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REVIEW

Pathogenic Cell in COPD: Mechanisms of Airway Remodeling, Immune Dysregulation, and Therapeutic Implications

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Abstract: The pathological alterations in COPD cells represent adaptive responses to COPD lesions, focusing on three primary pathological changes: abnormal repair and tissue remodeling, protease-antiprotease imbalance, and inflammatory amplification alongside immune disorder. These alterations ultimately result in a detrimental cycle of lung parenchymal destruction and airway structural remodeling. COPD manifests with diverse pathological phenotypes, pronounced heterogeneity, and a convoluted evolution process. However the role of pathological changes and mechanisms in pathological cells, as well as cellular senescence, metabolic reprogramming, and intercellular interaction networks in COPD, remains unclear. This review comprehensively encapsulates the most recent research advancements regarding the principal pathological cells in COPD, encompassing airway epithelial cells, fibroblasts, endothelial cells, and immune inflammatory cells. Elucidated the pathological alterations of these cells in relation to COPD, their influence on disease progression, and their clinical implications. Furthermore, Exosome-mediated miRNA transfer exacerbates inflammation and fibrosis, suggesting novel therapeutic targets. In summary, our work aims to provide a basic reference for research into the pathogenic mechanisms of this disease.

Keywords: chronic obstructive pulmonary disease, airway epithelial cells, fibroblasts, endothelial cells, immune inflammatory cells, extracellular vesicles, miRNA, NETosis, cellular senescence

Introduction

COPD is a serious chronic respiratory disorder that causes severe airflow limitation and permanent lung function decline, causing persistent dyspnoea, cough, and sputum.[1] It is predominantly induced by exposure to air pollutants, particularly cigarette smoking (cs), while also being linked to genetic, developmental, and social factors.[2] While environmental triggers are well-established, their impact on aberrant cell signaling-particularly via oxidative stress and epigenetic reprogramming-remains poorly understood. As on the most recent World Health Organization figures for 2023, the worldwide prevalence of COPD has attained 392 million patients, leading to around 3.2 million fatalities year, constituting 6% of all global deaths.[3] The fundamental pathophysiological mechanisms of COPD include: abnormal repair/tissue remodeling, protease-antiprotease imbalance, and inflammatory amplification/immune disorder.[4–6] The pathological changes in COPD cells signify adaptive responses to these injuries. Airway epithelial cells, fibroblasts, and endothelial cells are essential structural components that play a significant role in the abnormal repair mechanisms and tissue remodeling associated with COPD, leading to changes in airways, blood vessels, and the onset of tissue fibrosis.[7–9] Innate immune cells, including macrophages and neutrophils, exhibit antibacterial dysfunction while concurrently promoting inflammation.[10,11] Single-cell RNA sequencing results suggest that the compromised phagocytic function of macrophages may be associated with reduced expression of phagocytic-related receptors and mitochondrial

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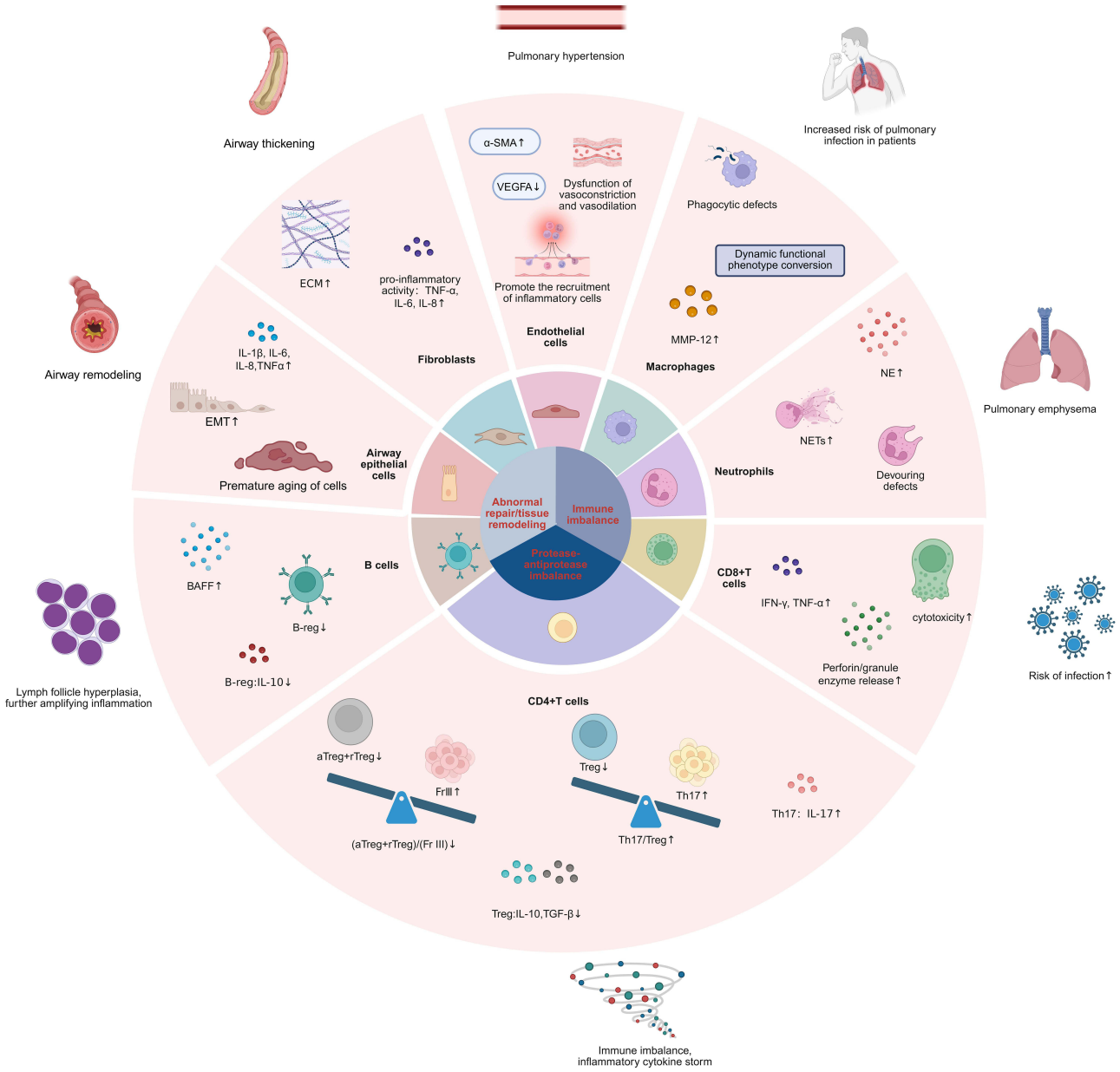
Graphical Abstract



dysfunction in COPD macrophages.[12] The imbalance between pro-inflammatory and anti-inflammatory subgroups of adaptive immune cells, such as T cells and B cells, may lead to disorders in immune homeostasis, thereby exacerbating inflammation.[13,14] Exosome-mediated cellular communication is central to the pathogenic cellular interactions in COPD, with data suggesting a close association between EVs, inflammation, and airway fibrosis in the condition.[15] This study outlines the pathological changes in airway epithelial cells, fibroblasts, endothelial cells, and inflammatory immune cells in the etiology of COPD, their impact on disease progression, and their potential therapeutic implications.

Methods

We conducted a comprehensive search in PubMed (https://pubmed.ncbi.nlm.nih.gov/) for English-language articles published between 2000 and 2025. The search strategy integrated MeSH terms and free-text keywords, such as "COPD", "Airway Epithelial Cells", "Fibroblasts", "Endothelial Cells", "Immune Inflammatory Cells", "Extracellular Vesicles", "miRNA", "NETosis", and "Cellular Senescence".Assess the eligibility of selected articles by screening titles and abstracts to decrease the total number of articles included in this review, ultimately resulting in the selection of 137 articles for analysis.

Airway Epithelial Cells in COPD

Definition and Function of Airway Epithelial Cells

The airway epithelium, a specialized cellular layer, borders the airways and serves as the primary barrier against external stimuli and pathogens, obstructing the invasion of bacteria, viruses, allergens, and airborne pollutants into the lungs.[16] Airway epithelial cells encompass ciliated cells, secretory cells, goblet cells, basal cells, a limited number of pulmonary neuroendocrine cells, and ionocytes.[17] This article only discusses the more significant cell types, including ciliated cells, secretory cells, goblet cells, and basal cells. Ciliated cells remove foreign debris from the airway, secretory cells generate airway surface-active substances, goblet cells release mucus, and basal cells repair cells.[18] In conclusion, the main function of epithelial cells is to keep the airways clean and unobstructed.

Pathologic Alterations of Airway Epithelial Cells in COPD

Alterations in Cell Structure and Function

In COPD airway epithelial cells, the diminished quantity of ciliated cells and the decreased frequency of ciliary movement may impair the airway's capacity to eliminate monstrosity and mucus.[19] Goblet cells are abundant and secrete substantial quantities of mucus, perhaps leading to mucus accumulation in the airways.[20] Basal cells proliferate, resulting in the narrowing of the airway.[21] Chronic impairment of the structure and function of airway epithelial cells diminishes airway barrier and leads to airway wall thickening. The cytokine secretion profile of airway epithelial cells in COPD exhibits alterations. Airway epithelial cells in COPD patients secrete several pro-inflammatory cytokines, including tumour necrosis factor (TNF-α), interleukin (IL)-1β, IL-6, and IL-8, when exposed to inflammatory stimuli.[22] The release of IL-8 and IL-6 was significantly elevated in the airway epithelial cells of COPD patients upon stimulation with cigarette smoke extract (CSE) and Pseudomonas aeruginosa lipopolysaccharide.[23] The heightened release of pro-inflammatory cytokines by airway epithelial cells serves a protective role; however, prolonged exposure may induce chronic inflammatory responses in the airways, potentially culminating in the death of airway epithelial cells and a reduction in their functionality.

Repeated Damage and Repair of Abnormalities

Airway epithelial cells are prone to damage as they are often exposed to air pollutants, among which CS exposure the most common.[18] CS causes airway "oxidative stress" by favoring oxidation over antioxidants, which increases intracellular ROS production.[24] ROS, mainly produced during mitochondrial oxidative phosphorylation, are reactive oxygen molecules that can directly kill bacteria but also damage normal cells.[25] When ROS exceeds cellular antioxidant defenses' scavenging capacity, they damage normal cells and activate an inflammatory response, leading to lung tissue damage.[24] Although injured airway epithelial cells can self-repair, the repair process is often abnormal. This is because oxidative stress damages cell membranes and DNA, reducing cellular repair ability, accelerates the aging of airway epithelial cells, and impedes regeneration.[26] In COPD, persistent damage to the airway epithelium and repair abnormalities contribute to airway remodeling.

Active EMT Process

Javier Milara et al showed that active EMT processes are present in airway epithelial cells of smokers and COPD patients.[27] Epithelial-mesenchymal transition (EMT) confers epithelial cells mesenchymal phenotypes, increasing their motility, invasiveness, and extracellular matrix synthesis.[28] In this process, epithelial cell markers like E-cadherin decrease, while mesenchymal cell markers like vimentin and α-SMA increase.[6] E-cadherin expression in patients with

COPD was approximately 50% of that observed in the normal group, while waveform protein levels were upregulated, suggesting active EMT.[29,30] EMT is a crucial pathophysiological process in COPD, which is related to airway fibrosis, airway remodeling, and malignant transformation.[31] Therefore, an active EMT process may be an important marker of airway remodeling in COPD.

Premature Cell Failure

Patients with COPD have notable premature cellular senescence, a critical characteristic of the disease.[32] Melissa Rivas et al have proposed that cellular senescence in the course of COPD is significantly linked to DNA damage, telomere disruption, and oxidative stress.[33] In COPD airway epithelial cells, activation of the p53/p21WAF1/CIP1 pathway induces cell cycle arrest and enhances the expression of senescence markers, suggesting the occurrence of premature cellular senescence.[34] The p53/p21WAF1/CIP1 pathway, alongside the p16INK4a/pRB pathway and the DNA damage response (DDR)-independent p21 nondependent pathway, significantly contributes to airway epithelial cell senescence. Activation of these pathways results in cell cycle arrest and the secretion of the senescence-associated secretory phenotype (SASP).[34] Cellular senescence is a state of irreversible growth arrest and eventually manifests itself as a senescence-associated secretory phenotype (SASP).[35] Through SASP, senescent cells maintain metabolic activity and secrete pro-inflammatory proteins and chemokines such TNF-α, IL-6, CXCL1, CXCL8, and CCL2, leading to an inflammatory response in COPD airways.[36] The premature failure of airway epithelial cells may be significantly associated with diminished airway epithelial cell function and the inflammatory response in COPD (Figure 1).

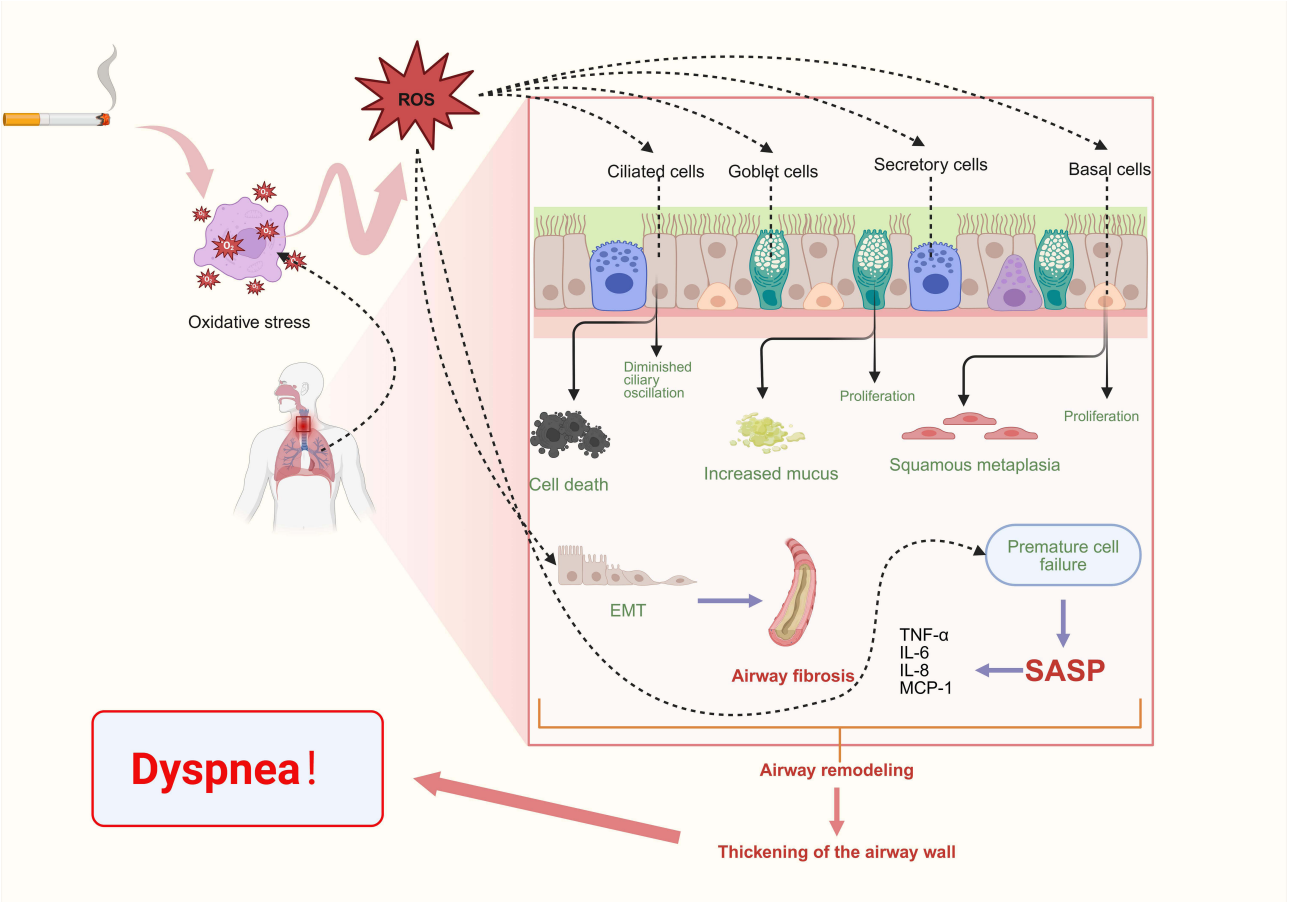


Figure 1 Pathological changes in airway epithelial cells in COPD.
Notes: ↑: increase; ↓: decrease. CS induces a "oxidative stress" reaction in the airway, resulting in the intracellular generation of substantial quantities of ROS, which can harm or modify the normal structure of epithelial cells and facilitate the senescence of EMT and airway epithelial cells, finally culminating in airway remodeling. (The data comes from humans). Created in BioRender. Bailey, L. (2025) https://BioRender.com/x22x526.
Abbreviations: ROS, reactive oxygen; MCP-1, monocyte chemotactic protein-1; SASP, senescence-associated secretory phenotype.

Pathological Alterations of Airway Epithelial Cells: Clinical Implications

The chronic inflammatory milieu in airway epithelial cells of COPD results in ongoing cellular damage. The airway epithelial cells undergo structural and functional changes in response to chronic damage, leading to pathological repair of the airway epithelium. This ultimately results in irreversible remodeling of the airways. Consequently, mitigating the inflammatory environment in the airways represents a feasible approach. Research indicates that COPD tissue cells demonstrate a propensity for premature aging.[32] The advancement of agents for the clearance of senescent cells aimed at repairing epithelial tissue represents a significant research focus. Cellular senescence induced by the p53 pathway can be suppressed through the application of p53 axis modulators.[37] Moreover, the inhibition of EMT represents a viable therapeutic approach.

Fibroblasts in COPD

Definition and Function of Fibroblasts

Fibroblasts are responsible for generating and secreting the primary components of the ECM, including collagen and elastin, and their main purpose is to participate in the repair and healing of injured tissue.[38] The ECM mainly consists of collagen, elastin, proteoglycans, glycosaminoglycans, fibronectin, and laminin.[39] Fibroblasts in COPD originate from three sources: (1) proliferation of lung fibroblasts, (2) transformation of epithelial cells into fibroblasts via EMT, and (3) the recruitment of progenitor cells.[40] Fibroblasts, typically regarded as connective tissue cells, have also been categorized through immunological studies as a "non-classical" part of the innate immune system, recognized as a "key immune sentinel cell."[41] Therefore, the immunological role of fibroblasts in COPD warrants further attention.

Pathologic Alterations of Fibroblasts in COPD

ECM Deposition and Compositional Abnormalities

It has been shown that a substantial increase in collagen deposition is observed in the airways and lung tissues of patients with COPD, which results from fibroblast activation and proliferation and leads to airway wall thickening and remodeling.[42] Normally, fibroblasts repair damaged tissues by producing the ECM. However, in COPD patients, fibroblasts proliferate and release large amounts of ECM components, such as collagen, fibronectin, and TGF-β, leading to lung tissue fibrosis.[39] It is noteworthy that pathological fibroblasts are associated with not only pulmonary fibrosis but also emphysema. Lung fibroblasts from patients with COPD produce ECM with abnormal levels of proteoglycan components; specifically, there is an increase in one type of proteoglycan, multifunctional proteoglycan (versican), and a decrease in another type, basement membrane proteoglycan (perlecan).[43] An increase in versican may impair the elastic retraction of the lungs, while a decrease in perlecan may affect basement-membrane integrity and lead to increased risk of infection and sensitivity of lung tissue, and changes in the content of these two proteoglycan components may be associated with the development of emphysema.[43]

Pro-Inflammatory Activity

Fibroblasts are crucial to the healing process. In COPD, fibroblasts exhibit pro-inflammatory activity. Emmanuel T Osei et al demonstrated that in COPD, airway epithelial cells stimulate lung fibroblasts to produce the inflammatory factor IL-8 via the secretion of IL-1α.[44] The research indicated that this mechanism is governed by miR-146a-5p, a short non-coding RNA, and that the synthesis of IL-1αby epithelial cells escalates when the expression of miR-146a-5p is diminished.[45] Research indicates that in individuals with COPD, miR-146a-5p levels are diminished in fibroblasts, resulting in elevated IL-1α from epithelial cells, which may enhance IL-8 secretion in lung fibroblasts.[45] This suggests that fibroblasts may display a pro-inflammatory phenotype in COPD and participate in the inflammatory response associated with the condition. Decreased levels of miR-146a-5p in COPD fibroblasts may correlate with DNA methylation and the suppression of transcription factors. Numerous studies indicate that the promoter region of the miR-146a gene, situated on chromosome 5q33.3, is rich in CpG islands. When this region undergoes methylation by DNA methyltransferases, such as DNMT1 and DNMT3A, the chromatin structure becomes more condensed, hindering the binding of RNA polymerase II and consequently directly suppressing the synthesis of the primary transcript (pri-miR-146a) of miR-146a-5p.[46,47] Pro-inflammatory transcription factors, such as NF-κB (eg, p65), can attach to the κB binding sites within the promoter region of miR-146a, functioning in a dual capacity: at low concentrations, they enhance miR-146a transcription (serving as negative feedback for inflammation), whereas under prolonged inflammatory stimuli,

excessive NF-κB activation enlists histone deacetylases, suppressing miR-146a transcription and instead facilitating IL-8 expression.[48,49] Furthermore, histone changes and chromatin remodeling may contribute to the repression of miR-146a-5p levels. Reports indicate that the expression of miR-146a can be suppressed by histone deacetylation facilitated by histone deacetylase 1, a crucial epigenetic enzyme that opposes both histone and non-histone acetylation.[50]

Pathological Alterations of Fibroblasts: Clinical Implications

Fibroblasts play a crucial role in the pathological processes of irreversible airway remodelling and lung tissue fibrosis in COPD. In this condition, fibroblasts secrete significant quantities of extracellular matrix (ECM) proteins, including collagen and fibronectin, which are integral to ECM remodelling. This remodelling contributes to lung parenchyma fibrosis and airway wall thickening. Consequently, the application of ECM modulators may mitigate airway remodelling and lung tissue fibrosis in COPD. Additionally, targeting and inhibiting the pro-fibrotic factor TGF-β through a specific signalling pathway can reduce fibroblast activity and collagen production.Although correlation reports in COPD are limited, research suggests that fibroblasts can produce pro-inflammatory factors like TNF-α, IL-6, IL-8, and chemokines like CXCL1 and CXCL2 to recruit and activate inflammatory cells.[51] Therefore, fibroblast-mediated inflammatory responses may represent a novel and valuable direction for research.

Endothelial Cells in COPD

Definition and Function of Endothelial Cells

Endothelial cells in COPD constitute the monolayer that lines the inner surface of the pulmonary vasculature, and they are crucial for regulating blood flow, maintaining hemostatic balance, modulating vascular tone, and engaging in neoangiogenesis[52] Endothelial cells are directly subjected to chronic inflammation and oxidative stress within the pulmonary circulatory system; consequently, the apoptosis rate of pulmonary vascular endothelial cells in COPD patients is significantly elevated, and exposure to cigarette smoke exacerbates this process.[53]

Pathologic Alterations of Endothelial Cells in COPD

Vascular endothelial cells in COPD undergo remodeling, resulting in considerable structural damage and functional impairments. Structurally, there is an elevation in vascular endothelial smooth muscle actin (SMA), a reduction in the endothelial cell markers CD31, KDR, and vascular endothelial growth factor A (VEGFA), and an increase in the pro-apoptotic molecule ceramide in patients with COPD. Furthermore, diminished expression of KDR and VEGFA negatively correlates with impaired lung function and the severity of emphysema.[54,55] Indicating that capillary remodeling transpires, characterized by the thickening of the smooth muscle layer of capillaries, vascular remodeling, and a reduction in the number of vascular endothelial cells.

Functionally, endothelial cells in COPD demonstrate reduced proliferation, migration, and differentiation capabilities.[56] The impairment of endothelial cells in COPD significantly contributes to the onset of inflammation. During inflammation, active endothelial cells release many adhesion molecules, including intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, facilitating the recruitment of immune inflammatory cells.[57] Moreover, endothelial cells exhibit an active inflammatory response characterized by the activation of inflammatory signaling pathways (eg, NF-κB) and oxidative stress-related genes (eg, iNOS, NOX4) within the pulmonary vascular endothelium of patients with COPD, resulting in elevated ROS.[58] This inflammatory response produces many mediators that intensify small airway inflammation and facilitate the process of small airway remodeling.[59] The vasculature of individuals with COPD demonstrates compromised endothelium-dependent vasodilation, potentially resulting in diminished lung function, exacerbations, and heightened cardiovascular incidents.[60] Moreover, research indicates that the quantity of endothelial progenitor cells is diminished in individuals with COPD, particularly in those with moderate to severe cases, but the count of circulating endothelial cells does not exhibit a substantial rise.[56] This may result in diminished endothelial cell repair in individuals with COPD. The vasodilatory function and malfunction of the vascular endothelium facilitate the infiltration of inflammatory cells in small airways and the accumulation of extracellular matrix, hence aggravating small airway remodeling.[59]

The pathogenic alterations In endothelial cells may be associated with vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-2α (HIF-2α).VEGF is a growth factor specific to endothelial cells, crucial for their proliferation, migration, and apoptosis prevention; diminished levels of VEGF in COPD patients may exacerbate emphysema.[60] Hypoxia-inducible factor-2α (HIF-2α) is a crucial regulator of vascular homeostasis and repair, and is significantly linked to pulmonary hypertension in COPD.[61]

Pathological Alterations of Endothelial Cells: Clinical Implications

Pathological changes in the endothelium in COPD may result in aggravation of emphysema, pulmonary hypertension, or an elevated risk of cardiovascular events associated with COPD. Consequently, facilitating the restoration of endothelial cell function and the repair of vascular endothelial barrier integrity is a viable therapeutic approach. This can be achieved through the transplantation of healthy endothelium cells, which can rectify elastase-induced alveolar damage and enhance pulmonary elasticity and respiratory performance.[54] Conversely, COPD may also be ameliorated by mitigating endothelial cell injury.

Macrophages in COPD

Definition and Function of Macrophages

As "scavengers" in the pulmonary system, lung macrophages breakdown and remove inhaled hazardous items such inorganic particles, viruses, bacteria, and fungi, and necrotic and apoptotic cells.[62] The primary macrophage subtypes are M1 and M2. Classically activated M1 macrophages release large quantities of proinflammatory cytokines and are bactericidal. M2 macrophages, or "alternatively activated macrophages", heal tissue and modulate the immune system.[62]

Pathologic Alterations of Macrophages in COPD

Dynamic Functional Phenotype Conversion

The conventional classification of macrophage polarization into pro-inflammatory M1 and anti-inflammatory M2 types is limited in its applicability to the research of macrophages associated with chronic inflammation. Macrophages in chronic inflammation exhibit more intricate transcriptome profiles, characterized by different phenotypic and functional alterations, rendering them unsuitable for classification into the binary states of M1 and M2.[63] Macrophage polarization is a dynamic process, with its phenotypic being adaptable and subject to change based on microenvironmental inputs.[64] This describes the dynamic nature of phenotypic switching, which denotes the capacity of macrophages to adapt their functional phenotype in response to alterations in microenvironmental cues. During the inflammatory response, macrophages may alternate between pro-inflammatory and anti-inflammatory phenotypes based on the type and concentration of inflammatory mediators.[65] This phenotypic change is continuous, indicating that macrophage phenotypes are not confined to the two extremes of M1 and M2, but rather exist along a continuous continuum.[66] Moreover, in contrast to the conventional perspective that M1 macrophages provide a pro-inflammatory function while M2 macrophages exhibit an anti-inflammatory role, it is now understood that the functional attributes of macrophages are not entirely distinct but rather exhibit some degree of overlap. Certain M1-type macrophages may demonstrate tissue repair activities under specific situations, whereas M2-type macrophages may engage in inflammatory responses under particular circumstances.[63] The processes of phenotypic conversion, cohabitation, and functional overlap illustrate the intricate complexity of macrophage populations and suggest new avenues for research on macrophages in COPD.

Phagocytic Defects

Studies have demonstrated that macrophages from COPD patients exhibit significantly decreased phagocytosis of respiratory pathogens such as Haemophilus influenzae and Streptococcus pneumoniae.[67] Sarah L O'Beirne et al proposed that this defect might be caused by mitochondrial dysfunction and decreased compensatory glycolysis in macrophages.[68] Their study also found that smokers and COPD patients' bronchoalveolar lavage fluid macrophage mitochondria had reduced coupling efficiency, proton leakage, and bioenergetic fitness index, which prevented them from synthesizing and maintaining ATP levels.[68] Insufficient ATP supply and diminished compensatory glycolysis hinder macrophages' energy availability, leading to a reduction in their typical phagocytic function. Furthermore, Belchamber et al found that COPD macrophages had elevated mitochondrial ROS after phagocytosing bacteria, which may increase intracellular oxidative stress and impair macrophage structure and function, decreasing phagocytosis.[67] In Bewley et al's study, although cells

had elevated basal ROS levels, their ROS-producing ability was insufficient to eliminate bacteria during infection. This may be because of the upregulation of the anti-apoptotic Mcl¯1 protein, which inhibited further ROS production.[25] This might partly explain the paradoxical phenomenon of elevated ROS levels and decreased macrophage sterilizing capacity.

Pathological Alterations of Macrophages: Clinical Implications

Impaired phagocytosis in macrophages significantly elevates the vulnerability of COPD patients, being a critical characteristic of the disease.[69,70] Research indicates that infections caused by Haemophilus influenzae and Streptococcus pneumoniae significantly contribute to acute exacerbations of COPD symptoms and a swift deterioration in lung function.[71] Impaired phagocytosis by macrophages reduces the clearance of these bacteria, thus making COPD patients more susceptible to acute exacerbation of chronic obstructive pulmonary diseases (AECOPD) due to infection. Thiosulfamide, an NRF2 activator, is anticipated to augment macrophage phagocytosis by stimulating NRF2 and elevating mannose receptor (MARCO) expression.[63] MMP-12 generated by macrophages is intricately linked to emphysema progression in COPD, making it a significant target for therapeutic intervention through MMP-12 inhibition.The MMP-12 inhibitors AS111793, MMP-408, and the combination MMP-9 and MMP-12 inhibitor AZD1236 effectively diminished emphysema-like pathological alterations in COPD.[72]

Neutrophils in COPD

Definition and Function of Neutrophils

Neutrophils are specialized granulocytes that grow in the bone marrow, enter the bloodstream, and quickly go to wounded tissues during infection or inflammation to phagocytose and eliminate pathogens.[73] Neutrophils eliminate pathogens through phagocytosis, degranulation, and the secretion of neutrophil extracellular traps (NETs).[74] NET is a DNA mesh generated by neutrophils that eliminates germs.[75] Research shows that COPD patients have higher peripheral blood neutrophils, which negatively correlates with disease severity and lung function measures (FEV1/FVC).[73] This indicates a direct link between the increase in neutrophils, the worsening of COPD, and the decline in lung function.

Pathologic Alterations of Neutrophils in COPD

Protease-Antiprotease Imbalance

The imbalance between proteases and antiproteases is a primary etiological factor in COPD, with neutrophils being the principal cells implicated in this illness. The imbalance between proteases and antiproteases is a primary etiological factor in COPD, with neutrophils being the principal cells implicated in this illness.[4,76] Neutrophils compromise significant extracellular matrix components, including elastin and collagen in lung tissue, by secreting serine proteases such as neutrophil elastase (NE) and MMP.[73,74] Macrophages can also release numerous MMP, facilitating the development of emphysema due to lung tissue degradation.[77] Typically, the activity of neutrophil proteases is strictly regulated. For example, the serine protease inhibitor α1-antitrypsin (α1-antitrypsin, α1-AT) prevents excessive tissue degradation by neutrophil proteases.[78] The primary role of α1-antitrypsin (α1-AT) is to neutralize NE in the lungs, thereby preserving a protease-antitrypsin equilibrium, and a deficiency of α1¯AT may disrupt this balance, so individuals with such a deficiency are at a higher risk of COPD.[79] In COPD, the regulatory mechanisms of neutrophil proteases are disrupted. Neutrophils are chemotactic to the lungs in response to CS exposure and other air pollutants stimulate, resulting in the overproduction of neutrophil proteases; additionally, oxidative stress may lead to the oxidative inactivation of α1¯AT, weakening its inhibitory effect on neutrophil proteases.[78]

Decreased Bacterial Clearance Capacity

Vincent D. Giacalone and his team found that neutrophils are less effective in killing Pseudomonas aeruginosa and Staphylococcus aureus, which are common in COPD patients' lungs.[80] Similar to macrophages, neutrophils may be defective in phagocytosis; however, there are still relatively few reports on this. K Guzik and his team demonstrated that CS-treated neutrophils had a significantly reduced ability to phagocytose bacteria like Staphylococcus aureus, and this phagocytic defect may also be present in neutrophils in smoking-associated COPD.[11] Neutrophils rely on oxygen-dependent mechanisms (e g, the production of superoxide and hydrogen peroxide) to kill bacteria; however, COPD

patients often suffer from localized or systemic hypoxia, which may impair neutrophil function and the bacterial killing ability of neutrophils.[81] Consequently, the decreased antimicrobial capacity of neutrophils may be related to hypoxia.

Elevated Levels of NETs

The rupture of the neutrophil cell membrane, which releases DNA and antimicrobial proteins, creates a DNA-entangled protein network (NETs) that ensnares pathogens.[82] This is called "NETosis" which is a neutrophil death method. Elevated concentrations of NETs are observable in the sputum of COPD patients throughout both exacerbation and stability phases of the condition.[83] However, NETs may be a double-edged sword in COPD patients. On the one hand, NETs exert an antimicrobial effect; on the other hand, in the absence or ineffectiveness of regulatory mechanisms, NETs may cause damage to normal cells.[84] Holly R Keir and her research team discovered that excessive concentrations of NETs resulted in tissue damage, impaired bacterial killing, and an increased inflammatory response.[85] Furthermore, NETs may elicit autoimmune responses. NETs present citrullinated protein autoantigens to the immune system, and citrullinated peptide fragments may be identified by the immune system as autoantigens, consequently initiating autoimmune responses and intensifying the inflammatory condition of COPD.[86] Thomas K Wright and et.al found that NET accumulation is linked to an inflammatory response, as it is associated with elevated levels of pro-inflammatory factors IL-8 and IL-1β, as well as increased gene expression of NLRP3, a key component of inflammatory vesicles.[87]

Pathological Alterations of Neutrophils: Clinical Implications

Emphysema is a major COPD symptom. The high number of neutrophils in COPD produces excessive proteases, which destroy lung tissue and cause emphysema.[4] Neutrophil-derived NETs are crucial for pathogen elimination; nevertheless, they also contribute to the inflammatory response and induce tissue damage in COPD patients, correlating with the severity of the disease.[83,85,87] The diminished antibacterial capacity of neutrophils may directly contribute to the heightened infection risk in COPD patients, potentially resulting in acute aggravation of the condition.[80]

T Cells In COPD

Definition and Function of T Cells

T cells are integral to adaptive immunity, identifying and eliminating infectious agents and abnormal cells.[88] T cells are categorized into cytotoxic T cells (CD8+ T) and helper T cells (CD4+ T), with the latter further classified into Th1, Th2, Th17, and Treg cells.[88] CD8+ T cells are crucial for identifying and eliminating virus-infected cells. They secrete cytotoxins to eliminate infected cells, therefore restricting viral multiplication and dissemination.[89] Th1 cells identify intracellular pathogens through the recognition of major histocompatibility complex (MHC) class I or class II molecules and secrete IL-2, TNF-α, and IFN-γ to facilitate cellular defense.[90] Th2 cells synthesize IL-4, IL-5, IL-10, and IL-13 to facilitate humoral immunity and attract eosinophils and basophils in response to infections, allergens, or toxins.[90] Consequently, Th2 cells are linked to airway hyperresponsiveness and allergic inflammatory reactions.Th17 cells possess the ability to generate proinflammatory cytokines, predominantly IL-17.[91] Treg cells are CD4+ T cells that express the FoxP3 transcription factor and CD25bright, with immunosuppressive properties.[92]

Pathologic Alterations of T Cells in COPD

Decreased Antiviral Capacity of CD8+ T Cells

Patients with COPD display elevated amounts of CD8+ T lymphocytes that release significant quantities of cytotoxic mediators (perforin and granzyme) and pro-inflammatory cytokines (IFN γ and TNF α), demonstrating pronounced cytotoxic effects.[93] This appears to contradict the persistent colonization of infections that is characteristic of chronic obstructive pulmonary disease. This may pertain to the suppression of CD8+ T cell function and neurotransmitter depletion resulting from prolonged inflammatory conditions and antigen exposure. CD8+ T cell activation occurs by the recognition of viral antigenic peptides and MHC I-like molecules on the surfaces of virus-infected cells, with these viral epitopes mostly produced by the immunoproteasome that degrades intracellular viral proteins.[94] However, Jie Chen et al demonstrated that CS disrupted MHC I synthesis and presentation, resulting in diminished activation of CD8+ T lymphocytes during viral infection.[89] Furthermore, the diminished antiviral efficacy of CD8+ T cells may be attributed

to increased PD-1 levels. PD-1 is a crucial immunosuppressive protein that inhibits T cell proliferation and cytokine production by attaching to its ligand, PD-L1, hence playing a significant role in limiting excessive immunological responses and maintaining immune tolerance.[95] Nonetheless, the impact of PD-1 in the lungs of COPD patients demonstrated a markedly increased production of CD8+ T cells, which may suppress the functionality of CD8+ T cells in COPD patients, resulting in diminished cytotoxicity.[95]

Th17/Treg Imbalance

Th17 cells secrete pro-inflammatory cytokines including IL-17A, IL-17F, IL-21, IL-22, and IL-23, facilitating the recruitment of neutrophils and macrophages, which amplifies the inflammatory response.[96] Treg cells, conversely, facilitate immunosuppression by the release of cytokines such as IL-10 and TGF-β.[97] An equilibrium between Th17 and Treg cells maintains immunological stability. This equilibrium is disturbed in patients with COPD. The Th17/Treg ratio is dramatically increased in the lung tissues of COPD patients, as confirmed in both human and animal models.[98] Although there is no substantial decrease in Treg cell populations in some COPD patients, the expression of the essential immunosuppressive cytokine IL-10 is reduced, indicating a possible deficiency in the anti-inflammatory function of Treg cells.[91] The diminished quantity and functionality of Treg cells in COPD may be associated with prolonged exposure to CS.[97] The increased Th17/Treg ratio may indicate a prevalent occurrence in COPD: the gradual depletion of anti-inflammatory cells and the dominance of pro-inflammatory cells, thereby contributing to the ongoing deterioration of the condition.

Imbalance of Treg Cell Subpopulations

There are three subtypes of Treg cells: resting Tregs (rTregs), activated Tregs (aTregs), and cytokine-secreting Tregs (Fr III), the first two of which are immunosuppressive, whereas the latter have pro-inflammatory capacity.[99] Fr III cells have been demonstrated to generate proinflammatory molecules including IL-2, IL-17, and IFN-γ, while exhibiting minimal or no inhibitory function.[100] Consequently, an additional balancing mechanism exists between the anti-inflammatory fraction of Treg cells (aTreg+ rTreg) and the pro-inflammatory subpopulation (Fr III). Jia Hou et al discovered that, in comparison to smokers, COPD patients exhibited a diminished ratio of (aTreg+rTreg)☹Fr III) in their peripheral blood, indicating a disruption of immunological homeostasis favoring inflammation, which correlated with increased CD8+ T cell activation.[100] Consequently, Treg cells are not merely immunosuppressive; they also exhibit pro-inflammatory activity. An imbalance between anti-inflammatory subpopulations (aTreg + rTreg) and pro-inflammatory subpopulations (Fr III) may significantly contribute to the inflammatory response in COPD.

Pathological Alterations of T Cells: Clinical Implications

The primary role of pathological T lymphocytes in COPD is to enhance the inflammatory response in affected patients. In typical circumstances, T cells uphold a fragile equilibrium between viral elimination and tissue injury; nevertheless, this equilibrium seems readily disturbed in individuals with COPD.In COPD, the concentrations of pro-inflammatory T cells, specifically Th1 and Th17, are elevated in both CD8+ and CD4+ T cells.[101,102] However, the quantity of immunosuppressive Treg cells often diminishes.[97] This imbalance exacerbates current inflammation and injury and may adversely affect the long-term prognosis of COPD patients. The influence of Th2 cells in COPD may be modest; yet, their elevated quantities may correlate with heightened airway mucus and airway hyperresponsiveness in individuals with COPD.[96] The quantity of CD8+ T cells correlates with the severity of emphysema, potentially due to the involvement of proteases such perforin and granzyme A or B, which are secreted by CD8+ T cells and may directly contribute to lung tissue degradation.[103] In conclusion, the therapy of T cells in COPD should prioritize the restoration of immunological homeostasis, including the utilization of Treg cell activators or the development of novel and more appropriate immunosuppressants.

B Lymphocytes in COPD

Definition and Function of B Cells

B lymphocytes, henceforth referred to as B cells, are a crucial component of adaptive immunity, primarily responsible for the production of antibodies to facilitate pathogen clearance.[104] Additionally, B cells perform numerous physiologic roles, including antigen absorption and transport, antigen delivery to T cells, cytokine and chemokine synthesis, and

directed migration to sites of inflammation.[105] B cells can differentiate into two subpopulations with opposing functions: effector B cells (B-effs), which secrete IL-6 and enhance the immunological response, and regulatory B cells (B-regs), which generate IL-10 and inhibit the immune response.[14]

Pathologic Alterations of B Cells in COPD

Reduced Levels of B-Regs and Defective Immunosuppression

Merel Jacobs et al discovered that, in comparison to non-smokers, the quantity of B-effs in the peripheral blood cells of smokers and COPD patients was generally normal; nevertheless, the proportion of B-regs was markedly diminished.[14] Furthermore, experimental evidence suggests that COPD B-regulatory cells have reduced production of the immunosuppressive cytokine IL-10, indicating a compromised immunosuppressive role of B-regulatory cells.[106] Irregularities in the quantity and functionality of B-regs may constitute a significant factor in the disturbance of immunological homeostasis in COPD patients and the facilitation of an inflammatory response.

Promotion of Lymphoid Follicle Formation and Expansion

In patients with COPD, the quantity and dimensions of pulmonary lymphoid follicles (LF) augment, representing a significant characteristic in the pathological progression of COPD and correlating with its severity.[107,108] LF is a unique immune tissue structure aberrantly developed by lymphoid tissue in non-lymphoid tissues and plays a significant role in immune function.[109] The formation of lymphoid follicles in the lungs of COPD patients is associated with high expression of BAFF, which promotes the development and proliferation of lymphoid follicles.[107] BAFF, a type II transmembrane homotrimeric protein within the tumor necrosis factor family, is a crucial cytokine that facilitates the maturation and survival of B cells.[110] B cells play an important role in fibrosis, as they can directly stimulate skin fibroblasts to secrete collagen and key pro-fibrotic factors such as TGF-β1, thereby promoting the fibrotic process.[111] BAFF can also affect TGF-β1 expression, thereby promoting fibroblast activation, proliferation, and collagen synthesis.[112] Neutralising B cell activating factor (BAFF) can reduce TGF-β1 production and collagen deposition.[112]

Pathological Alterations of B Cells: Clinical Implications

B-regs provide a protective function in immunological disorders by releasing anti-inflammatory cytokines, whereas B-effs produce pro-inflammatory cytokines, hence contributing to illness progression.[113] Consequently, the diminished immunosuppressive capability of B-regs may facilitate the propagation of the inflammatory response in COPD.[114] B cells gather and highly express IgA within lymphoid follicles, which might be an enhanced immune response to external pathogens or self-antigens but could also lead to the development of an autoimmune response.[109] Furthermore, BAFF generated from B-cells may significantly contribute to COPD. Francesca Polverino's team found that BAFF protein levels were increased in the lungs of COPD patients relative to nonsmokers, and that pulmonary BAFF expression correlated with airflow limitation and hypoxia, two critical clinical features of COPD.[115] Moreover, in a CS-exposed murine model, inhibiting BAFF has demonstrated a reduction in pulmonary inflammation and alveolar damage.[110] In conclusion, pathogenic B lymphocytes may significantly influence COPD progression by facilitating lymphoid follicle formation and elevating BAFF expression (Table 1).

Extracellular Vesicles in COPD

Definition and Function of Extracellular Vesicles

Extracellular vesicles (Evs) are vesicles composed of lipid bilayers that are secreted by cells. They encompass diverse bioactive substances, including proteins, lipids, and nucleic acids, and facilitate intercellular communication.[116] Evs modulate gene expression, proliferation, migration, and apoptosis of target cells through the transport of bioactive chemicals.[117] Evs are essential for communication among pathogenic cells in COPD, and numerous investigations have demonstrated that their communicative role accelerates disease progression.[118,119]

The quantity and composition of extracellular vesicles vary across different stages of COPD. Research conducted by Ourania S Kotsiou et al indicates that Evs present in the sputum of patients with COPD are markedly higher in comparison to healthy individuals.[120] Research conducted by Hannah E O'Farrell et al indicates that in AECOPD, Evs levels are markedly elevated, particularly those associated with inflammation, and exhibit a positive correlation with

Table 1 Pathological Changes and Significance of Immune Cells in COPD

Immune Cells	Pathological Changes	Impact on COPD	Clinical Implications
Macrophage	Phagocytic defects, Dynamic Functional Phenotype Conversion	Risk of infection↑, destruction of lung parenchyma	Restoring the phagocytic function of macrophages and regulating the polarisation direction of macrophages
Neutrophils	NE↑, MMP-9↑, NETs↑	Promotes inflammation, emphysema	NE inhibitor, MMP-9 inhibitor, NETs inhibitor
T cells			
CD8+ T cells	Cytotoxicity↓	Risk of infection↑	Restore CD8+T cell function
Th1	IL-2↑, IFN-γ↑, TNF-α↑	Promotes inflammation	Inhibits IFN-γ
Th2	-	Promotes mucus secretion and airway hyperresponsiveness	Need to pay attention to whether asthma is also present
Th17	Th17 ↑, IL-17A ↑	Promote inflammation	Targeted inhibition of IL-17 prevents acute exacerbations
Treg	Treg ↓, IL-10 ↓	Imbalance in inflammatory regulation	Expansion/activation of Treg
B cells			
B-effs	B-effs ↑, activity ↑	Autoimmune damage	B-cell targeted therapy
B-regs	B-regs ↓, IL-10↓	Imbalance in inflammatory regulation	Restoring B-regs function

Notes: ↑, increase; ↓, decrease; -, not applicable or omitted. This is a summary of the pathological changes in major immune cells in COPD, their impact on COPD, and their clinical significance.
Abbreviations: IL-2, interleukin-2; IFN-γ, interferon-α; TNF-α, tumor necrosis factor; NETs, neutrophil extracellular traps.

systemic inflammatory markers, including C-reactive protein, soluble tumor necrosis factor receptor 1, and IL-6.[121] Exosome levels correlate with the severity of COPD and are linked to inflammation levels in COPD patients.[122] Research reveals that infection can induce the production of extracellular vesicles (Evs), hence intensifying neutrophilic inflammation, which may be a potential mechanism driving COPD exacerbation.[123] In summary, extracellular vesicles facilitate inflammation and the advancement of illness in COPD.

Pathological Intercellular Communication Mediated by Extracellular Vesicles

Among the bioactive chemicals transported by Evs, miRNAs are the principal factors influencing COPD. This document primarily elucidates various EV-mediated pathogenic cellular interaction pathways in COPD. The initial pathway is the miR-21/pVHL/HIF-1α/EMT pathway. Xu Hui and et.al discovered that miR-21 in CSE-induced airway epithelial cell extracellular vesicles enhances the expression of downstream genes, including α-SMA and collagen I, via the pVHL/HIF-1α signaling pathway, resulting in the conversion of bronchial fibroblasts into myofibroblasts and subsequently initiating fibrosis.[124] The second pathway involves inhibiting miR-210/autophagy and activating and transforming fibroblasts. Researchers, including Yu Fujita, have established that miR-210 in extracellular vesicles from airway epithelial cells can directly target and inhibit ATG7, resulting in a reduced ratio of autophagy indicators LC3-II/LC3-I, therefore facilitating the transformation of fibroblasts into myofibroblasts.[125] The third pathway involves miR-125a-5p, IL1RN, and NF-κB. Wang Ruiying et al have demonstrated that in COPD, CSE triggers the release of miR-125a-5p from extracellular vesicles originating from airway epithelial cells, which activates the TLR4/NF-κB inflammatory pathway by downregulating IL1RN expression in macrophages, consequently facilitating the polarization of M1-type macrophages.[119] Besides miRNAs, extracellular vesicles derived from COPD cells can induce inflammatory responses in COPD by secreting pro-inflammatory substances. For instance, CSE-treated airway epithelial cells release Evs

containing pro-inflammatory cytokines, including IL-1, which induce fibroblasts to generate IL-8, thus facilitating the migration of neutrophils and monocytes and amplifying the local inflammatory response.[126] Furthermore, airway epithelial cells can directly release Evs containing IL-8, which facilitates the recruitment of immune cells, including neutrophils, and amplifies the local inflammatory response.[126] Collectively, exosome-mediated communication in pathogenic cells of COPD mostly induces inflammatory responses and facilitates airway fibrosis (Figure 2).

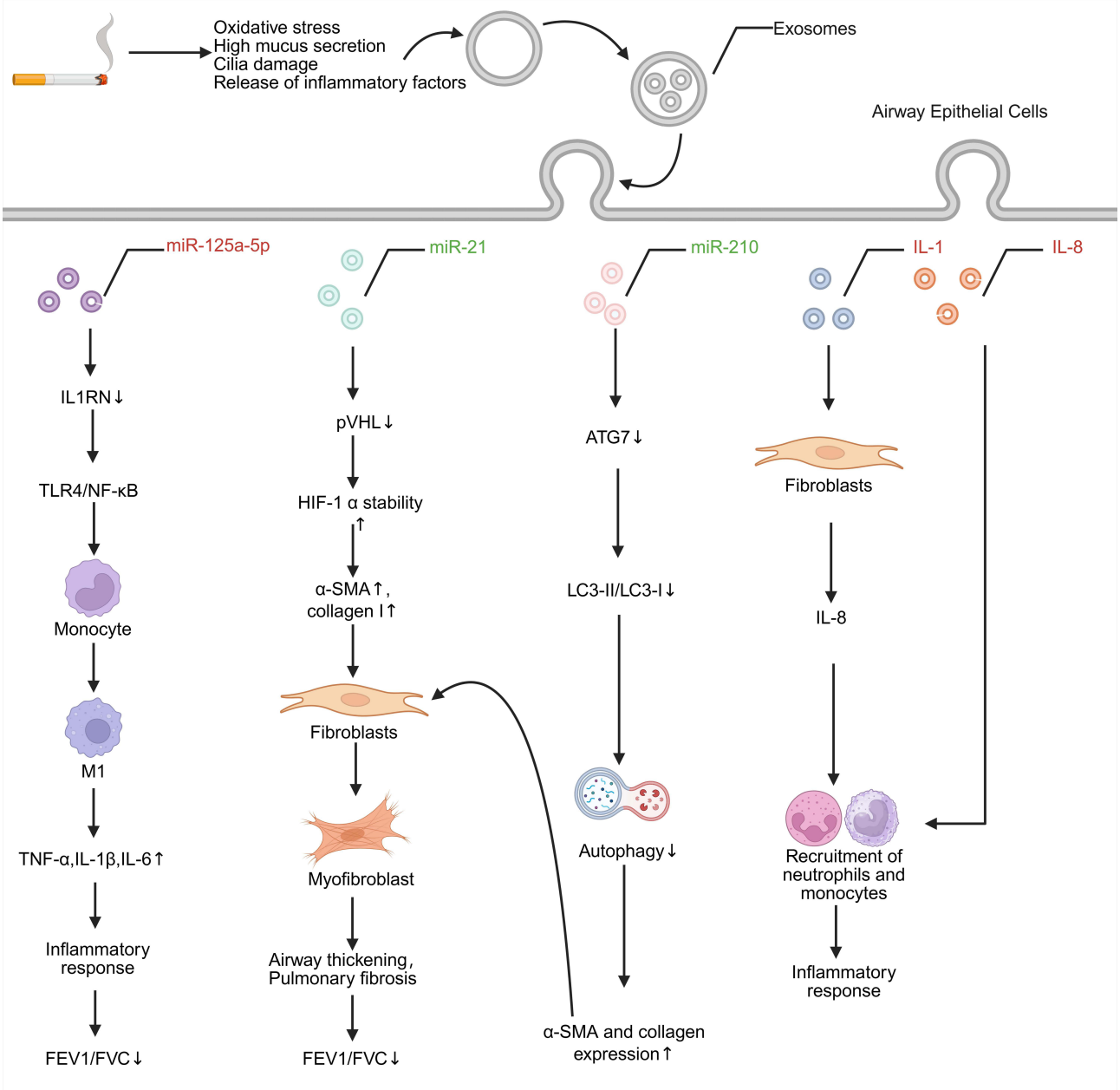


Figure 2 Pathological intercellular communication pathways mediated by extracellular vesicles in COPD.
Notes: ↑: increase; ↓: decrease. The expression of miR-125a-5p is negatively correlated with the FEV1/FVC ratio, r = 0.7801, P < 0.0001.[127] miR-21 expression is negatively correlated with the FEV1/FVC ratio, r = −0.42, P < 0.01.[124] miR-210 expression is negatively correlated with ATG7 expression in pulmonary fibroblasts, r = −0.581, p = 0.048, while ATG7 expression levels were positively correlated with FEV1/FVC, r = 0.583, p = 0.047.[125] (All experimental results correspond to human subjects). Created in BioRender. Bailey, L. (2025) https://BioRender.com/l95n163.
Abbreviations: IL1RN, interleukin-1 receptor antagonist; TLR4, Toll-like receptor 4; NF-κB, nuclear factor κB; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; pVHL, von Hippel-Lindau protein; HIF-1α, hypoxia-inducible factor-1α; ATG7, autophagy-related gene 7 protein; LC3, Microtubule-Associated Protein 1 Light Chain 3.

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Pathological Intercellular Communication Mediated by Extracellular Vesicles:clinical Implications

Extracellular vesicles and circulating microRNAs may serve as potential biomarkers for chronic obstructive pulmonary disease. Evs represent the physiological condition and microenvironment of their originating cells and exhibit stability in bodily fluids, including blood. Moreover, extracellular vesicles may represent a novel therapeutic target for COPD. A novel treatment strategy may be developed through the regulation of extracellular vesicle release and function. Inhibiting the release of pro-inflammatory extracellular vesicles from inflammatory cells or enhancing the release of anti-inflammatory extracellular vesicles may mitigate the inflammatory response in COPD. Alternatively, the development of an extracellular vesicle-based drug delivery system for the direct administration of therapeutic drugs to the targeted area may enhance drug efficacy and safety.

Conclusion

COPD is a complex heterogeneous disease characterized by diverse and often elusive pathological cellular lesions. The pathological alterations in COPD cells represent adaptive responses to disease progression, rendering these changes identifiable. The pathological changes in COPD cells are primarily linked to three core mechanisms: abnormal repair/tissue remodeling, protease-antiprotease imbalance, and inflammatory amplification/immune dysregulation. Prolonged exposure of airway epithelial cells to external stimuli can result in a cycle of recurrent damage and repair. To accommodate ongoing damage, airway epithelial cells engage in atypical repair processes and airway remodeling.[128] Fibroblasts also exhibit abnormal repair and tissue remodeling. In the repair process of diseased tissue cells in COPD, fibroblasts generate substantial quantities of ECM, resulting in airway constriction and pulmonary fibrosis.[7] Fibroblasts, traditionally viewed as cells involved in tissue repair, have been shown to possess pro-inflammatory functions in COPD and contribute to its chronic inflammatory response.[51] Therefore, the role of fibroblasts in COPD immunity may represent a novel research avenue. Endothelial cells in COPD serve as the primary initiators of the inflammatory process, facilitating the recruitment of immune inflammatory cells through the expression of diverse adhesion molecules.[57] In patients with COPD experiencing bacterial infections, neutrophils and macrophages demonstrate phagocytic dysfunction and impaired functionality, thereby directly elevating the risk of infection and contributing to acute inflammatory exacerbations.[10] Moreover, levels of NE and MMP-12 produced by neutrophils are significantly increased in COPD, resulting in lung tissue destruction associated with the condition. In COPD, the pathogenic changes in T cells mostly indicate a breakdown of immunological homeostasis. CD8+ T cells, Th1 cells, and Th17 cells inflict damage on lung tissue by exacerbating inflammatory responses, but in COPD patients, the protective function of Treg cells is diminished.[13,98,129,130] Preserving the equilibrium among these cells, including the Th17/Treg balance and the ratio of anti-inflammatory subpopulations (aTreg+rTreg) to pro-inflammatory subpopulations (Fr III) among Tregs, may provide a significant avenue for future investigation. Evs serve as a significant modality for intercellular communication in the pathophysiology of COPD. Their involvement not only promotes inflammatory responses and airway fibrosis in COPD but may also extend beyond these effects, necessitating further in-depth research.

Clinical treatment for COPD should focus on therapeutic measures that direct pathological cells towards appropriate repair, inhibit tissue remodeling, suppress protease activity, and incorporate immunosuppressants. The emphasis for airway epithelial cells should be on facilitating regeneration and appropriate repair while preventing airway remodeling. Inhibition of fibrotic activity in fibroblasts is essential, which can be achieved by blocking the transformation of fibroblasts into myofibroblasts, obstructing EMT, or enhancing the degradation of the ECM. The restoration of normal function in endothelial cells is essential, alongside the promotion of vascular endothelial barrier repair. The emphasis for macrophages should be on creating strategies to reinstate their phagocytic function. Targeted inhibition of NE and MMP-9, along with blocking NET formation, should be prioritized for neutrophils. In T cells, it is important to consider the regulation of imbalances in T cell subsets, such as the use of immunosuppressants or Treg activators to restore immune homeostasis. Enhancing the quantity of B-regs and reinstating their immunosuppressive function in B cells may represent a feasible approach. In light of the pronounced senescence tendency of pathological cells in COPD, the development of senescent cell clearance complexes to repair senescent tissues in COPD represents a viable future strategy.

In summary, studying pathological cells in COPD helps not only to understand the pathogenesis of the disease from a cytologic perspective but also to provide a fundamental basis for finding effective therapeutic targets.

Consent for Publication

All authors approved the final manuscript and the submission to this journal.

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Disclosure

The authors declare that they have no competing interests in this work.

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