identify terminal bronchiole pathology in COPD [62]	Performed on *ex vivo* samples, or explants, rather than on the patient [6, 61, 62]
PET	Molecular imaging; most commonly measuring ^{18}F-FDG uptake	Has been explored as a noninvasive biomarker for pulmonary inflammation [63] Ability to quantify inflammation is under investigation [63]	Validation of imaging approaches required; changes in lung air, blood and water volumes depending on disease severity can cause variations in signals [63]
Gas diffusion MRI	Noble gases such as ^{3}He and ^{129}Xe used to visualise lung structure	Could be used to monitor disease progression and response to therapy [59] Can detect microstructural changes in the lung, even in asymptomatic smokers [59] Quantitative microstructure data obtainable by measuring gas diffusion in alveoli; the technique can differentiate between patients with COPD and healthy individuals [64] Alveolar sizes can be visualised to form a picture of alveolar loss in COPD [64] Provides sensitive and reproducible data on gas exchange impairment in IPF, correlating with spirometry data [65]	Adaption of existing scanners is required [66]
SPECT	Radiotracers used to image the lung, where both airways and blood flow can be imaged	Both the airways and blood flow can be imaged, allowing the detection of comorbidities such as pulmonary embolism [67, 68] Can detect abnormalities in apparently healthy smokers [69]	Only semi-quantitative [69] Not as high resolution as other imaging methods [68] Takes a long time to acquire an image (*e.g.* 45 min) [68]
IOS	Noninvasive measurement of respiratory mechanics in response to pressure oscillations	A reliable tool for investigating proximal and peripheral airways resistance in patients with COPD [70] Peripheral airway resistance and compliance using IOS closely linked to COPD severity and exacerbations [58] Could be used as a screening tool for early-stage COPD [58] Useful for patients who cannot perform spirometry manoeuvres [71]	The minimal clinically important difference in IOS parameters needs to be established

Continued

TABLE 2 Continued

Technique	Description	Uses and advances made with the technique	Current limitations
OCT	A high-resolution optical imaging method	Resolution down to micrometre scale [72] Can be used to accurately measure distal airways [73] Could detect early changes to the distal airways and appears to be more sensitive than CT [72, 73]	Ultrafine bronchoscopy (with sedation) required to reach the distal airways [73]
Multiple-breath nitrogen washout	Noninvasive measurement of residual nitrogen in the airways to detect any abnormalities in gas distribution in the lung	Does not require maximal effort and can be used in a paediatric setting [74] Provides information on abnormalities in the small airways, including terminal bronchioles [75] Can detect abnormalities in early disease [76]	Limited standardisation, which impacts the availability of widely applicable reference values [75]
Breathomics	Exhaled breath analysis to detect changes in volatile organic compounds	Could be used to diagnose COPD and differentiate COPD from asthma [77] May be able to predict disease progression [77] Could help distinguish COPD phenotypes [77]	Results can be confounded by parameters such as medication use, comorbidities, smoking and study site [77]

CT: computed tomography; PET: positron emission tomography; ^{18}F-FDG: ^{18}F-2-fluoro-2-deoxy-D-glucose; MRI: magnetic resonance imaging; SPECT: single-photon emission computed tomography; IOS: impulse oscillometry; OCT: optical coherence tomography.

Dysregulated processes presenting opportunities for regeneration and repair

Cellular senescence

Accelerated ageing and senescence are evident in the lungs of patients with COPD and IPF [102, 103]. This can be brought on by DNA damage, mitochondrial dysfunction, telomere shortening, reduced autophagy and stem cell exhaustion, and involves cell cycle arrest and a secretory profile of inflammatory proteins. This is central to lung development and wound repair. In the healthy individual, once wound repair is complete, senescent cells are removed following apoptosis triggered by infiltrating immune phagocytes. However, if senescent cells are not removed, their abnormal secretory profile can lead to pathological tissue changes [104].

Several steps in the senescence pathway could be targeted to halt accelerated ageing and senescence. Cellular senescence is associated with a loss of anti-ageing molecules, such as certain sirtuins and Klotho [105, 106]. The microRNA miR-34a is increased by activation of the phosphoinosite-3-kinase (PI3K)-mammalian target of rapamycin (mTOR) pathway, and downregulates the expression of sirtuin-1 and sirtuin-6; up-regulation of miR-34a in the lungs and cells of patients with COPD results in loss of sirtuin-1 and -6 [106, 107]. miR-570 is also increased in COPD and is activated by p38 mitogen-activated protein kinase, resulting in the downregulation of sirtuin-1 [108]. Inhibition of miR-34a and miR-570 with antagomirs rescues the loss of sirtuin-1 and sirtuin-6, thereby preventing the induction of senescence [106, 108]; the therapeutic administration of antagomirs, possibly *via* inhaled exosomes [55], could therefore represent a strategy to reverse accelerated ageing [106, 108].

Oxidative stress, *via* increased reactive oxygen species production or decreased antioxidants, is central in driving senescence in COPD through the activation of the PI3K-mTOR pathway [102, 109]. Reactive oxygen species are potentially generated by the mitochondria in response to cigarette smoke [102, 103]. This results in secretion of a senescence-associated secretory phenotype of inflammatory proteins, which include pro-inflammatory cytokines, chemokines, growth factors and proteases and may account for the low-grade inflammation seen in COPD and the affected patient's systemic circulation [105, 110]. The mTOR inhibitor rapamycin prevents senescence and inhibits components of the senescence-associated secretory phenotype *in vitro* in pulmonary artery smooth muscle and pulmonary vascular endothelial cells isolated from patients with COPD [109]. The effective dose of rapamycin was low and did not affect cell

growth rate, suggesting relatively low doses may be sufficient for a therapeutic effect, thereby reducing potential toxicity.

Multiple cell types are affected by senescence in COPD and IPF, including epithelial, endothelial, fibroblast and smooth muscle cells in COPD [108, 109, 111] and epithelial cells and fibroblasts in IPF [104, 112, 113]. The elimination of senescent cells, or senolysis, is another approach to tackle senescence. Experimental models have shown that the senolytic agents dasatinib and quercetin kill senescent cells and improve lung function [114], and a pilot study of these agents in patients with IPF has shown improvements in physical function with an acceptable safety profile over a 3-week period [115]. The senolytic drug navitoclax (ABT-263) has also been found to reverse pulmonary fibrosis and induce apoptosis in myofibroblasts implicated in fibrosis in animal models [99, 100].

Wnt/β-catenin signalling

The Wnt signalling pathway guides cells to certain fates during lung development and maintains tissue homeostasis in adulthood [116]. Wnt/β-catenin signalling is reduced in mouse models of elastase- and cigarette smoke-induced emphysema, which were attenuated upon Wnt activation with improvements observed in alveolar epithelial structure and function [98]. Cells affected by this pathway include alveolar epithelial type II (ATII) cells in the alveolar epithelium, which have self-renewal properties and rely on Wnt/β-catenin signalling to differentiate to ATI cells in response to alveolar epithelial injury [116]. ATI cells cover the majority of the lung surface area (95–97%) and are responsible for gas exchange, a key lung function [117]. The noncanonical Wnt ligand WNT-5A, which is overexpressed in lungs from animal models of COPD and patients with COPD, antagonises the canonical Wnt/β-catenin signalling pathway resulting in the inhibition of murine lung epithelial cell wound healing and transdifferentiation from ATII to ATI cells *in vitro* [118]. Lung-specific overexpression of WNT-5A exacerbated the development of emphysema, and prophylactic inhibition of WNT-5A could recuperate alveolar cell function and attenuate lung pathogenesis in COPD animal models [118]. In addition, activation of canonical Wnt/β-catenin signalling with lithium chloride improved alveolar epithelial structure and function in experimental models of emphysema [98]. The canonical Wnt receptor frizzled-4 (FZD4) facilitates ATII to ATI transdifferentiation. FZD4 expression was reduced in patients with COPD, correlating positively with lung function and negatively with smoking (pack-years) [119]. Cigarette smoke directly downregulated FZD4 *in vivo* and *in vitro*, thereby preventing Wnt/β-catenin signalling and alveolar tissue repair [119].

Interestingly, activated Wnt/β-catenin signalling in IPF leads to an increase in the Wnt target, WNT-1-inducible signalling protein-1 (WISP1), which in turn induces the expression and secretion of profibrotic mediators, contributing to lung fibrosis [120, 121]. Using antibodies to neutralise WISP1, Königshoff *et al.* [121] showed reduced pulmonary fibrosis, implicating WISP1 as a potential therapeutic target in IPF.

Several novel approaches to activating and inhibiting Wnt/β-catenin signalling are now in development and look promising with regard to restoring normal lung function in COPD and IPF [97, 122]. These discoveries point to several approaches that could reinstate cell and tissue homeostasis in COPD and IPF.

Stem cell therapy

The basal stem cells (BSCs) in the cartilaginous airways of the lungs are considered to be multipotent lung progenitor cells [123, 124] and drive homeostasis of the normal epithelium and regeneration following injury [123]. Therefore, they could be a potential regeneration target; targeting their proliferation and directing differentiation and stem cell transplantation/bioengineering [123]. In a study of smokers, reductions in the number and function of BSCs were observed in those with COPD compared with those without COPD [125]. Interestingly, low BSC counts in smokers without COPD were associated with lower lung function than in those with high BSC counts [125], which could represent an early pre-diagnostic stage of COPD. However, BSCs isolated from heavy smokers undergoing lung cancer surgery were found to have an increased proliferate potential *in vitro* compared with never-smokers, whereas ATII cell proliferation decreased [126]. This is in part because BSCs repair damaged DNA by nonhomologous end-joining, which is faster but more error-prone than homologous repair and increases the risk of mutagenesis [126].

Elevated BSCs were observed in the bronchoalveolar lavage fluid from patients with IPF in comparison to healthy individuals [127]. Normally located at the bronchoalveolar duct junction, BSCs were enriched in the alveolar compartment and frequently within fibrotic lesions of patients with IPF [127, 128]. This suggests an unexpected role of BSCs in the pathogenic bronchiolisation of the alveoli in IPF, where bronchial cells appear in this compartment by migration or transdifferentiation [127, 128].

While BSCs theoretically represent an opportunity to reverse COPD- and IPF-associated damage, we need to distinguish between healthy BSCs and those potentially carrying DNA mutations to enhance the positive effects without increasing the risk of pathogenic changes. The interactions between BSCs and immune cells and their role in IPF pathogenesis also need to be understood before BSCs can be considered as therapy.

A population of mesenchymal progenitor cells positive for stage-specific embryonic antigen (SSEA)-4, a cell-surface protein expressed by stem cells, has been identified in the lungs of patients with IPF. These SSEA-4 cells were found to display a pathological gene expression pattern, and their progeny developed a pathological IPF fibroblast phenotype [129]; these cells could be targeted as a therapeutic intervention, although it remains to be seen whether some SSEA-4+ cells are beneficial.

Biological molecules

The vasculature should also not be overlooked when elucidating the mechanisms of lung degeneration and seeking targets for lung regeneration. Retinoic acid is a morphogen that drives tissue regeneration [130, 131] and can induce alveolar regeneration in animal models [47, 48]. In humans, retinoic acid is involved in maintaining the lung microvascular endothelium through up-regulating angiogenesis; in emphysema, expression of the retinoic acid-processing enzyme cytochrome P450 26A1 is elevated in the endothelium, potentially reducing the availability of retinoic acid [132]. It follows that retinoic acid could be a treatment option for lung regeneration; however, early-phase clinical trials of retinoic acid in emphysema have failed to show a clinical benefit [133–135], which underlines the need to understand more about retinoic acid in lung regeneration and whether retinoids can induce lung regeneration.

Hepatocyte growth factor (HGF; also known as scatter factor) promotes airway and bronchoalveolar branching in the developing lung [136, 137], possibly through interaction with vascular endothelial growth factor [138]. HGF also promotes the proliferation and survival of airway epithelial cells [139], plays a role in wound healing [140] and has been shown to improve airspace morphology in emphysema models [139]. Levels of both HGF and vascular endothelial growth factor are reduced in smokers with COPD in comparison to smokers without COPD and nonsmokers, which could contribute to pathogenesis [141], indicating that HGF-enhancing therapy could represent a treatment opportunity for COPD and IPF [142].

Receptor tyrosine kinase pathways have been implicated in aberrant lung remodelling, potentially through growth arrest-specific 6 ligand, TYRO3 protein kinase 3 and Axl [143]. Inhibiting this pathway led to decreased fibrotic responses *in vivo* and *in vitro*, suggesting that targeting the receptor tyrosine kinase pathway could be a promising therapeutic strategy [143].

Granulocyte colony-stimulating factor (G-CSF) has been found to be elevated in the lungs of patients with COPD [101]. Interestingly, deletion of G-CSF in a mouse model of COPD led not only to substantially less inflammation and reduced fibrosis in the lung parenchyma and small airways, but it also reduced systemic inflammation and led to improvements in the comorbidities associated with COPD [101], suggesting that G-CSF is a potential therapeutic target in COPD [101].

Role of the extracellular matrix

The extracellular matrix (ECM) plays a central role in guiding cell behaviour and in tissue repair and remodelling. An *ex vivo* model used bronchial ECM from patients with COPD that was stripped of cells and then repopulated with normal human bronchial cells. The model revealed that the COPD-derived ECM modified the gene expression profile of these healthy cells upon differentiation, altering the activity of mediators involved in regeneration, remodelling, apoptosis, vascularisation and inflammation [144]. Similarly, fibroblasts grown on a stiff matrix resembling a fibrotic ECM, as occurs in IPF, were driven to a myofibroblast phenotype with elevated fibrotic activity, compared with fibroblasts grown on a softer ECM resembling healthy tissue [145]. Such findings emphasise that we need to fully understand the contribution of the ECM in disease and lung regeneration, as the enzymes involved in ECM remodelling could be potential therapeutic targets.

Lessons for the future

Advances in treating obstructive lung diseases such as COPD and IPF have been slow, and improvements in patient outcomes and drug discovery have been poor in respiratory medicine compared with other diseases [146]. Currently, clinical trials require a large number of patients to be assessed over a long period to detect any differences in end-points [146], which could delay results and ultimately slow medical advances. The high costs of such large trials needed to show clinically meaningful effects have discouraged investment in new drug development; many drugs also fail in phase 2 and 3 clinical trials, leading to a rethinking of trial design [146, 147]. Clinical trial design needs to be "smarter". The design should focus on the biology of the disease and the drug mechanism of action, and end-points should be appropriate for

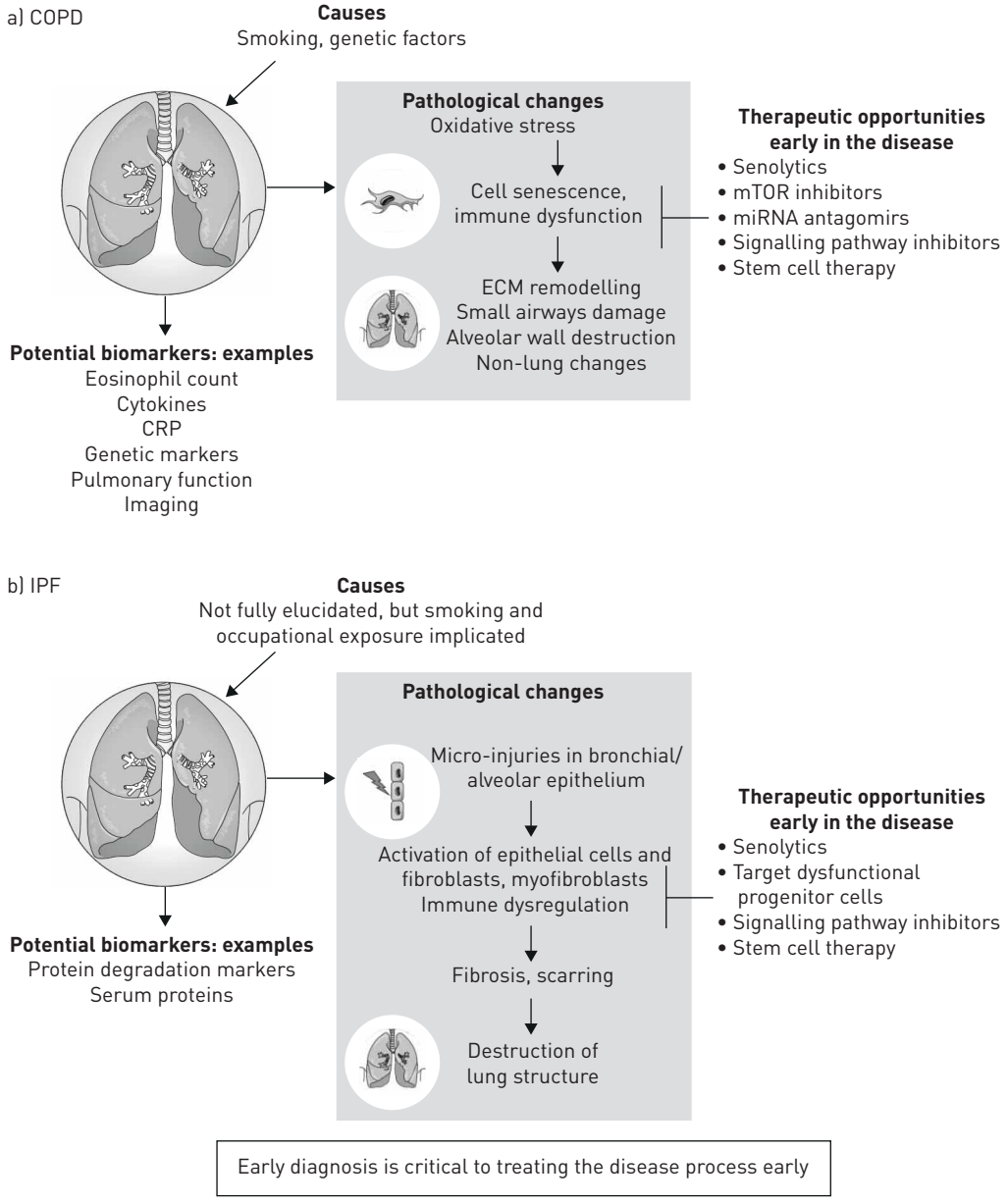

FIGURE 1 Causes, pathogenesis and opportunities for therapeutic intervention in a) COPD and b) idiopathic pulmonary fibrosis (IPF). CRP: C-reactive protein; ECM: extracellular matrix; miRNA: microRNA; mTOR: mammalian target of rapamycin.

the drug's mechanism of action to establish target engagement; improved proof-of-concept or adaptive trials could help rule out ineffective compounds early on to reduce wasted time and costs [146, 148]. If it is anticipated that a biological or clinical effect of the drug would be observed after a certain time, the trial need only last as long as that period. Also, only the subgroup of patients to whom the drug is targeted should be enrolled, even if this results in a relatively small number of patients. Furthermore, any group of patients responding particularly well to a drug should be closely investigated to understand why.

Recognition of the limitations in current therapies for COPD and IPF, which result in a substantial unmet clinical need, points to possible future treatment strategies. For example, a move to precision medicine as opposed to the "magic bullet" approach could lead to therapeutic advances in these highly complex diseases of varying endotypes. In addition, a change in mindset is needed from considering these diseases to be irreversible, to a focus on early diagnosis when reversibility may be possible (figure 1).

The advances in our knowledge of lung degeneration in COPD and IPF raise further questions. For example, is fibrosis a protective mechanism to prevent peripheral airway destruction? Do terminal

bronchioles undergo fibrosis? What is the mechanism for the loss of small airways in early disease? To understand and treat COPD and IPF more effectively, we need clear molecular profiles of the disease; we also need to understand why some areas of the lung are affected and why others are not.

Conclusion

In summary, the considerable body of research into COPD and IPF has yet to translate into improvements in clinical practice. A paradigm shift is required to move the focus to earlier in the disease course, to understand the disease mechanisms more fully, and to measure multiple aspects of the disease. COPD and IPF need to be redefined to better capture the patient populations involved and shift the conceptions about each disease. Novel technologies and the field of "-omics" are providing new insights into COPD and IPF, increasing our ability to predict outcomes and helping to identify new potential therapies to achieve lung regeneration.

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