The role of airway remodeling in the pathogenesis and treatment of chronic obstructive pulmonary disease

Abstract
Chronic obstructive pulmonary disease (COPD) is currently considered the third leading cause of death in the world. COPD represents an important public health challenge and a socio-economical problem that is preventable and treatable. The main cause of COPD is chronic inhalation of cigarette smoke, and other harmful constituents of air pollution, which cause epithelial injury, chronic inflammation and airway remodeling. Airway remodeling is most prominent in small airways. It is due to infiltration of the airways by inflammatory cells, such as neutrophils, eosinophils, macrophages, and immune cells, including CD8+ T-cells, Th1, Th17 lymphocytes, and innate lymphoid cells group 3. Fibroblasts, myofibroblasts, and airway smooth muscle (ASM) cells also contribute to airway remodeling by depositing extracellular matrix (ECM) proteins, which increase the thickness of the airway wall. Activated inflammatory cells and structural cells secrete cytokines, chemokines, growth factors, and enzymes which propagate airway remodeling. Airway remodeling is an active process which leads to thickness of the reticular basement membrane, subepithelial fibrosis, peribronchiolar fibrosis, and ASM cells hyperplasia and hypertrophy. It is also accompanied by submucosal glands and goblet cells hypertrophy and mucus secretion, and angiogenesis. Epithelial mesenchymal transition (EMT) plays a key role in airway remodeling. In patients with COPD and smokers, cellular reprogramming in epithelial cells leads to EMT, whereby epithelial cells assume a mesenchymal phenotype. Additionally, COPD is associated with increased parasympathetic cholinergic activity, which leads to ASM cells hypercontractility, increased mucus secretion, and vasodilatation. Treatment of COPD is intricate because of the heterogeneous nature of the disease, which requires specific treatment of the pathophysiological pathways, such as airway inflammation, ASM cell hypercontractility, and parasympathetic cholinergic hyperreactivity. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 strategy report recommends personalized approach for the treatment of COPD. However, some patients with COPD are unresponsive to the standards of care. They may require a triple combination of LABA/LAMA/ICS. Single-inhaler triple therapy (SITT), such as fluticasone furoate/vilanterol/umeclidinium has been shown to significantly improve symptoms and asthma control, reduce moderate and severe exacerbations, and to improve lung function.

Keywords: airway remodeling, COPD, EMT, triple therapy

Introduction
Chronic obstructive pulmonary disease (COPD) is currently considered the third leading cause of death in the world,1,2 and its prevalence, especially the milder form, is estimated to be about 25% of adults above 40 years.1 COPD represents an important public health challenge, and socio-economical problem that is preventable and treatable. It is a major cause of morbidity and mortality, which is projected to rise in the coming decade due to continuous exposure to cigarette smoke, particularly in low-and-middle-income countries.3,4 The main cause of COPD is chronic inhalation of cigarette smoke, and other indoor and outdoor harmful constituents of air pollution,5 which cause epithelial injury, chronic inflammation, and airway remodeling.

Severe COPD is characterized by frequent exacerbations. Exacerbations are the most disruptive aspect of COPD, and frequent exacerbations are associated with disease progression, decreasing lung function, worsening quality of life, and decreased physical activity levels. Frequent COPD exacerbations can have considerable impact on healthcare costs, and contributes to high mortality rate.6 Exacerbations require precision and personalized treatment targeting all the pathophysiological mechanisms of airway remodeling, which contributes to the severity of the disease.

Airway remodeling is a hallmark of asthma, but it also occurs in patients with chronic obstructive pulmonary disease. It involves mostly peripheral small airways,7,8 and to a lesser extent larger airways,9 causing thickening of the airway wall, and narrowing of the bronchial lumen.7,10,11 The airway structural changes lead to increase in airflow resistance, progressive and irreversible decline in pulmonary function,12,13 which correlates with the severity of COPD.4

Airway remodeling in COPD
Airway remodeling is an active process leading to epithelial cells metaplasia and desquamation; deposition of extracellular matrix (ECM) proteins by fibroblasts and myofibroblasts; thickness of the reticular basement membrane; subepithelial fibrosis; peribronchiolar fibrosis; and ASM cells hyperplasia and hypertrophy.4 It is also accompanied by submucosal glands and goblet cell hypertrophy and mucus hypersecretion.10,17 angiogenesis,18,19 and enhanced parasympathetic cholinergic activity.20 Peribronchiolar fibrosis plays
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Table 1: Mechanisms of airway remodeling in patients with chronic obstructive pulmonary disease

| Mechanism                                                                 |
|---------------------------------------------------------------------------|
| Epithelial inflammation due cigarette smoke, and pollutants               |
| Epithelial cell metaplasia and desquamation                                |
| Release of cytokines, chemokines, growth factors, enzymes, and adhesion molecules |
| Submucosal glands and goblet cell hyperplasia, and mucus hypersecretion    |
| Epithelial mesenchymal transition                                          |
| Activation of fibroblasts, and myofibroblasts                              |
| Deposition of extracellular matrix proteins                               |
| Reticular basement membrane thickening, and subepithelial fibrosis        |
| Peribronchial fibrosis                                                    |
| Airway smooth muscle hyperplasia, and hypertrophy                         |
| Angiogenesis, and exaggerated vasodilatation                              |
| Increase in parasympathetic cholinergic activity                          |
| Corticosteroid-resistance due to non-neuronal cholinergic system           |

Inflammatory and immune cells

Inflammatory cells, such as neutrophils, eosinophils, CD8+ macrophages, mast cells, and immune cells, including CD8+ T cells, Th1, Th17 lymphocytes, and innate lymphoid cells group 3,27,28 play a key role in airway inflammation and remodeling. They secrete inflammatory cytokines, chemokines, growth factors, adhesion molecules, and enzymes which orchestrate the remodeling process. Metalloproteinases (MMPs), especially MMP-9 secreted by neutrophils and macrophages play an important role in airway remodeling in patients with COPD and asthma.29 Integrins play a supportive role in propagating airway hyperresponsiveness, remodeling,30 and act synergistically with vascular endothelial growth factor (VEGF) to promote angiogenesis.31,32

Several chemokines, cytokines, growth factors secreted by activated inflammatory and immune cells, and structural cells participate in the airway remodeling process. They include chemokines, such as RANTES and c-c chemokines; cytokines, including interleukin-1β (IL-1β), IL-6, IL-8, IL-22, and TNF-α; bFGF, FGF, EGFR, and IGF.33,34-50 Table 2 shows the inflammatory mediators and growth factors responsible for airway remodeling in COPD.

Epithelial mesenchymal transition in COPD

Airway epithelial cells form the first line of defense against external insults, such as infectious microbes, allergens, toxic particulate matter, such as cigarette smoke, noxious pollutants, and gases.1 Epithelial cells are both proliferative and secretory. They produce and secrete several anti-bacterial peptides, antioxidants, proteases, anti-proteases, cytokines and growth factors,19,44 which propagate airway inflammation and remodeling. Inflammatory mediators and growth factors also promote epithelial mesenchymal transition (EMT). EMT plays a key role in airway remodeling in patients with COPD, and asthma. In patients with COPD and smokers, cellular reprogramming in epithelial cells,45 could lead to epithelial-mesenchymal transition,46 whereby epithelial cells progressively lose cellular polarity, and adhesiveness, and become migratory and assume a mesenchymal phenotype.47-50 During EMT, epithelial cells lose epithelial markers, such as E-cadherin, KRT5, KRT18, and ZO-1,31,51 and exhibit significant increase in mRNA transcripts and protein expression for mesenchymal markers, such as α-smooth muscle actin (α-SMA), vimentin, and collagen 1.32,53 One of the characteristic features of EMT is thickening and fragmentation of the reticular basement, which is due to increase in epithelial matrix metalloprotease activity, especially MMP-9.47

Table 2: Inflammatory mediators and growth factors involved in airway remodeling, angiogenesis, and mucus secretion in COPD

| Cytokines   | Chemokines |
|-------------|------------|
| IL-1β       | RANTES     |
| IL-6        | Eotaxins   |
| IL-8/CXCL8  | Gro-a      |
| IL-22       | Adhesion molecules |
| TNF-α       | Integrins (VCAM, ICAM, MAI/CAM) |
| MCP-1       | Mucus secretion |
| Growth factors | EGFR      |
| TGF-β       | Angiogenic factors |
| bFGF-I      | VEGF       |
| bFGF        | Angiopoietin-I |
| IGF         | IL-8/CXCL8 |

Abbreviations: bFGF, basic-fibroblast growth factor; EGFR, epidermal growth factor; EGRF, epidermal growth factor receptor; Gro-α, growth-regulated oncogene; IGF, insulin-like growth factor; IL, interleukin; MCP-1, monocyte chemotactic peptide-1; RANTES, regulated on activation, normal T-cell expressed and secreted; TGF, transforming growth factor; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor

 Transforming growth factor-β plays an important role in the induction of the EMT, and the TGF-β pathway is up-regulated in the

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bronchial epithelium of smokers and patients with COPD. EMT is most active in small airways of smokers and patients with COPD, leading to excessive deposition of ECM proteins by fibroblasts, and myofibroblasts, increasing airway wall thickness, and airflow obstruction. Airway remodeling also involves accumulation of myofibroblasts due to fibroblast-myofibroblast transition, ASM cell transition to myofibroblast, and endothelial cell transition to myofibroblast or by the recruitment of circulating fibroblastic stem cells (fibrocytes). TGF-β, IL-13, and connective tissue growth factor have been described to induce myofibroblast transition. The transformed myofibroblasts acquire a more proliferative, contractile and secretory-active myofibroblast phenotype. They acquire increased expression of extracellular matrix components, such as, vimentin, collagen type 1, and α-smooth muscle actin. The mechanisms by which fibroblasts transform into myofibroblast phenotype is believed to be mediated by increase in intracellular reactive oxygen species, decrease in cyclic AMP (cAMP), and phosphorylation of the extracellular signal-regulated kinase 1/2 (ERK1/2).

EMT, and fibroblast to myofibroblast transition play a key role in the deposition of ECM proteins, subepithelial fibrosis, and peri-bronchial fibrosis, which contributes to partial or total irreversible airway obstruction, and decline in pulmonary function in patients with COPD.

Parasympathetic cholinergic activity in COPD

Parasympathetic cholinergic activity to the airways is increased in patients with COPD, leading to ASM cells hypercontractility, mucus hypersecretion, vasodilatation and increased vascular permeability. Acetylcholine released by parasympathetic neurons and non-neuronal cells, such as epithelial cells, and fibroblasts can modulate airway inflammation and remodeling via M3 receptors. Additionally, acetylcholine from non-neuronal cells may contribute to corticosteroids in patients with COPD.

Anticholinergic muscarinic receptor antagonists block the effects of acetylcholine at muscarinic receptors, especially M3. They have been used for the treatment of COPD for several years, and are now used as add-on treatment for severe uncontrolled asthma. They are initiated at the Global Initiative for Asthma (GINA) strategy step 4 or 5 with or without biologics. Currently, there are no biologics which have proven efficacy in the add-on treatment of COPD.

Precision treatment of COPD

Treatment of severe COPD is difficult because of the complexity and heterogeneity mechanisms of airway remodeling, which is responsible for the partial or total irreversible airway obstruction, and progressive decline in lung function. Targeted therapies for COPD should include pharmacological agents that relieve bronchoconstriction due to hypercontractility of ASM cells, drugs that decrease parasympathetic cholinergic activity, and anti-inflammatory agents.

Despite access to the most up-to-date medicines currently available treatment of COPD is inadequate. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 Strategy report recommends a personalized approach for the management and treatment of COPD. The GOLD management strategy recommends treatment COPD according to the severity of the disease, annual rates of exacerbation, and pulmonary function (GOLD stage 1-4). The GOLD algorithm involves stepping up treatment from SABA or LABA, and adding a LAMA (LABA/LAMA), or an ICS (LABA/ICS). If symptoms persist, the algorithm recommends addition of ICS to LABA/LAMA regimen, or use a single-inhaler triple therapy consisting of LABA/LAMA/ICS (SITT). Despite strict adherence and proper inhaler technique some patients with COPD are uncontrolled at stage 2 of the GOLD step-up regimen, thus initiating ICS, preferably in combination with LABA/LAMA in the form of SITT. The GOLD stages for chronic obstructive pulmonary disease are shown in Table 3.

Table 3 GOLD strategies in the management of chronic obstructive pulmonary disease

| Stage | Clinical presentation | FEV1 | Treatment |
|-------|----------------------|------|-----------|
| Stage 1 | Mild                 | ≥ 80% | SABA, LABA or LAMA |
| Stage 2 | Moderate             | 50-79% | LABA/LAMA |
| Stage 3 | Severe               | 30-49% | LABA/LAMA or LABA/ICS |
| Stage 4 | Very severe          | ≥ 30%  | LABA/LAMA/ICS, or SITT |

Single-inhaler triple therapy

Single-inhaler triple therapy consisting of LABA, LAMA, and ICS have potent synergistic effect, and favourable pharmacological interaction in the treatment of COPD. LABA and LAMA bronchodilating effects are additive and may produce more bronchodilation at lower dosages of the two agents, thus minimizing side effects. Furthermore, addition of LAMA to LABA/ICS combination may have anti-remodeling activity in addition to bronchodilation and anti-inflammatory activity. Long-acting muscarinic receptor antagonists have been shown to have anti-inflammatory and anti-remodeling effects in mice model of COPD. LAMA have also been demonstrated to inhibit cigarette smoke-induced mucin hypersecretion in human bronchial epithelial cells, and inhibit cigarette smoke-induced lung fibroblast proliferation. Milara et al. have shown that aclidinium, an inhaled, long-acting muscarinic antagonist attenuates airway remodeling by decreasing expression of myofibroblast markers, such as collagen type 1, and α-smooth muscle actin.

Currenty, there are three single-inhaler triple therapy combinations which have been approved by the Food and Drug Administration (FDA) for maintenance treatment of COPD. They include: beclomethasone propionate/formoterol/glycopyrronium, budesonide/formoterol/glycopyrronium, and fluticasone furoate/vilanterol/umeclidinium (Table 4). The GOLD strategy recommends initiation of SITT at stage 4 (very severe COPD, with frequent exacerbations, and FEV1 ≤ 30%). Triple combination (LABA/LAMA/ICS) inhalers have been shown to significantly improve asthma symptoms control, reduce the frequency of moderate and severe exacerbations, and improve lung function compared with LAMA alone, and LABA/LAMA, or LABA/ICS single-inhaler dual therapy. SITT has been reported to reduce hospitalization due to COPD exacerbations, significantly improve the health-related quality of life, with encouraging data suggesting a reduction in all-case mortality. Noteworthy, SITT is convenient for patients, and may improve compliance.

Single-inhaler triple therapy should not be recommended to all patients with severe COPD, and should be personalized according to the GOLD strategy. SITT is associated with adverse effects, and may be contraindication in some patients with co-morbidities with COPD. Overall, the benefit/risk profile of SITT outweighs the high risks of pneumonia due to the immunosuppressive effects of ICS, which has been reported in some studies.

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Table 4 Single-inhaler dual and triple therapy combinations for the treatment of chronic obstructive pulmonary disease

| Single-inhaler dual therapy - LABA/LAMA | Formoterol/glycopyrronium |
|----------------------------------------|---------------------------|
| Formoterol                               | Fluticasone furoate/vilanterol/umeclidinium |
| Indacaterol/mometasone                   | Formoterol/budesonide     |
| Vilanterol/glycopyrronium                | Formoterol/budesonide     |
| Single-inhaler dual therapy - LABA/ICS   | Formoterol/beclomethasone dipropionate |
| Fluticasone furoate/umeclidinium         | Formoterol/mometasone     |
| Budesonide/umeclidinium                  | Fluticasone furoate/umeclidinium |

COPD patients with high eosinophil count ≥300 cell.µl⁻¹, and elevated biomarkers of Th2 inflammation, such as fractional exhaled nitric oxide (FeNO ≥ 50 ppb) may more favourably respond to SITT. The GOLD strategy recommends use of eosinophil count and FeNO in considering initiation of SITT. Conversely, eosinopenia (eosinophil count < 100 cell.µl⁻¹) increases the risk of pneumonia in patients with COPD.32-34 and ideally patients with eosinopenia should not be recommended for SITT. Moreover, patient with an eosinophil count of 50-100 cell.µl⁻¹ do not respond to ICS.35,36 Similarly, patients with bronchiectasis and recurrent respiratory infections, tuberculosis, and non-mycobacterial tuberculosis should not be initiated on maintenance SITT.34

The cardiovascular adverse effects of LABA and LAMA are synergistic, and SITT may not be suitable for patients with heart failure, mitral stenosis, cardiac arrhythmias, ischaemic heart disease, transient ischaemic attacks,37,38 stroke.39 Additionally, patient with HIV/AIDS on antiretroviral (ARV) regimen should not be recommended for SITT because glucocorticoids inhibit metabolism of protease inhibitor ARVs, and may increase the risk of Cushing’s syndrome.40

Conclusion

Chronic obstructive pulmonary disease represents an important public health challenge and a socio-economic problem that is preventable and treatable. Airway inflammation and remodeling play a key role in the pathogenesis of COPD, airway narrowing, increase in airway resistance, and progressive decline in pulmonary function. Activated inflammatory, immune, and structural cells infiltrating the smaller airway secrete chemokines, cytokines, growth factors and enzymes which propagate airway remodeling. Inflammatory mediators and growth factors are responsible for the epithelial mesenchymal transition which is the initiator of airway remodeling. There is increased parasympathetic cholinergic activity in the airways of patients with COPD. Targeted and personalized treatment of COPD should include bronchodilators, anti-inflammatory and anti-remodeling agents. Single-inhaler triple therapy has been shown to significantly improve symptoms control, reduce moderate and severe exacerbations, and improve lung function. However, maintenance SITT should not be initiated in patients where triple therapy is contraindicated, such as tuberculosis, cardiac failure, and osteoporosis.

Acknowledgments

None.

Conflicts of interest

None.

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