Chronic Obstructive Pulmonary Disease (COPD)

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Introduction to COPD

Chronic obstructive pulmonary disease (COPD) is a major health burden predicted to become the third most common cause of death and the fifth most common cause of disability worldwide by 2020 [1]. An international population-based COPD study in 2007 identified 10 % prevalence of mild or severe COPD in 12 different countries [2].

COPD is characterized by chronic obstructive bronchiolitis accompanied by fibrosis and emphysema represented by parenchymal destruction, airspace enlargement, loss of lung elasticity, and obstruction of the small airways [3]. In contrast, chronic bronchitis is defined by a productive cough with mucus hypersecretion but not necessarily airflow limitation [4]. Most COPD patients show all three pathological features: bronchiolitis, emphysema (breakdown of lung tissue), and mucus plugging. The obstruction and airflow limitation are progressive, irreversible, and associated with abnormal inflammation in response to harmful toxic particles and gases, such as tobacco smoke. This is in stark contrast to asthma, where the airflow obstruction is usually reversible (see chapter "Asthma"). Interestingly, COPD patients are resistant to corticosteroid therapy (see below) [4]. This fact illustrates a major difference in the inflammation process between the two diseases and necessitates research into novel therapies.

The disease prevalence is directly related to the prevalence of tobacco smoking. This is the main risk factor for disease development and progression, although outdoor, occupational, and indoor air pollutions are all major risk factors [5]. COPD is a heterogeneous disease, and among people with the same smoking history, not all will develop the disease due to differences in genetic predisposition. The best-documented genetic risk factor is a severe hereditary deficiency of α_1-antitrypsin, a circulating inhibitor of serine proteases implicated in disease progression (see below) [6].

Characteristic COPD symptoms are chronic dyspnea (shortness of breath), cough or sputum production, wheezing, and chest tightness. Clinical diagnosis requires spirometry measurements based on the forced expiratory volume in one second (FEV1) and classifies patients with COPD into four stages based on severity of symptoms, risk for exacerbations, and existing comorbidities (e.g., nutritional abnormalities, skeletal muscle dysfunction, and cardiovascular defects) [7].

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Pathophysiology of COPD and Metabolic Alterations

Histological COPD examinations show predominant involvement of peripheral airways (bronchioles) and parenchyma (alveoli), while asthma affects all airways but rarely the parenchyma [4]. Narrowing of the small airways, obstruction of the lumen with mucus, and emphysema all contribute to the airflow limitation in COPD (Fig. 1a).

There is clear evidence that chronic inflammation leads to narrowing of the airways and alveolar destruction [4]. Mucus secretion occurs in response to bacteria or irritants (inhaled particles).

The inflammation manifests itself by increased numbers of alveolar macrophages, neutrophils, and cytotoxic T cells (see chapter "Overview" under the part "Immune system") and a continuous release of multiple inflammatory mediators – cytokines, chemokines, lipids, and growth factors acting on the airway epithelium. Oxidative stress and imbalance between proteases and antiproteases intensify the inflammation (Fig. 1b) [4].

Macrophages play an essential role in the pathology of COPD (see Fig. 1b). They are activated by tobacco smoke and other harmful stimuli and release tumor necrosis factor-α (TNF-α), interleukin 8 (IL-8), CXC chemokines, monocyte chemotactic protein-1, leukotriene B4, proteases, and reactive oxygen species, thus intensifying the inflammation by recruiting even more immune cells and causing further damage to the tissue. The expression of most of these mediators is regulated by the transcription factor nuclear factor-κB (NF-κB), which is activated in the macrophages of COPD patients [4].

Other cell types involved in the pathology of COPD are cytotoxic $CD8^+$ T cells, eosinophils, dendritic cells, and epithelial cells (see chapter "Overview" under the part "Immune system" and Fig. 1b). Dendritic cells play a central role in the initiation of the immune response. $CD8^+$ T cells have been linked to epithelial cell death in addition to their cytokine release function [4]. The role of eosinophils is still uncertain but it seems to be greater in exacerbations [8]. Epithelial cells are an important source of inflammatory mediators, such as TNF-α and IL-8, contributing to the chronic inflammation, which induces local fibrosis [4]. Airway epithelial cells play an important role in defense against bacteria and inhaled particles by producing mucus and translocating immunoglobulins from blood into the alveolar lumen. Tobacco smoke and other harmful substances interfere with these processes and lead to increased epithelial cell proliferation, mucus secretion, obstruction of the airways, and compromised defense mechanisms [4]. Consequently, COPD patients are more susceptible to bacterial and viral infections as well as environmental pollution [9].

After exposure to tobacco smoke or inhalation of harmful particles, activated immune and epithelial cells in the lung produce high quantities of reactive oxygen species (ROS) such as superoxide anions and the highly reactive hydroxyl radicals. The antioxidant systems cannot counteract this excessive production. Therefore, the ROS damage lipids, proteins, and DNA and potentiate inflammation via various signaling factors (e.g., NF-κB, activator protein 1, and p38 mitogen-activated protein kinase) [10].

Various proteases and antiproteases are involved in the normal turnover of connective tissue components in the lung. Yet, in COPD patients, these are deregulated favoring parenchyma destruction and emphysema. In part, this imbalance is caused by high levels of serine proteases, including neutrophil elastase, cathepsins, and matrix metalloproteinases (MMPs), in response to inflammatory cytokines and oxidative stress, released by an increased number of activated neutrophils. Additionally, these proteases are potent stimulants of epithelial mucus secretion and thus contribute to both alveolar destruction and airway obstruction [4].

Besides pulmonary abnormalities, COPD patients have significant systemic effects (comorbidities), which can present as skeletal muscle dysfunction, osteoporosis (see chapter "Osteoporosis"), diabetes (see chapter "Diabetes mellitus"), heart failure (see chapter "Heart failure"), anemia, or depression (see chapter "Major depressive disorder") [7]. The mechanisms for most of these are unclear, but tissue hypoxia and systemic inflammation are likely to contribute to the pathologies.

Molecular links have been established between systemic oxidative stress, protein degradation, muscle and bone atrophy, cardiovascular and neurological comorbidities, and inflammation (e.g., TNF-α, IL-6, and IL-8) [11].

In conclusion, exposure to inhaled toxic agents leads to chronic irreversible inflammation, oxidative stress, and increased numbers of activated macrophages, neutrophils, and cytotoxic T cells, releasing multiple inflammatory mediators. This leads to further recruitment of immune cells, airway epithelium proliferation, mucus hypersecretion, and airflow limitation. Combination of inflammation, imbalance in the protease-antiprotease system, and local tissue remodeling (fibrosis) results in alveolar wall destruction and emphysema. Based on their compromised lung anatomy and function, COPD patients are more

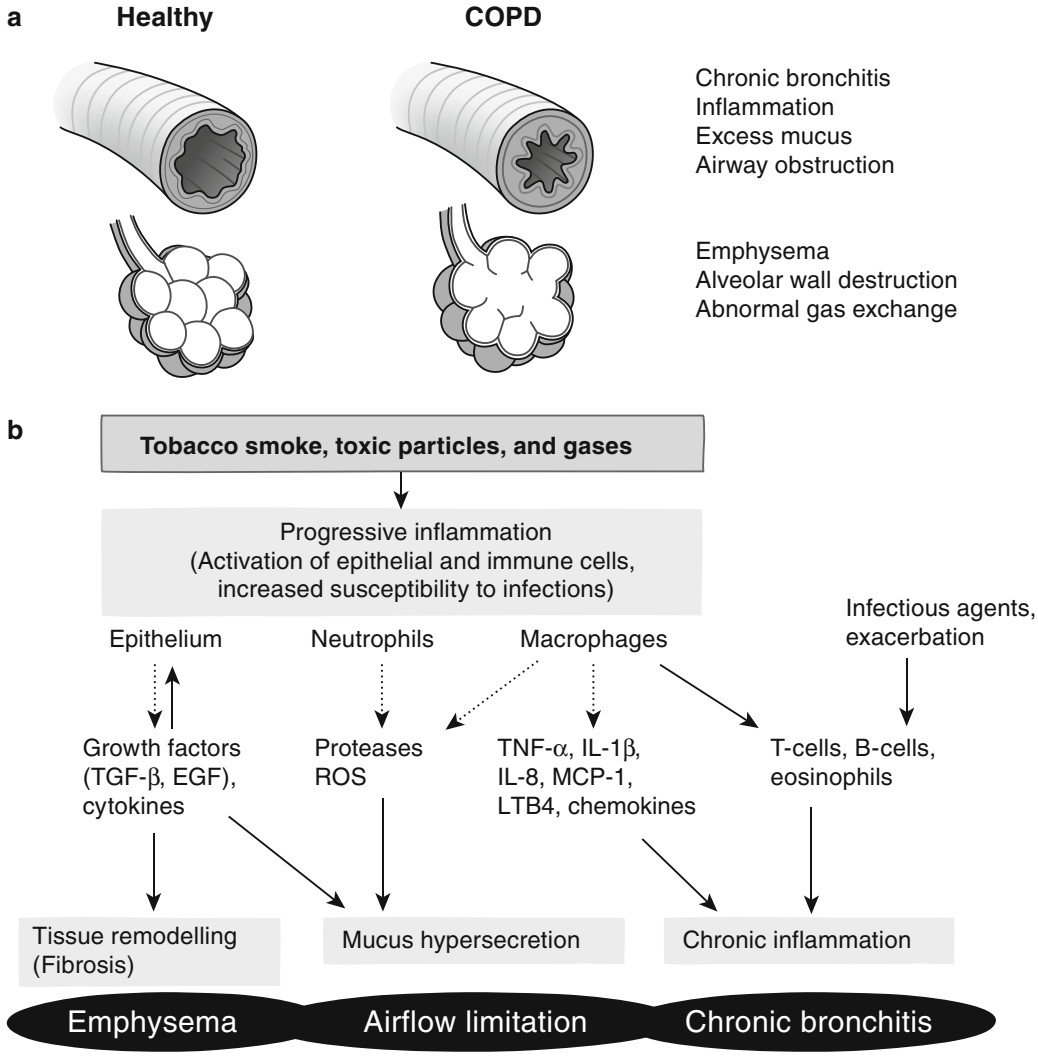

Fig. 1 Pathological hallmarks and implicated cell types in chronic obstructive pulmonary disease. (**a**) Comparison between healthy and chronic obstructive pulmonary disease (*COPD*) tissue in the upper (bronchi, above) and smaller airways (alveoli, below) and pathological manifestation of COPD – chronic bronchitis and emphysema, respectively. (**b**) Cellular components and molecular mechanisms of the inflammation and structural changes in the COPD lung tissue. *TGF-β* transforming growth factor β, *EGF* epidermal growth factor, *ROS* reactive oxygen species, *TNF-α* tumor necrosis factor-α, *IL* interleukin, *MCP-1* monocyte chemotactic protein-1, *LTB4* leukotriene B4

susceptible to exacerbations and often develop metabolic comorbidities.

Introduction to Treatment and Influence on Metabolism

COPD treatment aims to reduce the symptoms and exposure to risk factors. None of the existing COPD medical interventions (see Table 1 for the most common examples) has been shown to conclusively modify the long-term decline in lung function [7].

Smoking Cessation

Smoking cessation is the only therapeutic intervention so far shown to reduce disease progression [12]. However, the main problem with this approach is the nicotine addiction. There are several forms of nicotine replacement therapies, but their effectiveness is very low [13]. Efforts for more effective approaches continue, e.g., non-nicotinic drugs targeting neurotransmitter systems [14] and acetylcholine receptors [15].

Long-Acting Bronchodilators

Long-acting β2 agonists (LABA, e.g., formoterol, salmeterol) improve lung function by binding to β2 adrenergic receptor on smooth muscle cells (SMCs) surrounding the airways and inhibiting their contraction. Treatment with LABA leads to reduced symptoms and improved FEV1, exercise capacity, and health status [7]. This improvement reflects the increased expiratory flow resulting from widening of the obstructed airways. There are some concerns about side effects of LABA such as cardiac dysrhythmia and increased oxygen consumption, but lower doses are effective and safe [12]. In addition to dilating the airways, LABA have some indirect effects on inflammation leading to decreased neutrophil numbers and IL-8 levels [16].

Table 1 Summary of the most common COPD treatments, outcomes, and side effects

Treatment	Target	Results	Consequence	Side effects
LABA *Formoterol* *Salmeterol*	β2-Adrenergic receptor (SMCs)	Bronchodilation due to inhibition of airway SMC contraction	Improved FEV1, exercise capacity, general health status	Cardiac rhythm disturbance, somatic tremor, increased oxygen consumption
LABA *Tiotropium bromide*	Acetylcholine receptors (SMCs, submucosal gland cells)	Bronchodilation due to inhibition of airway SMC contraction and mucus secretion	Improved FEV1, exercise capacity, general health status; reduced exacerbations	Dryness of the mouth
Inhaled corticosteroids *Budesonide*	Glucocorticoid receptor (multiple cell types)	Minimal effect on lung function	Reduced exacerbations	Oral infections, skin bruising, increased risk of pneumonia
PDE4 inhibition *Roflumilast*	PDE4 (inflammatory and immune cells)	Reduced inflammation due to inhibition of cAMP hydrolysis	Improved FEV1, reduced exacerbations	Nausea, reduced appetite, abdominal pain, diarrhea, headache, sleep disturbance

LABA long-acting β2 agonists, *SMC* smooth muscle cell, *FEV1* forced expiratory volume in 1 s, *PDE4* phosphodiesterase-4

Tiotropium bromide binds to muscarinic acetylcholine receptors on airway SMCs and submucosal gland cells and inhibits contraction and mucus secretion. This bronchodilator effect translates into FEV1 increase and improved exercise capacity and health status [7]. Tiotropium bromide is well tolerated with the only side effect of mouth dryness [7]. There is some evidence that tiotropium bromide is effective in reducing exacerbations, although the mechanism is not well understood [17].

Corticosteroids

Corticosteroids act by binding to the ubiquitously expressed glucocorticoid receptor, which translocates to the nucleus and represses expression of inflammatory genes or induces expression of anti-inflammatory genes. Eosinophils seem to be the most steroid-responsive immune cells, but in contrast to asthma, they are not prominent in COPD [8]. In addition, alveolar macrophages from COPD patients appear to be steroid resistant [12]. When inhaled, especially in combination with LABA, corticosteroids (e.g., budesonide) have a modest effect on lung function decline and exacerbations. However, prolonged treatment increases the risk of infections (especially pneumonia) and skin bruising [7].

Phosphodiesterase-4 Inhibitors

Decrease of cellular cAMP levels activates inflammatory cells such as neutrophils, T cells, macrophages, and structural cells such as epithelial cells, SMCs, fibroblasts, mucus gland cells, and sensory neurons [12]. Phosphodiesterase-4 (PDE4) antagonists reduce inflammation by inhibiting PDE4-mediated cAMP hydrolysis. Treatment leads to improved FEV1 in moderate to severe COPD patients [7]. PDE4 inhibitors have several side effects such as nausea, diarrhea, headache, abdominal pain, and sleep disturbances probably due to low specificity and high systemic availability. Therefore, more specific PDE4 inhibitors (such as roflumilast [8]) and inhaled approaches to retain the drug in the lung are being currently considered [7].

Other Therapies

Other therapies include use of antibiotics during exacerbations and oxygen therapy in patients with chronic respiratory failure. There is a branch of COPD therapy based on non-pharmacological approaches including pulmonary rehabilitation (exercise and peripheral muscle training), nutritional supplementation (against weight loss, skeletal muscle waste, and osteoporosis if the respective comorbidities are present), and surgical treatment (lung transplantation or removal of part of the lung in order to increase effectiveness of respiratory muscles) [7].

Perspectives

Further research into the basic cellular, molecular, and genetic abnormalities of COPD is necessary. It is important to identify the genes determining why only some heavy smokers develop significant COPD. This can lead to identification of novel targets and better patient stratification for therapy.

Current research is focused on inflammatory mediator antagonists, e.g., inhibitors of lipids (e.g., leukotriene B4, prostaglandin E2), cytokines (e.g., TNF-α), and others. Antioxidants are considered as a potentially beneficial therapy. Based on the imbalance of proteases and antiproteases, studies targeting neutrophil elastase, MMPs, and cysteine proteases are ongoing. Finally, there is a growing interest in the potential use of stem cells for repair of the damaged lung tissue [8].

In conclusion, improved COPD therapies are urgently needed to provide long-term benefit in this common and important disease, for which no effective preventive therapy or cure exists.

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