Review

Epithelial-Mesenchymal Niche Dysfunction in COPD: Emerging Opportunities for Targeting Cellular Plasticity and Crosstalk

Jin Wu [1,2], Saverio Bellusci [1,3], Wenju Lu [4], Jin-San Zhang [1,2,*] and Chengshui Chen [1]

[1] Department of Pulmonary and Critical Care Medicine, The Quzhou Affiliated Hospital of Wenzhou Medical University (Quzhou People's Hospital), Quzhou 324000, China; wujin1519@wmu.edu.cn (J.W.); Saverio.Bellusci@innere.med.uni-giessen.de (S.B.); chenchengshui@wmu.edu.cn (C.C.)

[2] Medical Research Center, and Zhejiang Key Laboratory of Interventional Pulmonology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, China

[3] Laboratory of Extracellular Lung Matrix Remodelling, Department of Internal Medicine, Cardio-Pulmonary Institute and Institute for Lung Health, Justus-Liebig University Giessen, 35392 Giessen, Germany

[4] State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Department of Respiratory Medicine, Guangzhou Institute of Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou 511495, China; wlu92@gzhmu.edu.cn (W.L.)

* Corresponding author. E-mail: Zhang_JinSan@wmu.edu.cn (J.-S.Z.)

ABSTRACT: Chronic obstructive pulmonary disease (COPD) is a leading cause of global morbidity and mortality, characterized by progressive airway and alveolar remodeling. The disease pathogenesis is commonly driven by chronic environmental insults, leading to airway obstruction, emphysema, and chronic bronchitis. This review synthesizes emerging evidence that altered epithelial cell behavior and dysfunctional epithelial-mesenchymal interactions serve as pivotal drivers of COPD pathogenesis, orchestrating failed repair and structural degeneration. We detail how altered responses of airway (ciliated, club, basal, goblet) and alveolar (AT1 and AT2) epithelial cells lead to cellular senescence, metaplasia, defective regeneration, and barrier disruption, acting as primary instigators of pathogenesis. We also summarize current knowledge on the mechanisms of activation and pathogenic role of mesenchymal cells, which drive peribronchiolar fibrosis, alveolar destruction, and metabolic reprogramming, alongside the compromised reparative function of mesenchymal stem cells (MSCs). We emphasize how distinct mesenchymal niches (e.g., PDGFRα[Pos] MANCs, FGF10[Pos] lipofibroblasts, SFRP1[Pos] fibroblasts) and distinct epithelial stem/progenitor subpopulations critically contribute to pathogenesis. Key signaling pathways—including FGF10/FGFR2b, WNT, Hippo, NOTCH, and TGF-β—mediate epithelial-mesenchymal transition (EMT), stem cell niche function, and structural remodeling. By dissecting how epithelial injury responses and mesenchymal niche failure collaboratively drive COPD progression, we identify actionable targets to disrupt pathogenesis and restore endogenous repair. We propose targeting EMT, including inhibiting EMT/fibrosis, promoting alveolar regeneration, MSC-based therapies, exosome-delivered biomolecules, and precision cell transplantation strategies, as promising future therapeutic strategies.

Keywords: COPD; Stem cell; Epithelial-mesenchymal interaction; Signaling pathway; Structure remodeling; Therapy

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) ranks as the third leading cause of morbidity and mortality globally according to the World Health Organization [1]. The disease primarily manifests as persistent dyspnea that progresses to disability, complicated by acute, life-threatening exacerbations, which are often triggered by infections or tobacco use, particularly in the elderly. Following recent viral pandemics, a significant proportion of survivors developed chronic respiratory syndromes due to impaired lung homeostasis, ineffective repair, or incomplete regeneration [2–4].

COPD progression involves robust immune cell infiltration, epithelial/endothelial-mesenchymal transition (EMT/EndMT), and fibroblast-to-myofibroblast transition. These transformations drive airway/vascular remodeling, alveolar bronchiolization, and aberrant alveolar wall changes. Close epithelial-mesenchymal proximity enables critical signaling for stem cell niches, maintaining tissue homeostasis and directing injury repair through mesenchymal-derived signals [5].

Epithelial and mesenchymal cells constitute the primary lung airways and alveolar structures along with the connective tissues as well as the extracellular matrix (ECM) in maintaining the homeostasis environment. The epithelium lines the internal surfaces of the lungs, while the stroma comprises the connective tissue and vasculature. Disruption of this homeostatic balance by disease can lead to the exhaustion of airway epithelial stem cells and mesenchymal remodeling, contributing to chronic pulmonary diseases like COPD.

Epithelial heterogeneity and lineage functions are well-characterized in lung development and disease. Proximal airways contain distinct cell types, including myoepithelial cells, basal cells, club cells, ciliated cells, goblet cells, and tuft cells [6–8]. Basal cells, marked by tumor protein 63 (TP63) and keratin 5 (KRT5), act as stem cells in the trachea, capable of migrating, proliferating, and differentiating into ciliated and club cells to restore lung function after injury [9–11]. In the distal regions of the mouse lungs, the epithelial lining is simpler, composed primarily of club and ciliated cells [10,12,13]. Club cells, marked by secretoglobin family 1A member 1 (SCGB1A1, also known as CC10 or CCSP) and cytochrome P450 family 2 subfamily f polypeptide 2 (CYP2F2), exhibit regenerative capacity in response to injury, such as naphthalene-induced damage [12]. Bronchioalveolar stem cells (BASCs) at the terminal bronchioles and alveolar junctions are marked by both Scgb1a1and surfactant protein C (SP-C) that regenerate bronchiolar/alveolar epithelia [12–17]. The alveolar units, responsible for gas exchange, are composed of alveolar Type 2 cells (AT2s) and AT1 cells surrounded by heterogeneous mesenchymal cells. AT2 cells are recognized as potent stem cells in response to injury. Several subpopulations of AT2 cells have been identified, including Axin2^{Pos} bipotent, Sca1^{Pos}, Krt8^{Pos} transitional, Cd44^{High}, and Pd-l1^{High}Sp-C^{Low} cells, which contribute to alveolar repair and regeneration [18–31].

Mesenchymal niche studies in COPD are comparatively limited. Recent advances have revealed the lineage hierarchies of mesenchymal cells in lung diseases. Zepp et al., identified a population of platelet derived growth factor receptor alpha positive (Pdgfrα^{Pos}) mesenchymal alveolar niche cells (MANCs), which are WNT-responsive and critical for maintaining AT2 cells in the mouse distal lung [32]. Pdgfrα also serves as a marker for lipofibroblasts and supports AT2 function [6,33]. Furthermore, recent studies identified another distinct population of Pdgfrα^{Pos} cells, emerging from the proximal airway niche following naphthalene-induced club cell depletion, termed Repair Supportive Mesenchymal Cells (RSMCs) [30,31]. Derived from the *Acta2*^{Pos} lineage, these cells exhibit enhanced capacity to support club-cell regeneration in vitro and express high levels of Fibroblast growth factor 10 (Fgf10), a key growth factor for branching morphogenesis and lung repair in response to bleomycin-induced injury in mice, human idiopathic pulmonary fibrosis (IPF), and COPD [34–38].

Beyond these populations, Axin2^{Pos} mesenchymal cells contribute to de novo airway smooth muscle cells (ASMC) formation after injury, ASMCs expressing leucine-rich repeat-containing G-protein coupled receptor 6 (Lgr6) promote epithelial repair through a Wnt-Fgf10-signaling axis [39,40]. Other notable mesenchymal populations include secreted frizzled related protein 1 positive (Sfrp1^{Pos}) transitional fibroblasts and collagen triple helix repeat containing 1 positive (Cthrc1^{Pos}) myofibroblasts, recognized as the primary collagen producers during pulmonary fibrosis [41–43]. The spatial distribution between epithelial and mesenchymal cells facilitates direct cell-cell contact and intercellular communications mediated by secreted components such as growth factors, exosomes. Key signaling pathways, including TGF-β, FGF, Hippo, PPARγ, WNT, and SHH, tightly regulate these communications, ensuring tissue homeostasis and promoting repair.

While the intricate epithelial and mesenchymal interplay has been extensively documented as a central driver in the pathogenesis of pulmonary fibrosis, parallel investigations within the COPD context remain remarkably scarce. Although IPF and COPD exhibit distinct core pathological features, they share fundamental dysregulations in key biological processes governed by epithelial-mesenchymal crosstalk. These shared pathological mechanisms include aberrant epithelial-mesenchymal signaling, dysregulated cellular proliferation and differentiation, and impaired stem cell-mediated regeneration [44]. In this review, we aim to elucidate alterations in epithelial and mesenchymal cell lineages and their interactions that contribute to COPD phenotypes. By synthesizing the current body of knowledge on these cellular transformations, interactions, and regulatory mechanisms, we seek to illuminate potential future research avenues and identify novel COPD therapeutic targets.

2. Epithelial Cell Response in COPD

Disruptions in epithelial cell function are a primary cause of COPD progression, driven by processes such as cellular senescence, apoptosis, ferroptosis, and inflammation [45–48]. These pathological events lead to epithelial cell damage, exhaustion, and impaired attempts at regeneration. Chronic exposure to cigarette smoke, the leading risk factor for COPD, along with repeated respiratory infections, induces significant alterations in epithelium, including the loss of ciliated cells [49–51], an increase in goblet cell numbers, shortened cilia and reduced ciliary beat frequency, all of which compromise the airway's ability to clear mucus and pathogens [52–54]. Epithelial injury triggers a persistent immune response, driving alveolar destruction (emphysema) and airway remodeling, often resulting in peribronchial fibrosis and an increase in airway smooth muscle mass [50,55]. These changes also result in excess mucus hyperproduction, a key feature of chronic bronchitis (Figure 1A) [56,57].
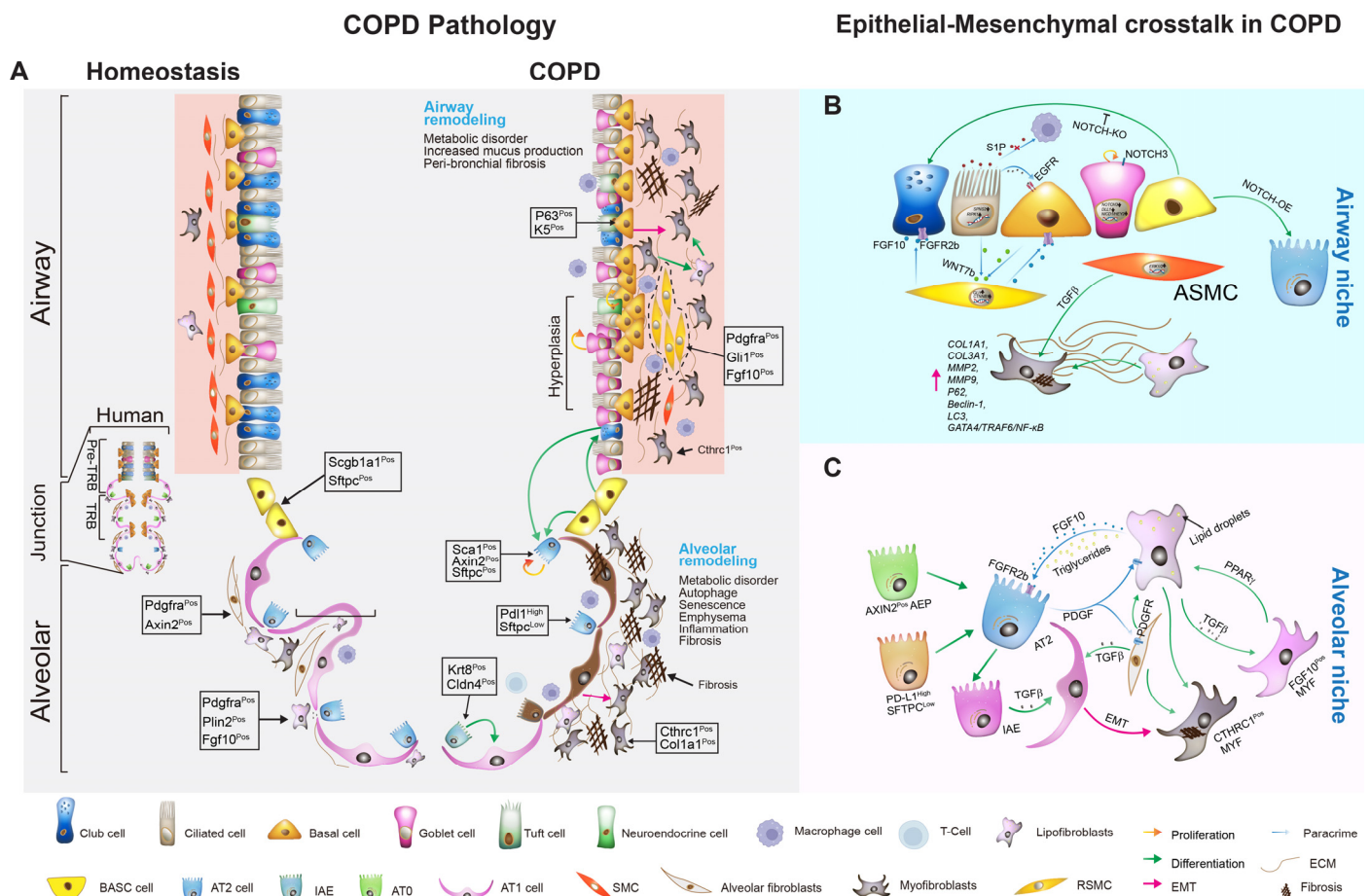

Figure 1. Cellular dynamics in lung homeostasis and COPD. (**A**) The left panel illustrates key cell types and their spatial distribution in the airway and alveolar regions, including human terminal respiratory bronchioles (TRB) under healthy conditions (Homeostasis), club cells, ciliated cells, basal cells, goblet cells, tuft cells, neuroendocrine cells, BASCs (mouse), AT0 (human), AT2, and AT1 cells. Specific cell markers, adjacent fibroblasts, and the extracellular matrix (ECM) are also depicted. The right panel shows changes in cellular states and marker expression during COPD, highlighting airway remodeling, hyperplasia of goblet and basal cells, flattened ciliated cells, and a fibrotic phenotype. These cellular and signaling alterations are associated with key COPD symptoms and pathological features, including metabolic dysregulation, emphysema, inflammation, and fibrosis. (**B**) The dynamic interactions between ASMCs, RSMCs, and key signaling pathways, including the FGF10-FGFR2b axis, WNT signaling, EGFR activation, and NOTCH signaling in "Airway Niche". (**C**) The "Alveolar Niche," focusing on the interactions between AT2 cells and adjacent fibroblasts via FGF10-FGFR2b and PDGFRα signaling. It emphasizes the role of PPARγ-regulated lipid metabolism, showcasing the importance of the lipofibroblast niche in supporting AT2 cells. The involvement of TGF-β signaling in EMT is also shown, linking to fibrosis with downstream effects mediated by Cthrc1[Pos] MYFs.

2.1. Airway Epithelial Cell Responses in COPD

2.1.1. Ciliated Cells

Ciliated epithelial cells line the airway and maintain effective mucociliary clearance by moving mucus and trapping pathogens out of the respiratory tract [58]. In COPD, smoking and aging critically impair the structure and function of these cells, leading to inefficient clearance of mucus [59,60]. One of the molecular pathways affected involves Spinster 2 (SPNS2), which regulates sphingosine-1-phosphate (S1P) secretion. Reduced SPNS2 levels in ciliated cells impair macrophage phagocytosis, further compromising lung defense mechanisms [61]. Additionally, receptor-interacting protein kinase 1 (RIPK1) levels are notably elevated in the ciliated cells of COPD patients. RIPK1 contributes to airway inflammation and remodeling, and blocking RIPK1 has been shown to reduce emphysema and lung function decline (Figure 1A) [62].

2.1.2. Club Cells

Club cells, predominantly found in bronchioles, are important for airway repair, immunomodulation, anti-inflammatory functions, and detoxification [63]. In COPD, there is a notable reduction in club cells, which correlates with the disease's severity [64]. These cells produce SCGB1A1, which modulates immune responses and inhibits harmful enzymes, thereby reducing inflammation and promoting repair mechanisms [65–68]. When club cells are ablated in animal models, there is a loss of epithelial regeneration capacity, resulting in squamous metaplasia and fibrosis, changes also observed in the airways of COPD patients [69]. Notably, CCSP therapy has shown promise in reducing inflammation and supporting lung repair, highlighting its potential as a therapeutic target in COPD [70–72]. Furthermore, club cells also act as facultative stem cells, with the ability to regenerate alveolar epithelial cells after injury. Recent studies have demonstrated that club cells can differentiate into AT2 cells, contributing to alveolar repair during emphysema (Figure 1A) [73,74]. However, club cell-derived AT2 cells exhibit defects in generating alveolar structures in COPD compared to healthy controls, suggesting an impaired regenerative response in the disease state [74].

2.1.3. Basal Cells

Basal cells serve as stem cells for the airway epithelium, playing a key role in maintaining and regenerating the epithelial lining, which is heavily impacted by smoking [75]. These cells are responsible for maintaining the stem cell pool through self-renewal and for giving rise to differentiated progenitors that form ciliated and secretory cells. In COPD, basal cell hyperplasia is observed, along with mucous hyperplasia, contributing to chronic airway remodeling [76]. Basal cells reside in the basal layer of the epithelium, just above the basement membrane, where they can interact with underlying stromal and immune cells. This interaction is likely crucial for the development of airway fibrosis and inflammation [77,78]. Basal cells express markers such as KRT5, KRT13, and TP63, which are critical for their differentiation and the formation of the normal airway epithelium [79–81]. While basal cells are typically involved in repair processes following injury, their regenerative capacity is diminished, leading to persistent remodeling of the airway in COPD [79,82,83]. Additionally, basal cells express Epidermal Growth Factor Receptor (EGFR), which is activated by EGF produced by ciliated cells in response to cigarette smoke, further driving airway remodeling (Figure 1A) [51,84].

2.1.4. Goblet Cells

Goblet cell hyperplasia is a prominent characteristic of COPD that contributing to airway obstruction [85]. Increased mucin production and hypersecretion of mucus are driven by goblet cell proliferation through the NOTCH signaling pathway [85]. Goblet cells not only act as progenitors to ciliated cells but also play a key role in rapidly escalating mucus production in response to airway insults [86]. Overproduction of mucus in chronic bronchitis aggravates airflow limitation by blocking small airways, leading to epithelial remodeling and airway collapse [87]. Despite their clinical significance, the precise mechanisms behind goblet cell hyperplasia in COPD remain poorly understood, and therapeutic options are limited. Recent research on pulsed focused ultrasound offers potential as a novel strategy for selectively reducing goblet cell hyperactivity, providing a promising avenue for COPD treatment [88].

2.2. Additional Airway Epithelial Cells

In addition to the well-characterized epithelial cell types described above, several less-studied cell types in the airway epithelium—including ionocytes, pulmonary neuroendocrine cells (PNECs), and tuft cells—may significantly contribute to the COPD pathogenesis.

Ionocytes are recently identified epithelial cells that express high levels of CFTR (cystic fibrosis transmembrane conductance regulator) chloride channels, playing a crucial role in maintaining airway surface hydration. Their dysfunction, especially when influenced by cigarette smoke exposure, causes mucus dehydration and impaired mucociliary clearance, exacerbating symptoms in COPD patients [89]. PNECs are rare epithelial cells that secrete neuropeptides to modulate airway smooth muscle tone and immune responses. In the context of COPD, PNEC hyperplasia and alterations in neuropeptide secretion may exacerbate airway remodeling and chronic inflammation, contributing to disease progression [90]. Tuft cells, also known as brush cells in the airway, have been found to play roles in innate immune regulation and airway epithelial repair. They release signaling molecules that can modulate inflammation and contribute to the dysregulation of immune responses within the airways of COPD patients [91].

Therefore, airway epithelial cells are critical in the pathogenesis of COPD, contributing to chronic inflammation, mucus hypersecretion, airway remodeling, and alveolar destruction. A deeper understanding of these cellular responses is crucial for developing targeted therapies that can mitigate disease progression and improve the quality of life for COPD patients.

2.3. Alveolar Epithelial Cells in COPD

Bronchiolization of alveolar regions, a key feature of emphysema, is largely attributed to alveolar epithelial hyperplasia during the repair process following inflammatory damage in COPD. The alveolar epithelium consists mainly of AT1 and AT2 cells. AT2 cells, functioning as resident stem cells, are crucial for alveolar regeneration after injury [33].

In healthy lungs, AT2 cells tend to proliferate and differentiate into AT1 cells responsible for gas exchange [92]. However, in COPD Lungs, proportion of AT2 cells lose their ability to regenerate, resulting in impaired alveolar repair [93]. The interferon-gamma (IFN-γ) and LHX9 signaling axis has been implicated in maintaining a subset of AT2 cells that retain stem cell functionality and resistance to apoptosis under chronic cigarette smoke exposure [93–95]. This preservation is also thought to be supported by fatty acid oxidation mechanisms. Additionally, exposure to PM2.5 particles disrupts the differentiation of AT2 cells into AT1 cells, as evidenced by reduced claudin-4 (CLDN4) expression in AT2 cells following exposure [96]. Recent scRNA-seq analyses of lung tissue from COPD patients have identified a distinct subpopulation of AT2 cells with altered metabolic processes, further contributing to the pathogenesis of emphysema [97]. Moreover, abnormal T cell proliferation in COPD may inhibit the renewal capabilities of AT2 cells, exacerbating the condition [98]. In contrast to the mouse lung, the human lung features a distinct airway architecture, including respiratory bronchioles—a transitional region absent in mice. Within these structures lies a unique secretory cell population, respiratory airway secretory (RAS) cells, which serve as unidirectional progenitors for AT2 cells. NOTCH and WNT signaling modulate this process. Notably, RAS cells exhibit transcriptional alterations associated with smoking induced COPD, leading to aberrant AT2 cell states. This human-specific progenitor population plays a vital role in maintaining alveolar homeostasis and is implicated in chronic lung pathology [99].

AT1 cells tightly adhere to pulmonary venous capillary endothelial cells, covering approximately 95% of the alveolar surface, and are essential for gas exchange. Damage to AT1 cells results in alveolar structure remodeling [100]. Previous studies in a transgenic mouse model have identified two AT1 cell subpopulations: terminally differentiated Hopx^{Pos}Igfbp2^{Pos} cells and plastic Hopx^{Pos}Igfbp2^{Neg} cells. Igfbp2^{Neg} cells demonstrate *in vitro* transdifferentiation potential into AT2 cells and organoid formation (indicating an intermediate differentiation state), Igfbp2 marks terminal AT1 commitment [101]. However, dual recombinase-mediated lineage tracing studies—which enable specific AT1 labeling—show that AT1 cells do not generate AT2 cells during bleomycin-induced injury *in vivo* [73]. Whether AT1 cells, which align with structurally remodeled capillary endothelia, undergo damage and remodeling remains unknown—a key area for future investigation [102]. Therefore, strategies targeting AT1 preservation or functional restoration via AT2-to-AT1 differentiation may also mitigate emphysematous destruction in COPD.

3. Activation and Therapeutic Applications of Mesenchymal Cells in COPD

3.1. Mesenchymal Cell Activation in COPD

Beyond the important role of dysfunction in lung epithelia, COPD additionally features progressive remodeling of both airway and alveolar structures, primarily driven by fibroblasts, particularly myofibroblasts. Although mesenchymal niches are known to play critical roles in fibrotic epithelial repair and regeneration, their response, regulation, and signaling mechanisms in COPD are still poorly understood. COPD primarily affects the small conducting airways, where thickening of the airway walls and peribronchiolar fibrosis cause narrowing [103,104]. This fibrosis is partly driven by senescent fibroblasts that secrete increased levels of collagen types 1A1 (COL1A1) and 3A1 (COL3A2) and upregulate matrix metalloproteinases (MMP2, MMP9), promoting a profibrotic environment and inducing the differentiation of bronchial smooth muscle cells into myofibroblasts [105,106].

ASMCs in COPD exhibit metabolic disturbances, including the accumulation of lactate, glutamine, fatty acids, and amino acids. TGF-β stimulation restores fatty acid oxidation, enhances ribose-5-phosphate production, and promotes nucleotide biosynthesis [107]. This metabolic reprogramming supports ASMC growth and is linked with altered redox balance and reduced mitochondrial oxidative stress. Inhibiting glycolysis and glutamine depletion reduces ASMC proliferation in COPD [94]. ASMCs also show increased fibronectin production and upregulation of autophagy markers, potentially accelerating cellular senescence [108,109].

Environmental exposures such as CSE (Cigarette smoking exposure) and particulate matter (PM2.5) further exacerbate mesenchymal cell dysfunction. CSE exposure induces pro-proliferative and profibrotic characteristics in fibroblasts through NF-κB activation [110]. CSE also increases oxidative and ER stress in human lung fibroblasts, promoting their differentiation into myofibroblasts and impairing their ability to support epithelial progenitor function, while activation of the WNT/β-catenin signaling pathway partially restores this impaired function [111]. PM2.5 exposure triggers a senescence-associated secretory phenotype in ASMCs, enhancing collagen-I and α-SMA synthesis via the GATA4/TRAF6/NF-κB signaling pathway [112].

FGF10 is crucial for maintaining the alveolar AT2 stem cell niche [99]. Studies have demonstrated that FGF10 expression is reduced in COPD lungs, disrupting alveolar homeostasis. Remarkably, overexpression of *Fgf10* has been shown to reverse established emphysema in mice, underscoring its therapeutic potential [36]. Given that Fgf10 is primarily produced by alveolar fibroblasts, an imbalance between fibroblasts and epithelial cells likely contributes to the alveolar remodeling observed in COPD. These intricate biological processes illustrate how mesenchymal cell dysfunction drives the structural changes that exacerbate the obstructive nature of the disease. Although research into FGF10-targeted therapies is still in its early stages, the advancements in cell-based precision therapies targeting this pathway are promising.

3.2. Mesenchymal Stem Cells as Therapies Against COPD

Mesenchymal stem cells (MSCs) have shown significant promise as cell-based therapies in regenerative medicine due to their multipotent differentiation capacity, self-renewal abilities, immunoregulatory properties, and paracrine effects. MSCs have been extensively studied in respiratory diseases such as COPD, asthma, and idiopathic pulmonary fibrosis, demonstrating their potential to regenerate lung tissue [113–121]. Transplantation of human umbilical cord-derived MSCs (hUC-MSCs) or their extracellular vesicles (EVs) have shown efficacy in reducing peribronchial and perivascular inflammation, alveolar septal thickening, and goblet cell hyperplasia in COPD rat models. These interventions also reduce alveolar septal loss and downregulate NF-κB subunit P65 levels in affected tissues [117]. Transplantation of MSCs also alleviates COPD by regulating oxidative stress-related pathways [122].

Lung resident MSCs (LR-MSCs) are found in comparable numbers in smokers and never-smokers, indicating that the MSC reservoir in COPD patients remains intact [123]. However, MSCs from current smokers demonstrated diminished capacity to inhibit CD8[Pos] T-cell proliferation. This impairment was accentuated by *in vitro* exposure to CSE, which reduced the T-cell immunomodulatory capabilities of LR-MSCs [123]. These results suggest that tobacco smoke-induced oxidative stress can compromise the immunomodulatory and homeostatic functions of LR-MSCs. Furthermore, COPD MSCs show decreased production of Fgf10, essential for effective alveolar repair, and this process can be rescued by activating FGF10/FGFR2b signaling [36,124].

During the COVID-19 pandemic, systemic administration of allogeneic MSCs was investigated as a treatment for virus-associated pneumonia. MSCs' anti-inflammatory properties and ability to remodel the extracellular matrix offer a potential strategy to prevent pulmonary fibrosis. Despite promising results in clinical trials, outcomes have been mixed,

potentially due to persistent bronchial inflammation, which may attenuate MSC efficacy [125,126]. Despite challenges, MSCs offer a promising approach for addressing chronic inflammation and remodeling in COPD (Figure 2).
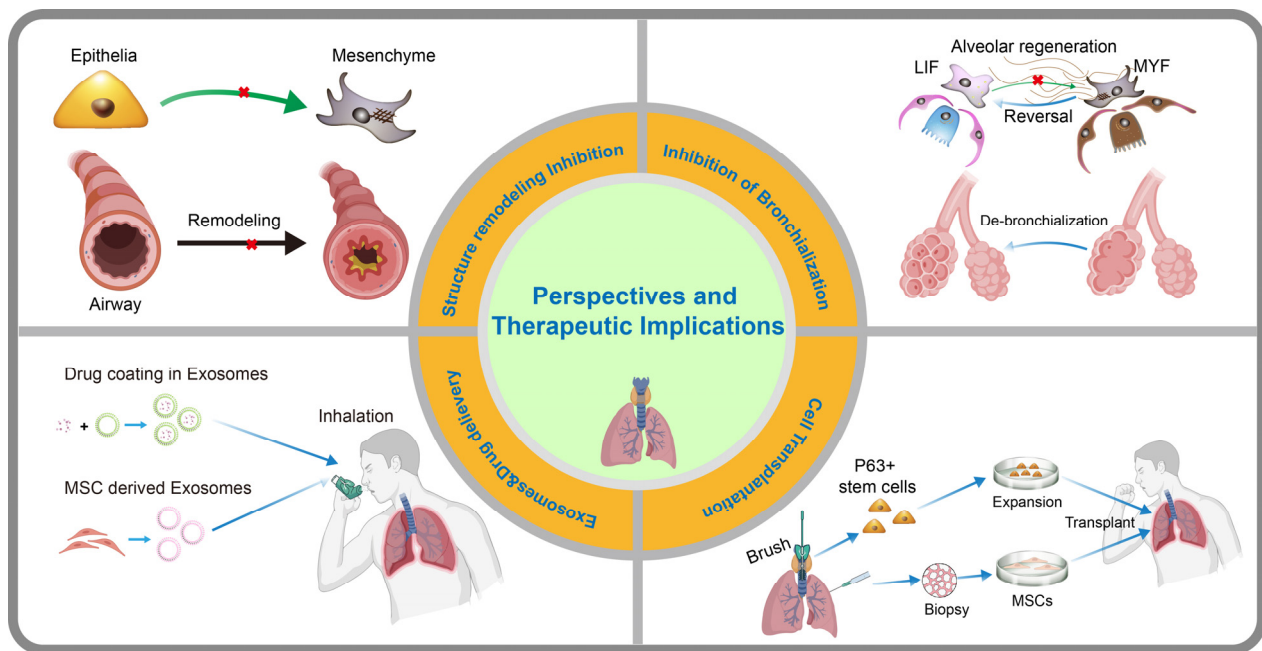

Figure 2. Perspectives and therapeutic implications of airway and alveolar regeneration in COPD. Based on current insight, several perspectives and therapeutic implications for COPD treatment have been summarized. (**Top Left**): Inhibition of EMT and airway remodeling is critical for preventing pathological transition of epithelial cells into mesenchymal phenotypes, thereby maintaining airway integrity. (**Top Right**): Inhibition of bronchiolization and promotion of de-bronchiolization within the alveolar niche support alveolar regeneration through reversal of pathological changes. (**Bottom Left**): Exosome/Exosome-delivered drugs can be administered via inhalation, enabling targeted delivery to lung tissues for regenerative therapy. (**Bottom Right**): Cell-based therapies involve isolation (biopsy), *in vitro* expansion, and transplantation of lung epithelial cells to restore respiratory function. This integrative approach aims to advance therapeutic strategies for lung diseases by targeting multiple pathways involved in COPD.

In conclusion, mesenchymal cells, including fibroblasts and MSCs, are critical in the pathogenesis and potential treatment of COPD, despite the fact that fibroblasts drive structural remodeling. Further research is needed to fully understand mesenchymal mobilization and optimize MSC-based strategies for COPD.

4. Cellular Interactions and Key Signaling Pathways in COPD

4.1. Epithelial-to-Mesenchymal Transformation in COPD

The pulmonary epithelial cell lining is a vital barrier against environmental toxins and infections. In COPD, epithelial cells undergo transformation into mobile mesenchymal cells through epithelial-mesenchymal transition (EMT), a process triggered by diseases, infections, or injuries, and mediated by pathways like TGF-β signaling (Figure 1B) [127,128]. EMT is observed not only in lung development but also in respiratory diseases such as COPD, lung cancer, and asthma, where it contributes to excessive collagen and ECM protein deposition [127,129,130].

In COPD, transcription factors like Snail1 are notably upregulated, particularly in cases with α1-antitrypsin deficiency, signifying increased EMT activity [131]. Additionally, transcription factors like Twist demonstrate increased nuclear translocation in smokers, correlating with greater airflow obstruction [132]. E-cadherin, an adhesion molecule essential for interepithelial junctions, is significantly decreased in smokers and COPD patients, with its reduction linked to more severe airflow limitations [133,134].

Moreover, mesenchymal markers, including N-cadherin, vimentin, α-SMA, type I collagen, and fibronectin, are elevated in COPD patients, promoting increased cell migration, tissue fibrosis, and airflow restriction [135,136]. New biomarkers such as β2-microglobulin (β2M) and sphingosine-1-phosphate (S1P) are under investigation for their roles in EMT regulation and their correlation with declining lung function in smoking-induced COPD [137,138]. Further research highlights the role of Cullin 4A (CUL4A); silencing this gene inhibits EMT in smoke-exposed lung cells, demonstrating its potential in altering disease progression [139,140]. This emerging understanding of EMT biomarkers could contribute to more effective management of smoking-related COPD.

4.2. Key Signaling Pathways Involved in Epithelial-Mesenchymal Interactions

Cellular signaling pathways regulating epithelial-mesenchymal interactions play crucial roles in lung development, homeostasis, and disease. Among these pathways, paracrine-acting FGFs are particularly important in cellular processes such as proliferation, survival, migration, differentiation, and metabolism [141]. Mesenchyme-derived Fgf10, which binds predominantly to Fgfr2b expressed by epithelial cells, plays a key role in maintaining lung stem/progenitor cell homeostasis, promoting wound healing, and protecting against oxidant-induced DNA damage [29,142–145]. FGF10 haploinsufficiency correlates with impaired lung function and is linked to COPD through single nucleotide polymorphisms (SNPs) near the *Fgf10* locus [146–148]. In advanced COPD, decreased Fgf10 expression in the alveolar walls' been noted. While overexpression of *Fgf10* stimulates AT2 cell proliferation and enhances epithelial progenitor markers via the β-catenin pathway, underscoring its potential in alveolar regeneration (Figure 1B) [20,36].

Further studies indicate that precise regulation of the Yap-WNT7b-FGF10 pathway is critical for maintaining airway epithelial quiescence and preventing excessive remodeling. Dysregulation of Hippo signaling, seen in COPD, leads to defective repair mechanisms. Elevated nuclear YAP, FGFR2b, and WNT7b levels in the squamous metaplastic regions of the airway epithelium in COPD patients support this conclusion [144]. Meanwhile, WNT5a and WNT5b, secreted by lung fibroblasts, negatively impact epithelial progenitor proliferation. Specifically, WNT5b inhibits the growth and differentiation of alveolar epithelial progenitors in a WNT/β-catenin-dependent manner, suggesting therapeutic potential in modulating WNT signaling to enhance alveolar repair, particularly in aging lungs affected by COPD [149]. The role of Fam13a, another key player, has been explored in chronic CSE mouse models. *Fam13a* deficiency ameliorates the negative effects of CSE on lung epithelial stem cell regeneration via activation of the WNT signaling pathway. Additionally, in human cells and animal models of COPD, CSE has been shown to increase the expression of COPD-related markers, including type I collagen and ERK1/2 activation. This pathway also plays a crucial role in regulating mitochondria fission and fusion, which in turn controls ASMC proliferation (Figure 1B) [150,151].

The NOTCH signaling pathway is also compromised in COPD, with significant downregulation of NOTCH3, DLL1, and downstream targets such as HES5 and HEY1/2 in COPD patients compared to non-smokers. Despite this global inhibition, NICD1/HEY2 expression is upregulated in regions of mucosal hyperplasia in COPD patients, indicating persistent NOTCH activation, likely triggered by cigarette smoking, which skews differentiation towards the goblet cell lineage (Figure 1B) [152,153]. Additionally, the involvement of SHH signaling in COPD, pulmonary fibrosis, and fibroblast expansion suggests its role in ECM deposition [154,155]. Genome-wide association studies (GWAS) have identified a locus near HHIP on chromosome 4q31, associated with reduced lung function and altered HHIP gene expression, further implicating this pathway in COPD pathogenesis [156,157].

These subpopulation-specific injury-response mechanisms may play a significant role in COPD. Despite the growing prevalence of single-cell RNA sequencing analysis, contemporary research seldom focuses on the responses among these heterogeneous populations. A deeper understanding of epithelial-mesenchymal interactions and key signaling pathways in COPD could provide critical insights for developing targeted therapies to slow disease progression and enhance tissue repair.

5. Implications of Epithelial-Mesenchymal Niche for COPD Therapy

Current management of COPD relies on three principal therapeutic modalities: pharmacological interventions targeting airway smooth muscle contraction and inflammatory pathways; extracellular vesicle-based strategies delivering regulatory biomolecules to modulate fibrotic and immune responses; and cellular transplantation approaches utilizing diverse progenitor sources to enhance tissue repair (Table 1). While these interventions provide symptomatic relief and attenuate disease progression, they exhibit limited capacity to restore the fundamental regenerative potential of compromised pulmonary epithelia. This critical gap underscores the imperative to elucidate the mechanisms governing airway and alveolar stem cell dysfunction in COPD. Emerging insights into epithelial-mesenchymal-immune crosstalk now illuminate novel regenerative strategies to reactivate endogenous repair programs, redirect aberrant differentiation trajectories, and reestablish functional niche microenvironments.

Table 1. Therapeutic applications on COPD.

Treatments	Sources	Targets	References
Drug treatments	Beta-agonists	β2 receptor on BSMCs	PMID:22314182 PMID:35311415
	LAMA/LABA/ICS	Glucocorticoid receptor on epithelial cells and endothelial cells of bronchial vessels	PMID:37690008 PMID:31305147 PMID:9563367 PMID:37852657
	Anti-muscarinics, Anti-cholinergics	Muscarinic receptors on ASMCs, inflammatory cells, and airway epithelial cells	PMID:27787709
	Theophylline	Adenosine receptor	PMID:30085566
Extracellular vesicles	EVs carrying miR-210	Myofibroblast	PMID:33712504
	(hUC-MSC)-derived EVs	Goblet cells, inflammatory cells	PMID:33436065
	EVs carrying miR-21	Myofibroblast	PMID:33712504
	EVs carrying miR-181c	Fibroblast, osteoblast, Endothelial cells and epithelial cells	PMID:28806967
Cell transplantation	P63[Pos] progenitor cells	/	PMID:38354225
	Bone marrow derived mononuclear cells	/	PMID:24255620
	Adipose tissue-derived stromal cells	/	PMID:17049053
	BM-MSCs	/	PMID:35725505 PMID:20842104 PMID:34974799
	iPSC-MSCs	/	PMID:28911970
	DASCs	/	PMID:33960563

5.1. Airway Stem Cells in Regeneration

Epithelial dysfunction, manifested through cellular damage, senescence, and exhaustion, represents a core pathological feature of COPD. However, the regulatory hierarchy and signaling mechanisms governing epithelial responses remain poorly defined compared to diseases like asthma or IPF. Recent evidence reveals a unique AT2 subpopulation (asATII) co-expressing SP-C and SCGB3A2 within emphysematous alveoli of advanced COPD patients. These cells, potentially derived from migratory airway club cells in experimental models, exhibit critically impaired regenerative capacity in functional assays [74].

Epithelial-mesenchymal crosstalk is pivotal for lung regeneration. For example, bronchiolar stem cells (BSCs) rely on Fgf10 secreted by mesenchymal cells for their function. Overexpression of *Fgf10* during lung development results in ectopic BSC formation in the airways [158]. After injury in mice, surviving epithelial cells secrete Wnt7b, which induces Fgf10 expression in ASMCs, promoting secretory cell regeneration [158,159]. The HIPPO signaling pathway modulates BSC stability through the Fgf10-Fgfr2b axis [160,161]. The BSCs have also been reported to maintain functional intraepithelial airway macrophages [162], suggesting their significant potential in regulating airway repair. Furthermore, recent studies indicate that RSMCs in non-cartilaginous airways express high levels of Fgf10, which promotes club cell proliferation. These findings highlight that epithelial regeneration is closely modulated by mesenchymal signaling pathways [145].

These findings underscore a paradoxical phenomenon: while airway-derived progenitors are able to translocate to replenish alveolar compartments, their functional exhaustion ultimately limits repair. Future studies may focus on delineating the crosstalk between proximal and distal epithelial populations, such as BASCs, alongside signaling pathways regulating club cell fate. Such insights may inform cell-based transplantation strategies to reactivate endogenous repair programs (Figure 2) [163]. It is also important to determine whether RSMCs contribute to basal and club cell repair in COPD, particularly in exhausted epithelia. However, excessive activation of these pathways may lead to hyperplasia, emphasizing the need for a balanced approach to regenerative therapy (Figure 1B).

5.2. Alveolar Stem Cells and Their Niches in COPD

Alveolar stem cells and their mesenchymal niches play a pivotal role in lung regeneration. A subset of AT2 cells expressing a high level of Cd44 exhibits enhanced proliferation and organoid-forming capabilities. It has been further reported that Gli1[Pos] adventitial fibroblasts are a crucial component in supporting the Cd44[High] AT2 cells through their production of hyaluronan [18,164,165]. WNT signaling is critical in maintaining AT2 progenitor cells, although there is variability in their dynamics across different studies [166]. During lung injury repair, intermediate cell populations (e.g., KRT8[High] and CLDN4[High] alveolar epithelial cells) emerge, influenced by TGFβ and P53 signaling pathways [167,168]. In human lungs, a recent study integrated spatial transcriptomics and single-cell RNA sequencing of micro dissected distal airways, identified LGR5[Pos] fibroblasts, terminal and respiratory bronchiolar secretory cells (TRB-SCs), and alveolar type-0 (AT0) cells. Organoid and connectome analyses reveal LGR5[Pos] fibroblasts as a niche signaling center in contact with epithelia. The AT0 cells represent a transient bipotent state during AT2 regeneration in primates, capable of differentiating into AT1s or TRB-SCs. These findings redefine human lung cell hierarchies and illuminate an epithelial transitional state critical in development, regeneration, and disease, which differs from mouse studies [169]. Epithelial-immune crosstalk is equally important, the PD-1/PD-L1 inhibitory pathway, known for regulating T-cell activation, critically mediates this interaction. IAAPs, characterized by high PD-L1 and low SP-C expression, contribute significantly to alveolar regeneration (Figure 1C) [29,170,171]. These cells warrant further investigation in COPD, with potential for immune-targeted interventions to enhance regeneration. Elucidating how these stem cells respond and adapt within COPD's chronic inflammatory milieu, and whether their reparative functions are impaired, will be essential [172]. Therefore, a major goal is to develop strategies that either enhance the growth and transformation potential of these stem cells or modulate niche signals to rebuild functional alveoli, countering structural and functional decline in COPD. Understanding the precise responses and therapeutic potential of defined alveolar epithelial progenitor subpopulations in COPD represents a critical frontier for regenerative approaches.

Pulmonary fibrosis, a hallmark of advanced COPD, is driven by mesenchymal populations like myofibroblasts. PDGFRα-positive alveolar fibroblasts form a supportive niche for AT2 cells, facilitating their function and repair. SFRP1-positive fibroblasts transition into matrix-producing myofibroblasts in response to TGFβ signaling, and contribute to tissue repair post-injury [173–175]. Lipofibroblasts, marked by TCF21 and FGF10, support alveolar epithelial regeneration through paracrine signaling and ECM remodeling [176–179]. Whether other populations like MANCs and LGR5-positive fibroblasts contribute to the mesenchymal niche in COPD requires further validation [169,180].

Analogous to IPF, key therapeutic targets in COPD may include progenitors driving collagen production. For instance, LEPR[Pos] alveolar fibroblasts are a key source of pathological CTHRC1[Pos] fibroblasts, and targeting Runx2 shows therapeutic potential [181]. Strategies to deplete these cells from fibrotic tissues, by targeting specific receptors, may prove beneficial. Additional approaches include targeting FGF10, PDGFRα, or TCF21; inhibiting TGFβ-driven SFRP1[Pos] fibroblast-to-myofibroblast transition; or conversely activating lipogenic pathways via BMP2/PPARγ agonists—all potentially slowing COPD progression (Figure 1C).

6. Conclusions

Both airway and alveolar stem cell niches are vital for lung regeneration, offering significant therapeutic potential for treating COPD. However, balancing regeneration with pathological remodeling presents a challenge. Understanding epithelial-mesenchymal interactions is critical to developing targeted therapies that promote healthy lung regeneration while preventing aberrant repair processes. Further investigation may focus on the origin and development of stem cell lineages that contribute to regeneration in COPD. Translating bench research to bedside applications, such as stem cell implantation, extracellular vesicle based drug treatments or delivery, and cell-based targeted therapies, will be essential for advancing COPD treatment (Figure 2).

Author Contributions

Conceptualization: J.-S.Z., J.W., C.C.; Writing—original draft: J.W.; Writing—review and editing: J.-S.Z., W.L., S.B.; Figures and Table creation: J.W., J.-S.Z.; Resource and Funding acquisition: J.-S.Z., W.L., C.C.

Ethics Statement

No ethical statement to declare.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Declaration of Competing Interest

The authors declared there is no conflict of interest.

References

1. Dong F, Su R, Ren Y, Yang T. Burden of chronic obstructive pulmonary disease and risk factors in China from 1990 to 2021: Analysis of global burden of disease 2021. *Chin. Med. J. Pulm. Crit. Care Med.* **2025**, *3*, 132–140.
2. Barnes PJ. Chronic obstructive pulmonary disease. *N. Engl. J. Med.* **2000**, *343*, 269–280.
3. Christenson SA, Smith BM, Bafadhel M, Putcha N. Chronic obstructive pulmonary disease. *Lancet* **2022**, *399*, 2227–2242.
4. Stolz D, Mkorombindo T, Schumann DM, Agusti A, Ash SY, Bafadhel M, et al. Towards the elimination of chronic obstructive pulmonary disease: a Lancet Commission. *Lancet* **2022**, *400*, 921–972.
5. Abohalaka R. Bronchial epithelial and airway smooth muscle cell interactions in health and disease. *Heliyon* **2023**, *9*, e19976.
6. Zepp JA, Morrisey EE. Cellular crosstalk in the development and regeneration of the respiratory system. *Nat. Rev. Mol. Cell. Biol.* **2019**, *20*, 551–566.
7. Hogan B, Tata PR. Cellular organization and biology of the respiratory system. *Nat. Cell Biol.* **2019**, doi:10.1038/s41556-019-0357-7.
8. Pardo-Saganta A, Law BM, Gonzalez-Celeiro M, Vinarsky V, Rajagopal J. Ciliated cells of pseudostratified airway epithelium do not become mucous cells after ovalbumin challenge. *Am. J. Respir. Cell. Mol. Biol.* **2013**, *48*, 364–373.
9. Kotton DN, Morrisey EE. Lung regeneration: mechanisms, applications and emerging stem cell populations. *Nat. Med.* **2014**, *20*, 822–832.
10. Reynolds SD, Reynolds PR, Pryhuber GS, Finder JD, Stripp BR. Secretoglobins SCGB3A1 and SCGB3A2 define secretory cell subsets in mouse and human airways. *Am. J. Respir. Crit. Care Med.* **2002**, *166*, 1498–509.
11. Zhang JS, Dhlamini Q, Guo Q, Quan M, Wu J, Lyu H, et al. Progress and Gaps in Respiratory Disease Research and Treatment: Highlights of the IRM 2024 in Shanghai. *J. Respir. Biol. Transl. Med.* **2024**, *1*, 10021.
12. Giangreco A, Reynolds SD, Stripp BR. Terminal bronchioles harbor a unique airway stem cell population that localizes to the bronchoalveolar duct junction. *Am. J. Pathol.* **2002**, *161*, 173–182.
13. Reynolds SD, Hong KU, Giangreco A, Mango GW, Guron C, Morimoto Y, et al. Conditional clara cell ablation reveals a self-renewing progenitor function of pulmonary neuroendocrine cells. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2000**, *278*, L1256–1263.
14. Jones-Freeman B, Starkey MR. Bronchioalveolar stem cells in lung repair, regeneration and disease. *J. Pathol.* **2020**, *252*, 219–226.
15. Hong KU, Reynolds SD, Giangreco A, Hurley CM, Stripp BR. Clara cell secretory protein-expressing cells of the airway neuroepithelial body microenvironment include a label-retaining subset and are critical for epithelial renewal after progenitor cell depletion. *Am. J. Respir. Cell. Mol. Biol.* **2001**, *24*, 671–681.
16. Peake JL, Reynolds SD, Stripp BR, Stephens KE, Pinkerton KE. Alteration of pulmonary neuroendocrine cells during epithelial repair of naphthalene-induced airway injury. *Am. J. Pathol.* **2000**, *156*, 279–286.
17. Reynolds SD, Giangreco A, Power JH, Stripp BR. Neuroepithelial bodies of pulmonary airways serve as a reservoir of progenitor cells capable of epithelial regeneration. *Am. J. Pathol.* **2000**, *156*, 269–278.
18. Chen Q, Suresh Kumar V, Finn J, Jiang D, Liang J, Zhao YY, et al. CD44(high) alveolar type II cells show stem cell properties during steady-state alveolar homeostasis. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2017**, *313*, L41–L51.
19. Zacharias WJ, Frank DB, Zepp JA, Morley MP, Alkhaleel FA, Kong J, et al. Regeneration of the lung alveolus by an evolutionarily conserved epithelial progenitor. *Nature* **2018**, *555*, 251–255.

20. Nabhan AN, Brownfield DG, Harbury PB, Krasnow MA, Desai TJ. Single-cell Wnt signaling niches maintain stemness of alveolar type 2 cells. *Science* **2018**, *359*, 1118–1123.

21. Travaglini KJ, Nabhan AN, Penland L, Sinha R, Gillich A, Sit RV, et al. A molecular cell atlas of the human lung from single-cell RNA sequencing. *Nature* **2020**, *587*, 619–625.

22. Liu Y, Kumar VS, Zhang W, Rehman J, Malik AB. Activation of type II cells into regenerative stem cell antigen-1(+) cells during alveolar repair. *Am. J. Respir. Cell. Mol. Biol.* **2015**, *53*, 113–124.

23. Choi J, Park JE, Tsagkogeorga G, Yanagita M, Koo BK, Han N, et al. Inflammatory Signals Induce AT2 Cell-Derived Damage-Associated Transient Progenitors that Mediate Alveolar Regeneration. *Cell Stem Cell* **2020**, *27*, 366–382.e7.

24. Kobayashi Y, Tata A, Konkimalla A, Katsura H, Lee RF, Ou J, et al. Persistence of a regeneration-associated, transitional alveolar epithelial cell state in pulmonary fibrosis. *Nat. Cell Biol.* **2020**, *22*, 934–946.

25. Riemondy KA, Jansing NL, Jiang P, Redente EF, Gillen AE, Fu R, et al. Single cell RNA sequencing identifies TGFβ as a key regenerative cue following LPS-induced lung injury. *JCI Insight* **2019**, *5*, e123637.

26. Strunz M, Simon LM, Ansari M, Kathiriya JJ, Angelidis I, Mayr CH, et al. Alveolar regeneration through a Krt8+ transitional stem cell state that persists in human lung fibrosis. *Nat. Commun.* **2020**, *11*, 3559.

27. Verheyden JM, Sun X. A transitional stem cell state in the lung. *Nat. Cell Biol.* **2020**, *22*, 1025–1026.

28. Wu H, Yu Y, Huang H, Hu Y, Fu S, Wang Z, et al. Progressive pulmonary fibrosis is caused by elevated mechanical tension on alveolar stem cells. *Cell* **2021**, *184*, 845–846.

29. Ahmadvand N, Khosravi F, Lingampally A, Wasnick R, Vazquez-Armendariz AI, Carraro G, et al. Identification of a novel subset of alveolar type 2 cells enriched in PD-L1 and expanded following pneumonectomy. *Eur. Respir. J.* **2021**, *58*, 2004168.

30. Kathiriya JJ, Wang C, Zhou M, Brumwell A, Cassandras M, Le Saux CJ, et al. Human alveolar type 2 epithelium transdifferentiates into metaplastic KRT5(+) basal cells. *Nat. Cell Biol.* **2022**, *24*, 10–23.

31. Quan M, Guo Q, Yan X, Yu C, Yang L, Zhang Y, et al. Parkin deficiency aggravates inflammation-induced acute lung injury by promoting necroptosis in alveolar type II cells. *Chin. Med. J. Pulm. Crit. Care Med.* **2024**, *2*, 265–278.

32. Zepp JA, Zacharias WJ, Frank DB, Cavanaugh CA, Zhou S, Morley MP, et al. Distinct Mesenchymal Lineages and Niches Promote Epithelial Self-Renewal and Myofibrogenesis in the Lung. *Cell* **2017**, *170*, 1134–1148.e10.

33. Barkauskas CE, Cronce MJ, Rackley CR, Bowie EJ, Keene DR, Stripp BR, et al. Type 2 alveolar cells are stem cells in adult lung. *J. Clin. Invest.* **2013**, *123*, 3025–3036.

34. Morrisey EE, Hogan BL. Preparing for the first breath: genetic and cellular mechanisms in lung development. *Dev. Cell* **2010**, *18*, 8–23.

35. Bellusci S, Grindley J, Emoto H, Itoh N, Hogan BL. Fibroblast growth factor 10 (FGF10) and branching morphogenesis in the embryonic mouse lung. *Development* **1997**, *124*, 4867–4878.

36. Hadzic S, Wu CY, Gredic M, Pak O, Loku E, Kraut S, et al. Fibroblast growth factor 10 reverses cigarette smoke- and elastase-induced emphysema and pulmonary hypertension in mice. *Eur. Respir. J.* **2023**, *62*, 2201606.

37. El Agha E, Kramann R, Schneider RK, Li X, Seeger W, Humphreys BD, et al. Mesenchymal Stem Cells in Fibrotic Disease. *Cell Stem Cell* **2017**, *21*, 166–177.

38. El Agha E, Moiseenko A, Kheirollahi V, De Langhe S, Crnkovic S, Kwapiszewska G, et al. Two-Way Conversion between Lipogenic and Myogenic Fibroblastic Phenotypes Marks the Progression and Resolution of Lung Fibrosis. *Cell Stem Cell* **2017**, *20*, 261–273.e3.

39. Lee JH, Tammela T, Hofree M, Choi J, Marjanovic ND, Han S, et al. Anatomically and Functionally Distinct Lung Mesenchymal Populations Marked by Lgr5 and Lgr6. *Cell* **2017**, *170*, 1149–1163.e12.

40. Liu X, Zhang X, Liang J, Noble PW, Jiang D. The concept of Sfrp1(+) transitional fibroblasts: the key to dissociating lineage heterogeneity and fate of invasive fibroblasts in pulmonary fibrosis? *Eur. Respir. J.* **2024**, *63*, 2400498.

41. Mukhatayev Z, Adilbayeva A, Kunz J. CTHRC1: An Emerging Hallmark of Pathogenic Fibroblasts in Lung Fibrosis. *Cells* **2024**, *13*, 946.

42. Feng Y, Hu J, Liu F, Shang Y. Collagen Triple Helix Repeat Containing 1 Deficiency Protects Against Airway Remodeling and Inflammation in Asthma Models In Vivo and In Vitro. *Inflammation* **2023**, *46*, 925–940.

43. Tsukui T, Sun KH, Wetter JB, Wilson-Kanamori JR, Hazelwood LA, Henderson NC, et al. Collagen-producing lung cell atlas identifies multiple subsets with distinct localization and relevance to fibrosis. *Nat. Commun.* **2020**, *11*, 1920.

44. Liu G, Philp AM, Corte T, Travis MA, Schilter H, Hansbro NG, et al. Therapeutic targets in lung tissue remodelling and fibrosis. *Pharmacol. Ther.* **2021**, *225*, 107839.

45. Tang X, Li Z, Yu Z, Li J, Zhang J, Wan N, et al. Effect of curcumin on lung epithelial injury and ferroptosis induced by cigarette smoke. *Hum. Exp. Toxicol.* **2021**, *40*, S753–S762.

46. Wei T, Wang X, Lang K, Song Y, Luo J, Gu Z, et al. Peroxiredoxin 6 Protects Pulmonary Epithelial Cells From Cigarette-related Ferroptosis in Chronic Obstructive Pulmonary Disease. *Inflammation* **2024**, *48*, 662–675.

47. Peng K, Yao YX, Lu X, Wang WJ, Zhang YH, Zhao H, et al. Mitochondrial dysfunction-associated alveolar epithelial senescence is involved in CdCl(2)-induced COPD-like lung injury. *J. Hazard. Mater.* **2024**, *476*, 135103.

48. Liu W, Liang W, Zhang C, Liu H, Li H, Zhou L, et al. LncR-GAS5 decrease in adenine phosphoribosyltransferase expresssion via binding TAF1 to increase kidney damage created by CIH. *Heliyon* **2024**, *10*, e33084.

49. Kurie JM, Shin HJ, Lee JS, Morice RC, Ro JY, Lippman SM, et al. Increased epidermal growth factor receptor expression in metaplastic bronchial epithelium. *Clin. Cancer Res.* **1996**, *2*, 1787–1793.

50. Shaykhiev R, Zuo WL, Chao I, Fukui T, Witover B, Brekman A, et al. EGF shifts human airway basal cell fate toward a smoking-associated airway epithelial phenotype. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 12102–12107.

51. Bals R, Hiemstra PS. Innate immunity in the lung: how epithelial cells fight against respiratory pathogens. *Eur. Respir. J.* **2004**, *23*, 327–333.

52. Rogers DF. The airway goblet cell. *Int. J. Biochem. Cell Biol.* **2003**, *35*, 1–6.

53. Leopold PL, O'Mahony MJ, Lian XJ, Tilley AE, Harvey BG, Crystal RG. Smoking is associated with shortened airway cilia. *PLoS ONE* **2009**, *4*, e8157.

54. Ramos EM, De Toledo AC, Xavier RF, Fosco LC, Vieira RP, Ramos D, et al. Reversibility of impaired nasal mucociliary clearance in smokers following a smoking cessation programme. *Respirology* **2011**, *16*, 849–855.

55. Carlier FM, de Fays C, Pilette C. Epithelial Barrier Dysfunction in Chronic Respiratory Diseases. *Front. Physiol.* **2021**, *12*, 691227.

56. Coyne CB, Vanhook MK, Gambling TM, Carson JL, Boucher RC, Johnson LG. Regulation of airway tight junctions by proinflammatory cytokines. *Mol. Biol. Cell* **2002**, *13*, 3218–334.

57. Chen R, Cui Y, Ip MS, Mak JC. Cigarette smoke induces endoplasmic reticulum stress-associated mucus hypersecretion via orosomucoid 1-like protein 3 in airway epithelia. *Free Radic. Res.* **2025**, *59*, 342–355.

58. Dong X, Ding M, Zhang J, Ogülür I, Pat Y, Akdis M, et al. Involvement and therapeutic implications of airway epithelial barrier dysfunction in type 2 inflammation of asthma. *Chin. Med. J.* **2022**, *135*, 519–531.

59. Bailey KL. Aging Diminishes Mucociliary Clearance of the Lung. *Adv. Geriatr. Med. Res.* **2022**, *4*, e220005.

60. Alter P, Baker JR, Dauletbaev N, Donnelly LE, Pistenmaa C, Schmeck B, et al. Update in Chronic Obstructive Pulmonary Disease 2019. *Am. J. Respir. Crit. Care Med.* **2020**, *202*, 348–355.

61. Tran HB, Jersmann H, Truong TT, Hamon R, Roscioli E, Ween M, et al. Disrupted epithelial/macrophage crosstalk via Spinster homologue 2-mediated S1P signaling may drive defective macrophage phagocytic function in COPD. *PLoS ONE* **2017**, *12*, e0179577.

62. Van Eeckhoutte HP, Donovan C, Kim RY, Conlon TM, Ansari M, Khan H, et al. RIPK1 kinase-dependent inflammation and cell death contribute to the pathogenesis of COPD. *Eur. Respir. J.* **2023**, *61*, 2201506.

63. Hiemstra PS, Bourdin A. Club cells, CC10 and self-control at the epithelial surface. *Eur. Respir. J.* **2014**, *44*, 831–832.

64. Gamez AS, Gras D, Petit A, Knabe L, Molinari N, Vachier I, et al. Supplementing defect in club cell secretory protein attenuates airway inflammation in COPD. *Chest* **2015**, *147*, 1467–1476.

65. Snyder JC, Reynolds SD, Hollingsworth JW, Li Z, Kaminski N, Stripp BR. Clara cells attenuate the inflammatory response through regulation of macrophage behavior. *Am. J. Respir. Cell. Mol. Biol.* **2010**, *42*, 161–171.

66. Katavolos P, Ackerley CA, Clark ME, Bienzle D. Clara cell secretory protein increases phagocytic and decreases oxidative activity of neutrophils. *Vet. Immunol. Immunopathol.* **2011**, *139*, 1–9.

67. Tokita E, Tanabe T, Asano K, Suzaki H, Rubin BK. Club cell 10-kDa protein attenuates airway mucus hypersecretion and inflammation. *Eur. Respir. J.* **2014**, *44*, 1002–1010.

68. Pilette C, Godding V, Kiss R, Delos M, Verbeken E, Decaestecker C, et al. Club cell protein 16 and disease progression in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **2013**, *188*, 1413–1419.

69. Perl AK, Riethmacher D, Whitsett JA. Conditional depletion of airway progenitor cells induces peribronchiolar fibrosis. *Am. J. Respir. Crit. Care Med.* **2011**, *183*, 511–521.

70. Pilette C, Godding V, Kiss R, Delos M, Verbeken E, Decaestecker C, et al. Reduced epithelial expression of secretory component in small airways correlates with airflow obstruction in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **2001**, *163*, 185–194.

71. Shijubo N, Itoh Y, Yamaguchi T, Imada A, Hirasawa M, Yamada T, et al. Clara cell protein-positive epithelial cells are reduced in small airways of asthmatics. *Am. J. Respir. Crit. Care Med.* **1999**, *160*, 930–933.

72. Kelly FL, Kennedy VE, Jain R, Sindhwani NS, Copeland CF, Snyder LD, et al. Epithelial clara cell injury occurs in bronchiolitis obliterans syndrome after human lung transplantation. *Am. J. Transplant.* **2012**, *12*, 3076–3084.

73. Liu K, Meng X, Liu Z, Tang M, Lv Z, Huang X, et al. Tracing the origin of alveolar stem cells in lung repair and regeneration. *Cell* **2024**, *187*, 2428–2445.e20.

74. Hu Y, Hu Q, Ansari M, Riemondy K, Pineda R, Sembrat J, et al. Airway derived emphysema-specific alveolar type II cells exhibit impaired regenerative potential in COPD. *Eur. Respir. J.* **2024**, *64*, 2302071.

75. Rock JR, Onaitis MW, Rawlins EL, Lu Y, Clark CP, Xue Y, et al. Basal cells as stem cells of the mouse trachea and human airway epithelium. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 12771–12775.

76. Shaykhiev R. Airway Epithelial Progenitors and the Natural History of Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Crit. Care Med.* **2018**, *197*, 847–849.

77. Araya J, Cambier S, Markovics JA, Wolters P, Jablons D, Hill A, et al. Squamous metaplasia amplifies pathologic epithelial-mesenchymal interactions in COPD patients. *J. Clin. Invest.* **2007**, *117*, 3551–3562.

78. Rao W, Wang S, Duleba M, Niroula S, Goller K, Xie J, et al. Regenerative Metaplastic Clones in COPD Lung Drive Inflammation and Fibrosis. *Cell* **2020**, *181*, 848–864.e18.

79. Whetstone CE, Ranjbar M, Omer H, Cusack RP, Gauvreau GM. The Role of Airway Epithelial Cell Alarmins in Asthma. *Cells* **2022**, *11*, 1105.

80. Préfontaine D, Hamid Q. Airway epithelial cells in asthma. *J. Allergy Clin. Immunol.* **2007**, *120*, 1475–1478.

81. Jones DL, Morley MP, Li X, Ying Y, Zhao G, Schaefer SE, et al. An injury-induced mesenchymal-epithelial cell niche coordinates regenerative responses in the lung. *Science* **2024**, *386*, eado5561.

82. Warner SM, Hackett TL, Shaheen F, Hallstrand TS, Kicic A, Stick SM, et al. Transcription factor p63 regulates key genes and wound repair in human airway epithelial basal cells. *Am. J. Respir. Cell. Mol. Biol.* **2013**, *49*, 978–988.

83. Stevens PT, Kicic A, Sutanto EN, Knight DA, Stick SM. Dysregulated repair in asthmatic paediatric airway epithelial cells: the role of plasminogen activator inhibitor-1. *Clin. Exp. Allergy* **2008**, *38*, 1901–1910.

84. Nadel JA, Burgel PR. The role of epidermal growth factor in mucus production. *Curr. Opin. Pharmacol.* **2001**, *1*, 254–258.

85. Jing Y, Gimenes JA, Mishra R, Pham D, Comstock AT, Yu D, et al. NOTCH3 contributes to rhinovirus-induced goblet cell hyperplasia in COPD airway epithelial cells. *Thorax* **2019**, *74*, 18–32.

86. Rogers DF. Airway goblet cells: responsive and adaptable front-line defenders. *Eur. Respir. J.* **1994**, *7*, 1690–1706.

87. Kim V, Criner GJ. Chronic bronchitis and chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **2013**, *187*, 228–237.

88. Zhu H, Leng J, Ju R, Qu S, Tian J, Leng H, et al. Advantages of pulsed electric field ablation for COPD: Excellent killing effect on goblet cells. *Bioelectrochemistry* **2024**, *158*, 108726.

89. Montoro DT, Haber AL, Biton M, Vinarsky V, Lin B, Birket SE, et al. A revised airway epithelial hierarchy includes CFTR-expressing ionocytes. *Nature* **2018**, *560*, 319–324.

90. Noguchi M, Furukawa KT, Morimoto M. Pulmonary neuroendocrine cells: physiology, tissue homeostasis and disease. *Dis. Model Mech.* **2020**, *13*, dmm046920.

91. Strine MS, Wilen CB. Tuft cells are key mediators of interkingdom interactions at mucosal barrier surfaces. *PLoS Pathog.* **2022**, *18*, e1010318.

92. Desai TJ, Brownfield DG, Krasnow MA. Alveolar progenitor and stem cells in lung development, renewal and cancer. *Nature* **2014**, *507*, 190–194.

93. Okutomo K, Fujino N, Yamada M, Saito T, Ono Y, Okada Y, et al. Increased LHX9 expression in alveolar epithelial type 2 cells of patients with chronic obstructive pulmonary disease. *Respir. Investig.* **2022**, *60*, 119–128.

94. Tsutsumi A, Ozaki M, Chubachi S, Irie H, Sato M, Kameyama N, et al. Exposure to Cigarette Smoke Enhances the Stemness of Alveolar Type 2 Cells. *Am. J. Respir. Cell. Mol. Biol.* **2020**, *63*, 293–305.

95. Irie H, Ozaki M, Chubachi S, Hegab AE, Tsutsumi A, Kameyama N, et al. Short-term intermittent cigarette smoke exposure enhances alveolar type 2 cell stemness via fatty acid oxidation. *Respir. Res.* **2022**, *23*, 41.

96. Yu H, Lin Y, Zhong Y, Guo X, Lin Y, Yang S, et al. Impaired AT2 to AT1 cell transition in PM2.5-induced mouse model of chronic obstructive pulmonary disease. *Respir. Res.* **2022**, *23*, 70.

97. Sauler M, McDonough JE, Adams TS, Kothapalli N, Barnthaler T, Werder RB, et al. Characterization of the COPD alveolar niche using single-cell RNA sequencing. *Nat. Commun.* **2022**, *13*, 494.

98. Wang C, Hyams B, Allen NC, Cautivo K, Monahan K, Zhou M, et al. Dysregulated lung stroma drives emphysema exacerbation by potentiating resident lymphocytes to suppress an epithelial stem cell reservoir. *Immunity* **2023**, *56*, 576–591.e10.

99. Basil MC, Cardenas-Diaz FL, Kathiriya JJ, Morley MP, Carl J, Brumwell AN, et al. Human distal airways contain a multipotent secretory cell that can regenerate alveoli. *Nature* **2022**, *604*, 120–126.

100. Thompson BT, Chambers RC, Liu KD. Acute Respiratory Distress Syndrome. *N. Engl. J. Med.* **2017**, *377*, 562–572.

101. Wang Y, Tang Z, Huang H, Li J, Wang Z, Yu Y, et al. Pulmonary alveolar type I cell population consists of two distinct subtypes that differ in cell fate. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, 2407–2412.

102. Bhattarai P, Lu W, Hardikar A, Dey S, Gaikwad AV, Shahzad AM, et al. Endothelial to mesenchymal transition is an active process in smokers and patients with early COPD contributing to pulmonary arterial pathology. *ERJ Open Res.* **2024**, *10*, 00767-2023.

103. Hogg JC. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. *Lancet* **2004**, *364*, 709–721.

104. McDonough JE, Yuan R, Suzuki M, Seyednejad N, Elliott WM, Sanchez PG, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. *N. Engl. J. Med.* **2011**, *365*, 1567–1575.

105. Barnes PJ. Small airway fibrosis in COPD. *Int. J. Biochem. Cell Biol.* **2019**, *116*, 105598.

106. Eapen MS, Lu W, Hackett TL, Singhera GK, Mahmood MQ, Hardikar A, et al. Increased myofibroblasts in the small airways, and relationship to remodelling and functional changes in smokers and COPD patients: potential role of epithelial-mesenchymal transition. *ERJ Open Res.* **2021**, *7*, 00876-2020.

107. Michaeloudes C, Kuo CH, Haji G, Finch DK, Halayko AJ, Kirkham P, et al. Metabolic re-patterning in COPD airway smooth muscle cells. *Eur. Respir. J.* **2017**, *50*, 1700202.

108. Araya J, Tsubouchi K, Sato N, Ito S, Minagawa S, Hara H, et al. PRKN-regulated mitophagy and cellular senescence during COPD pathogenesis. *Autophagy* **2019**, *15*, 510–526.

109. Fang L, Zhang M, Li J, Zhou L, Tamm M, Roth M. Airway Smooth Muscle Cell Mitochondria Damage and Mitophagy in COPD via ERK1/2 MAPK. *Int. J. Mol. Sci.* **2022**, *23*, 13987.

110. Krimmer DI, Burgess JK, Wooi TK, Black JL, Oliver BG. Matrix proteins from smoke-exposed fibroblasts are pro-proliferative. *Am. J. Respir. Cell. Mol. Biol.* **2012**, *46*, 34–39.

111. Khedoe PP, van Schadewijk WA, Schwiening M, Ng-Blichfeldt JP, Marciniak SJ, Stolk J, et al. Cigarette smoke restricts the ability of mesenchymal cells to support lung epithelial organoid formation. *Front. Cell Dev. Biol.* **2023**, *11*, 1165581.

112. Cheng PP, Yu F, Chen SJ, Feng X, Jia ZH, Hu SH, et al. PM2.5 exposure-induced senescence-associated secretory phenotype in airway smooth muscle cells contributes to airway remodeling. *Environ. Pollut.* **2024**, *347*, 123674.

113. El Omar R, Beroud J, Stoltz JF, Menu P, Velot E, Decot V. Umbilical cord mesenchymal stem cells: the new gold standard for mesenchymal stem cell-based therapies? *Tissue Eng. Part B Rev.* **2014**, *20*, 523–544.

114. Abbaszadeh H, Ghorbani F, Derakhshani M, Movassaghpour AA, Yousefi M, Talebi M, et al. Regenerative potential of Wharton's jelly-derived mesenchymal stem cells: A new horizon of stem cell therapy. *J. Cell Physiol.* **2020**, *235*, 9230–9240.

115. Wang P, Cui Y, Wang J, Liu D, Tian Y, Liu K, et al. Mesenchymal stem cells protect against acetaminophen hepatotoxicity by secreting regenerative cytokine hepatocyte growth factor. *Stem Cell Res. Ther.* **2022**, *13*, 94.

116. Chen Y, Huang H, Li G, Yu J, Fang F, Qiu W. Dental-derived mesenchymal stem cell sheets: a prospective tissue engineering for regenerative medicine. *Stem Cell Res. Ther.* **2022**, *13*, 38.

117. Ridzuan N, Zakaria N, Widera D, Sheard J, Morimoto M, Kiyokawa H, et al. Human umbilical cord mesenchymal stem cell-derived extracellular vesicles ameliorate airway inflammation in a rat model of chronic obstructive pulmonary disease (COPD). *Stem Cell Res. Ther.* **2021**, *12*, 54.

118. Antunes MA, Lapa e Silva JR, Rocco PR. Mesenchymal stromal cell therapy in COPD: from bench to bedside. *Int. J. Chron. Obstruct. Pulmon. Dis.* **2017**, *12*, 3017–3027.

119. Yen BL, Yen ML, Wang LT, Liu KJ, Sytwu HK. Current status of mesenchymal stem cell therapy for immune/inflammatory lung disorders: Gleaning insights for possible use in COVID-19. *Stem Cells Transl. Med.* **2020**, *9*, 1163–1173.

120. Feng B, Zhu J, Xu Y, Chen W, Sheng X, Feng X, et al. Immunosuppressive effects of mesenchymal stem cells on lung B cell gene expression in LPS-induced acute lung injury. *Stem Cell Res. Ther.* **2020**, *11*, 418.

121. Wang YY, Li XZ, Wang LB. Therapeutic implications of mesenchymal stem cells in acute lung injury/acute respiratory distress syndrome. *Stem Cell Res. Ther.* **2013**, *4*, 45.

122. Zhou Y, Zhou W, Li Y, Zhang J. MSCs regulate oxidative stress through the Nrf2 pathway to treat chronic obstructive pulmonary disease. *BMC Pulm. Med.* **2025**, *25*, 304.

123. Cruz T, Lopez-Giraldo A, Noell G, Guirao A, Casas-Recasens S, Garcia T, et al. Smoking Impairs the Immunomodulatory Capacity of Lung-Resident Mesenchymal Stem Cells in Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Cell. Mol. Biol.* **2019**, *61*, 575–583.

124. Kruk DM, Wisman M, Noordhoek JA, Nizamoglu M, Jonker MR, de Bruin HG, et al. Paracrine Regulation of Alveolar Epithelial Damage and Repair Responses by Human Lung-Resident Mesenchymal Stromal Cells. *Cells* **2021**, *10*, 2860.

125. Najar M, Martel-Pelletier J, Pelletier JP, Fahmi H. Novel insights for improving the therapeutic safety and efficiency of mesenchymal stromal cells. *World J. Stem Cells* **2020**, *12*, 1474–1491.

126. Paris GC, Azevedo AA, Ferreira AL, Azevedo YM, Rainho MA, Oliveira GP, et al. Therapeutic potential of mesenchymal stem cells in multiple organs affected by COVID-19. *Life Sci.* **2021**, *278*, 119510.

127. Jolly MK, Ward C, Eapen MS, Myers S, Hallgren O, Levine H, et al. Epithelial-mesenchymal transition, a spectrum of states: Role in lung development, homeostasis, and disease. *Dev. Dyn.* **2018**, *247*, 346–358.

128. Dongre A, Weinberg RA. New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer. *Nat. Rev. Mol. Cell Biol.* **2019**, *20*, 69–84.

129. Kim DH, Xing T, Yang Z, Dudek R, Lu Q, Chen YH. Epithelial Mesenchymal Transition in Embryonic Development, Tissue Repair and Cancer: A Comprehensive Overview. *J. Clin. Med.* **2017**, *7*, doi: 10.3390/jcm7010001..

130. Knight DA, Grainge CL, Stick SM, Kicic A, Schuliga M. Epithelial Mesenchymal Transition in Respiratory Disease: Fact or Fiction. *Chest* **2020**, *157*, 1591–1596.

131. Koczulla AR, Jonigk D, Wolf T, Herr C, Noeske S, Klepetko W, et al. Krüppel-like zinc finger proteins in end-stage COPD lungs with and without severe alpha1-antitrypsin deficiency. *Orphanet. J. Rare Dis.* **2012**, *7*, 29.

132. Mahmood MQ, Walters EH, Shukla SD, Weston S, Muller HK, Ward C, et al. β-catenin, Twist and Snail: Transcriptional regulation of EMT in smokers and COPD, and relation to airflow obstruction. *Sci. Rep.* **2017**, *7*, 10832.

133. Zheng L, Jiang YL, Fei J, Cao P, Zhang C, Xie GF, et al. Circulatory cadmium positively correlates with epithelial-mesenchymal transition in patients with chronic obstructive pulmonary disease. *Ecotoxicol. Environ. Saf.* **2021**, *215*, 112164.

134. Shirahata T, Nakamura H, Nakajima T, Nakamura M, Chubachi S, Yoshida S, et al. Plasma sE-cadherin and the plasma sE-cadherin/sVE-cadherin ratio are potential biomarkers for chronic obstructive pulmonary disease. *Biomarkers* **2018**, *23*, 414–421.

135. Mahmood MQ, Sohal SS, Shukla SD, Ward C, Hardikar A, Noor WD, et al. Epithelial mesenchymal transition in smokers: large versus small airways and relation to airflow obstruction. *Int. J. Chron. Obstruct. Pulmon. Dis.* **2015**, *10*, 1515–1524.

136. Milara J, Peiró T, Serrano A, Cortijo J. Epithelial to mesenchymal transition is increased in patients with COPD and induced by cigarette smoke. *Thorax* **2013**, *68*, 410–420.

137. Nomura T, Huang WC, Zhau HE, Josson S, Mimata H, Chung LW. β2-Microglobulin-mediated signaling as a target for cancer therapy. *Anticancer Agents Med. Chem.* **2014**, *14*, 343–352.

138. De Cunto G, Brancaleone V, Riemma MA, Cerqua I, Vellecco V, Spaziano G, et al. Functional contribution of sphingosine-1-phosphate to airway pathology in cigarette smoke-exposed mice. *Br. J. Pharmacol.* **2020**, *177*, 267–281.

139. Sharma P, Nag A. CUL4A ubiquitin ligase: a promising drug target for cancer and other human diseases. *Open Biol.* **2014**, *4*, 130217.

140. Ren Y, Zhang Y, Fan L, Jiao Q, Wang Y, Wang Q. The cullin4A is up-regulated in chronic obstructive pulmonary disease patient and contributes to epithelial-mesenchymal transition in small airway epithelium. *Respir. Res.* **2019**, *20*, 84.

141. Ornitz DM, Itoh N. The Fibroblast Growth Factor signaling pathway. *Wiley Interdiscip. Rev. Dev. Biol.* **2015**, *4*, 215–266.

142. Yuan T, Volckaert T, Redente EF, Hopkins S, Klinkhammer K, Wasnick R, et al. FGF10-FGFR2B Signaling Generates Basal Cells and Drives Alveolar Epithelial Regeneration by Bronchial Epithelial Stem Cells after Lung Injury. *Stem Cell Rep.* **2019**, *12*, 1041–1055.

143. Gupte VV, Ramasamy SK, Reddy R, Lee J, Weinreb PH, Violette SM, et al. Overexpression of fibroblast growth factor-10 during both inflammatory and fibrotic phases attenuates bleomycin-induced pulmonary fibrosis in mice. *Am. J. Respir. Crit. Care Med.* **2009**, *180*, 424–436.

144. Volckaert T, Yuan T, Chao CM, Bell H, Sitaula A, Szimmtenings L, et al. Fgf10-Hippo Epithelial-Mesenchymal Crosstalk Maintains and Recruits Lung Basal Stem Cells. *Dev. Cell* **2017**, *43*, 48–59.e5.

145. Moiseenko A, Vazquez-Armendariz AI, Kheirollahi V, Chu X, Tata A, Rivetti S, et al. Identification of a Repair-Supportive Mesenchymal Cell Population during Airway Epithelial Regeneration. *Cell Rep.* **2020**, *33*, 108549.

146. Hadzic S, Wu CY, Avdeev S, Weissmann N, Schermuly RT, Kosanovic D. Lung epithelium damage in COPD - An unstoppable pathological event? *Cell Signal* **2020**, *68*, 109540.

147. Kruk DM, Wisman M, Bruin HG, Lodewijk ME, Hof DJ, Borghuis T, et al. Abnormalities in reparative function of lung-derived mesenchymal stromal cells in emphysema. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2021**, *320*, L832–L844.

148. Klar J, Blomstrand P, Brunmark C, Badhai J, Håkansson HF, Brange CS, et al. Fibroblast growth factor 10 haploinsufficiency causes chronic obstructive pulmonary disease. *J. Med. Genet.* **2011**, *48*, 705–709.

149. Wu X, van Dijk EM, Ng-Blichfeldt JP, Bos IS, Ciminieri C, Königshoff M, et al. Mesenchymal WNT-5A/5B Signaling Represses Lung Alveolar Epithelial Progenitors. *Cells* **2019**, *8*, 1147.

150. Su Y, Han W, Kovacs-Kasa A, Verin AD, Kovacs L. HDAC6 Activates ERK in Airway and Pulmonary Vascular Remodeling of Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Cell. Mol. Biol.* **2021**, *65*, 603–614.

151. Aravamudan B, Thompson M, Sieck GC, Vassallo R, Pabelick CM, Prakash YS. Functional Effects of Cigarette Smoke-Induced Changes in Airway Smooth Muscle Mitochondrial Morphology. *J. Cell Physiol.* **2017**, *232*, 1053–1068.

152. Boucherat O, Chakir J, Jeannotte L. The loss of Hoxa5 function promotes Notch-dependent goblet cell metaplasia in lung airways. *Biol. Open* **2012**, *1*, 677–691.

153. Danahay H, Pessotti AD, Coote J, Montgomery BE, Xia D, Wilson A, et al. Notch2 is required for inflammatory cytokine-driven goblet cell metaplasia in the lung. *Cell Rep.* **2015**, *10*, 239–252.

154. Elias JA, Lee CG, Zheng T, Ma B, Homer RJ, Zhu Z. New insights into the pathogenesis of asthma. *J. Clin. Invest.* **2003**, *111*, 291–297.

155. Hogg JC, Timens W. The pathology of chronic obstructive pulmonary disease. *Annu. Rev. Pathol.* **2009**, *4*, 435–459.

156. Wilk JB, Chen TH, Gottlieb DJ, Walter RE, Nagle MW, Brandler BJ, et al. A genome-wide association study of pulmonary function measures in the Framingham Heart Study. *PLoS Genet.* **2009**, *5*, e1000429.

157. Zhou X, Baron RM, Hardin M, Cho MH, Zielinski J, Hawrylkiewicz I, et al. Identification of a chronic obstructive pulmonary disease genetic determinant that regulates HHIP. *Hum. Mol. Genet.* **2012**, *21*, 1325–1335.

158. Volckaert T, Campbell A, Dill E, Li C, Minoo P, De Langhe S. Localized Fgf10 expression is not required for lung branching morphogenesis but prevents differentiation of epithelial progenitors. *Development* **2013**, *140*, 3731–3742.

159. Volckaert T, Dill E, Campbell A, Tiozzo C, Majka S, Bellusci S, et al. Parabronchial smooth muscle constitutes an airway epithelial stem cell niche in the mouse lung after injury. *J. Clin. Invest.* **2011**, *121*, 4409–4419.

160. Tata PR, Mou H, Pardo-Saganta A, Zhao R, Prabhu M, Law BM, et al. Dedifferentiation of committed epithelial cells into stem cells in vivo. *Nature* **2013**, *503*, 218–223.

161. Zhao R, Fallon TR, Saladi SV, Pardo-Saganta A, Villoria J, Mou H, et al. Yap tunes airway epithelial size and architecture by regulating the identity, maintenance, and self-renewal of stem cells. *Dev. Cell* **2014**, *30*, 151–165.

162. Kooistra T, Saez B, Roche M, Egea-Zorrilla A, Li D, Anketell D, et al. Airway basal stem cells are necessary for the maintenance of functional intraepithelial airway macrophages. *Cell Rep.* **2025**, *44*, 115860.

163. Wang Y, Meng Z, Liu M, Zhou Y, Chen D, Zhao Y, et al. Autologous transplantation of P63(+) lung progenitor cells for chronic obstructive pulmonary disease therapy. *Sci. Transl. Med.* **2024**, *16*, eadi3360.

164. Chen Q, Hirai H, Chan M, Zhang J, Cho M, Randell SH, et al. Characterization of perivascular alveolar epithelial stem cells and their niche in lung homeostasis and cancer. *Stem Cell Rep.* **2024**, *19*, 890–905.

165. Zhang J, Liu Y. Epithelial stem cells and niches in lung alveolar regeneration and diseases. *Chin. Med. J. Pulm. Crit. Care Med.* **2024**, *2*, 17–26.

166. Hogan BL, Barkauskas CE, Chapman HA, Epstein JA, Jain R, Hsia CC, et al. Repair and regeneration of the respiratory system: complexity, plasticity, and mechanisms of lung stem cell function. *Cell Stem Cell* **2014**, *15*, 123–138.

167. Adams TS, Schupp JC, Poli S, Ayaub EA, Neumark N, Ahangari F, et al. Single-cell RNA-seq reveals ectopic and aberrant lung-resident cell populations in idiopathic pulmonary fibrosis. *Sci. Adv.* **2020**, *6*, eaba1983.

168. Habermann AC, Gutierrez AJ, Bui LT, Yahn SL, Winters NI, Calvi CL, et al. Single-cell RNA sequencing reveals profibrotic roles of distinct epithelial and mesenchymal lineages in pulmonary fibrosis. *Sci. Adv.* **2020**, *6*, eaba1972.

169. Kadur Lakshminarasimha Murthy P, Sontake V, Tata A, Kobayashi Y, Macadlo L, Okuda K, et al. Human distal lung maps and lineage hierarchies reveal a bipotent progenitor. *Nature* **2022**, *604*, 111–119.

170. Ahmadvand N, Carraro G, Jones MR, Shalashova I, Noori A, Wilhelm J, et al. Cell-Surface Programmed Death Ligand-1 Expression Identifies a Sub-Population of Distal Epithelial Cells Enriched in Idiopathic Pulmonary Fibrosis. *Cells* **2022**, *11*, 1593.

171. Lv YQ, Cai GF, Zeng PP, Dhlamini Q, Chen LF, Chen JJ, et al. FGF10 Therapeutic Administration Promotes Mobilization of Injury-Activated Alveolar Progenitors in a Mouse Fibrosis Model. *Cells* **2022**, *11*, 2396.

172. Chioccioli M, Liu S, Magruder S, Tata A, Borriello L, McDonough JE, et al. Stem cell migration drives lung repair in living mice. *Dev. Cell* **2024**, *59*, 830–840.e4.

173. El Agha E, Thannickal VJ. The lung mesenchyme in development, regeneration, and fibrosis. *J. Clin. Invest.* **2023**, *133*, e170498.

174. Wu J, Chu X, Chen C, Bellusci S. Role of Fibroblast Growth Factor 10 in Mesenchymal Cell Differentiation During Lung Development and Disease. *Front. Genet.* **2018**, *9*, 545.

175. Konkimalla A, Konishi S, Macadlo L, Kobayashi Y, Farino ZJ, Miyashita N, et al. Transitional cell states sculpt tissue topology during lung regeneration. *Cell Stem Cell* **2023**, *30*, 1486–1502.e9.

176. Higham A, Quinn AM, Cançado JE, Singh D. The pathology of small airways disease in COPD: historical aspects and future directions. *Respir. Res.* **2019**, *20*, 49.

177. Yang J, Antin P, Berx G, Blanpain C, Brabletz T, Bronner M, et al. Guidelines and definitions for research on epithelial-mesenchymal transition. *Nat. Rev. Mol. Cell. Biol.* **2020**, *21*, 341–352.

178. Kheirollahi V, Wasnick RM, Biasin V, Vazquez-Armendariz AI, Chu X, Moiseenko A, et al. Metformin induces lipogenic differentiation in myofibroblasts to reverse lung fibrosis. *Nat. Commun.* **2019**, *10*, 2987.

179. Nasri A, Foisset F, Ahmed E, Lahmar Z, Vachier I, Jorgensen C, et al. Roles of Mesenchymal Cells in the Lung: From Lung Development to Chronic Obstructive Pulmonary Disease. *Cells* **2021**, *10*, 3467.

180. Taghizadeh S, Heiner M, Vazquez-Armendariz AI, Wilhelm J, Herold S, Chen C, et al. Characterization in mice of the resident mesenchymal niche maintaining AT2 stem cell proliferation in homeostasis and disease. *Stem Cells* **2021**, *39*, 1382–1394.

181. Fang Y, Chung SS, Xu L, Xue C, Liu X, Jiang D, et al. RUNX2 promotes fibrosis via an alveolar-to-pathological fibroblast transition. *Nature* **2025**, *640*, 221–230.