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Pathology of Chronic Obstructive Pulmonary Disease

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Chronic obstructive pulmonary disease is one of the leading causes of death and morbidity worldwide. Despite intensive investigation, its pathology and pathophysiology are not well understood. The hallmarks of the disease are irreversible airflow limitation and chronic inflammation. Small airway obstruction due to progressive inflammation and fibrosis, and the loss of elastic recoil mediated by elastolysis and apoptosis equally contribute to pathologic changes. However, it is debated to what extent the obstruction of large airways leads to altered lung function. Three morphologic entities are described in the literature under one disease; chronic bronchitis, obstructive bronchiolitis and emphysema may appear in the same patient at the same time. The authors review pathologic changes observed in chronic obstructive pulmonary disease, including acute exacerbations and secondary pulmonary hypertension as severe but common complications of the disease. Furthermore, we detail recent scientific evidences for major cellular and molecular inflammatory pathway activation. These mechanisms result in accelerated apoptosis, remodeling and increased proinflammatory cytokine release. Targeting intracellular pathological changes may lead to the discovery of a new generation of drugs that could reduce chronic obstruction before airway irreversibility is established. (Pathology Oncology Research Vol 12, No 1, 52–60)

Key words: chronic bronchitis, obstructive bronchiolitis, emphysema, inflammation

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide. At present, it is the 4th most common cause of death among adults, and it is estimated to rank 3rd by 2020.[13] Because of its increasing incidence, the World Health Organization (WHO) and the US National Institute of Health experts formed the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD), and described the Global Strategy for the Diagnosis, Management and Prevention of COPD. Their report was published in 2001 and updated in 2003. The importance of COPD need to be further emphasized in Central and Eastern Europe because of the high prevalence of smoking. According to WHO statistics, in this region the prevalence of COPD is also the highest.[35] Recent Hungarian statistics show that the prevalence of COPD is 609.27 cases/100,000, but due to the late diagnosis of the disease the real number is underestimated.[2] COPD is calculated to affect 400,000-500,000 people in Hungary. Although considerable attention is paid to the prevention and treatment of the disease, the complex pathology and the progressive nature of COPD is not well understood.

The GOLD definition describes COPD as "A disease state characterized by airflow limitation that is not fully reversible. The limitation is usually progressive and associated with and abnormal inflammatory response of the lungs to noxious particles or gases." GOLD criteria use lung function parameters such as forced expiration volume in 1 s (FEV1) compared to predicted FEV1 and FEV1/FVC (forced vital capacity) to classify the severity of the disease.

The most prominent pathological and pathophysiological changes seen in COPD are progressive airflow limitation and peripheral airway inflammation. Airflow limitation results from the loss of elastic recoil of the parenchyma and from the increase in airway resistance. In emphy-

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Table 1. **Cellular and structural changes in the lung in chronic obstructive pulmonary disease**

Central airways wall	Increase in macrophages and T lymphocytes (particularly $CD8^+$ T lymphocytes). Neutrophils in severe disease
Lumen	Neutrophils
Peripheral airways	Goblet cell metaplasia and mucous plugging Smooth muscle cell hypertrophy. Fibrosis. Inflammation (particularly $CD8^+$ T lymphocytes). All inflammatory cells including neutrophils in severe disease
Parenchyma	Inflammation (particularly $CD8^+$ T lymphocytes). Destruction (centriacinar and panacinar emphysema). Fibrosis
Pulmonary arteries	Endothelial dysfunction. Intima thickening Medial thickening (less frequently). Adventitial inflammation (particularly $CD8^+$ T lymphocytes)

sematous lungs, parenchyma destruction and loss of alveolar integrity is observed, which lead to reduced recoil and collapsed small airway lumens. Inflammatory cell immigration to the small airways, together with fibrosis and smooth muscle cell proliferation results in reduced diameter and increased resistance. It is not yet clear whether mucus hypersecretion adds to airflow limitation.[54] Mucus hypersecretion is typical in central airways in patients with chronic bronchitis. There is increasing evidence that larger airways are also involved in the inflammatory process in COPD.[48]

Despite similarities in altered lung function, clinical signs and symptoms of COPD manifest as different pathologic entities. Chronic bronchitis, emphysema and obstructive bronchiolitis are the three morphological forms of COPD, however, these diseases can be present in mixed forms in the same patient.[18] Although it is somewhat artificial to separate these diseases, in this review we describe them separately to give more insight of the complexity of COPD. Furthermore, we would like to draw attention to the systemic consequences of severe COPD, including pulmonary hypertension and skeletal muscle wasting.

Chronic bronchitis

Chronic bronchitis is defined clinically by a productive cough lasting for at least 3 months, recurring in at least 2 consecutive years, if it cannot be attributed to other pulmonary or cardiac condition.[33] Chronic bronchitis results from mucus hypersecretion, which does not always lead to airway obstruction. In pathology, chronic bronchitis also means certain microscopic and macroscopic changes in the airway structure, such as mucus production, epithelial changes, airway inflammation, smooth muscle cell hypertrophy and submucosal bronchial gland enlargement.

Macroscopically, mucus overflow is observed that affects mainly the intermediate bronchi, 2-4 mm in diameter. Microscopically, mucus is present in lumen and goblet cell hyperplasia is observed in the bronchial wall. In chronic bronchitis, goblet cells expand to the bronchioli to the expense of ciliated epithelial cells, serous and Clara cells.

In chronic bronchitis epithelial atrophy, squamous cell metaplasia and ciliar abnormalities were described in small bronchi. Despite these changes, the epithelium is intact and thickness of reticular basement membrane is in normal range. This is a key difference between asthma and chronic bronchitis/COPD pathology. Epithelial injury and thickening of the basal membrane is observed early on in asthma.[38,40]

Inflammation is observed in the mucosa, in the smooth muscle cell layers and submucosal glands. Inflammation is a better pathologic marker of chronic bronchitis than mucous gland hypertrophy. In large airways (>2 mm) mononuclear cell, macrophage, $CD8^+$ T lymphocyte and plasma cell involvement was observed in stable COPD and during exacerbations of chronic bronchitis.[49,50,52] The role of neutrophil leukocytes is not yet clear. Neutrophils are seen in the large airway walls only during exacerbations and in severe COPD. Neutrophils, however, are observed early on in the airway lumen and in the sputum.[7] In small airways, $CD8^+$ T lymphocyte-mediated inflammation is dominant, but in severe forms of the disease other inflammatory cells, including neutrophils infiltrate the airway walls. Cell involvement in COPD is shown in *Table 1*.

$CD8^+$ cytotoxic T lymphocytes infiltrate all levels of the bronchial tree in COPD. There are at least two theories for the $CD4^+/CD8^+$ ratio shift in the disease. First, $CD8^+$ T cells frequently occur on site of viral infections. It is suggested that repeated viral infections lead to the excessive recruitment of lymphocytes. $CD8^+$ cells release tumor necrosis factor-α, a potent proinflammatory mediator that leads to airway injury.[30] Second, Enelow and colleagues demonstrated that lymphocytes are activated by lung autoantigens and cause lung injury.[9] It is speculated that tobacco smoke can induce autoantigen response in the

lung, which causes the increased presence of $CD8^+$ T lymphocytes. The role of inflammatory cell mediators in progression of COPD is detailed below in "Inflammatory mediators in COPD".

Smooth muscle cell hypertrophy is often observed in chronic bronchitis, but it is difficult to assess due to the fact that some bronchi do not have a complete smooth muscle layer. Airway thickening is more prominent in obstructive bronchiolitis than in chronic bronchitis.

Submucosal bronchial gland enlargement is a key feature in chronic bronchitis and it was described early on.[44] The Reid index, which is a calculated ratio: submucosal gland layer thickness/total airway wall thickness (from epithelium base to inner cartilage surface) is greater than 0.5 (normal index is 0.3).[43] Furthermore, the proportion of mucous glands in the acini is increased and that of serous ones is reduced. Serous glands produce lysozyme and lactoferrin that have antibacterial activity. The thick mucous plugs likely clotting airways and the reduced serous activity may contribute to common bacterial infections in COPD.[13] The degeneration of bronchial cartilage appears in a late phase of chronic bronchitis.[14]

As mentioned above, mucus hypersecretion is a hallmark of chronic bronchitis (*Figure 1*). It is observed as chronic cough and sputum production in patients with chronic bronchitis. Mucus hypersecretion is a result of local peptidergic and spinal cholinergic sensory nerve activation. Besides mucus production it directly induces neutrophil elastase and chymase production. There is cumulating data that epidermal growth factor receptor (EGFR) plays a central role in mucus overproduction. It is suggested to be the final common pathway by which noxa, including tobacco smoke, causes mucus hyperplasia.[45,60] EGF, together with other growth factors, may stimulate submucosal gland and goblet cell proliferation in chronic bronchitis. Tobacco smoke itself can activate the EGFR pathway and cause mucus hypersecretion.[6] It is still debated whether mucus hypersecretion has a role in airway obstruction.[54] Epidemiological data suggest that hypersecretion is a risk factor for obstruction, and mucus contributes to reduced airflow.[64] Two large clinical trials, however, showed that the presence of chronic bronchitis does not predict the development of airflow limitation.[10,63] Furthermore, in a recent analysis of 153 COPD patients' bronchial biopsy data, Hogg and colleagues did not find correlation between the luminar content and the severity of small airway obstruction.[15]

Obstructive bronchiolitis

Obstructive bronchiolitis is an inflammatory condition that involves small and peripheral airways (<2 cm in diameter).

The typical histological feature of the disease is collapsed lumen with increased mucus, unlike in asthma where the lumen is maintained.[61] Lumen closure is due to high surface tension and small airway instability caused by mucus hypersecretion. Mucus hypersecretion is a result of goblet cell metaplasia. Goblet cells replace Clara and serous cells in the small airways, and mucus production dominates over surfactant secretion. The destabilized bronchioles collapse.

Macrophages and $CD8^+$ T lymphocytes dominate small airway inflammation.[39,49] When peribronchiolar inflammation was compared in smokers with or without COPD, $CD8^+$ T lymphocyte numbers were increased in the former group.[49] The inflammatory changes in the small airways showed a positive correlation with the airflow obstruction in COPD.[15,53] However, this correlation was weaker between inflammation seen in large airways and the accelerated decline of FEV_1 in COPD.[15,25,26] In mild to moderate stable COPD

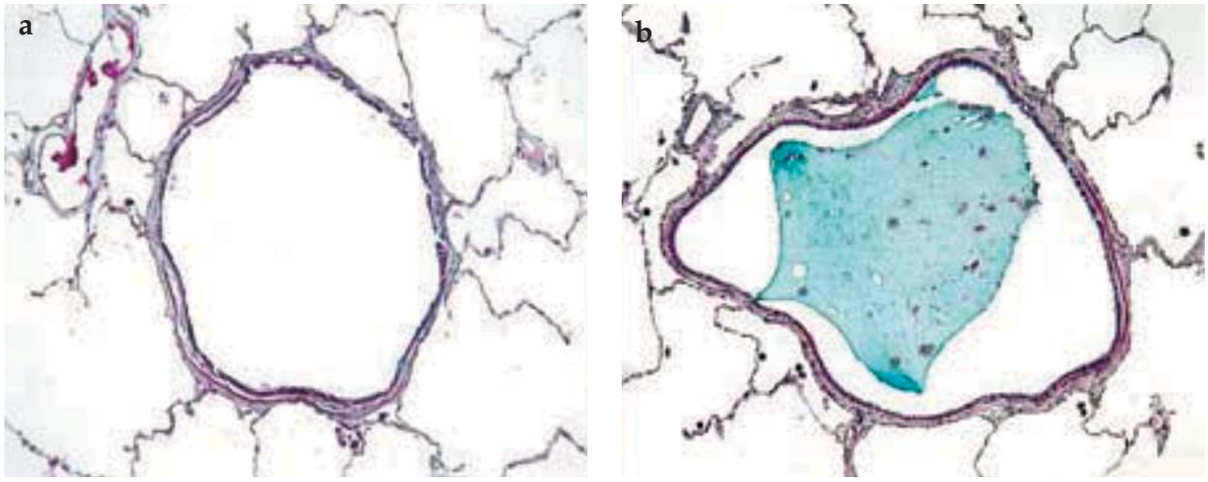

Figure 1. *Mucus plugging in chronic obstructive pulmonary disease (200x magnification).* ***(a)*** *Normal alveolar lumen.* ***(b)*** *Eosinophilic mucous fills alveoli in chronic obstructive pulmonary disease. The shape of alveolus is deformed.*

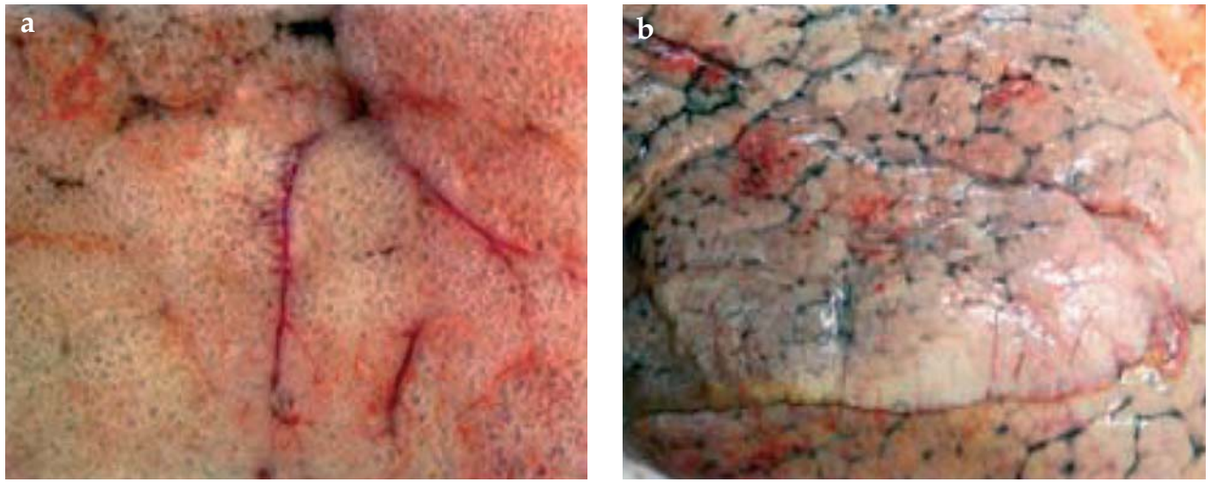

Figure 2. *Macroscopic changes in the lung in centrilobular and panlobular emphysema.* ***(a)*** *Centrilobular emphysema,* ***(b)*** *panlobular emphysema*

macrophages, while in severe to very severe disease neutrophil leukocytes were the predominant inflammatory components observed.[15] Interestingly, during mild exacerbations eosinophils, while in severe exacerbations neutrophil leukocytes are the major inflammatory cells in the airway wall.[13]

Increased numbers of fibroblasts and myofibroblasts, and enhanced amount of extracellular matrix was detected in the subepithelium of small airways in obstructive bronchiolitis. The suggested mechanism is repetitive injury and healing that leads to fibrosis and scar tissue similar to what is seen during wound healing.[18] The structural remodeling leads to small airway narrowing, that contributes to increased peripheral airway resistance. Pulmonary vessel remodeling is also observed in severe COPD (see below in "Pulmonary vascular disease"). The working definition of remodeling is: "It is an alteration in size, mass, or number of tissue structural component that occurs during growth or in response to injury and/or inflammation."[18] Growth factors such as epidermal growth factor (EGF), fibroblast growth factor (FGF), granulocyte-macrophage colony stimulating factor (GM-CSF), platelet derived growth factor (PDGF), transforming growth factor (TGF) and hepatocyte growth factor (HGF) families are known to contribute to normal lung development.[18] It is suggested that in chronic diseases when the tissue is already damaged and inflamed, remodeling activity persists leading to abnormal airway function. Environmental noxa like tobacco smoke, chronic infection or occupational inhalation hazards may cause inappropriate remodeling.

Small airway narrowing is further enhanced by smooth muscle cell hypertrophy and mural edema, mostly observed in small bronchi and bronchioli. Smooth muscle cell hypertrophy is one of the key findings in obstructive bronchiolitis.

Progressing inflammation destroys the alveolar attachment of small bronchi, which provides support for bronchioli to remain open during expiration. The loss of alveolar attachments contributes to the loss of elastic recoil of the lung, and airways collapse before emptying. Matrix metalloproteinases (MMPs) have a key role in both promoting remodeling and the destruction of alveolar attachments (see below in "Inflammatory mediators in COPD").

It is a matter of debate whether the obstruction of bronchioli due to bronchiolitis or the loss of elastic recoil due to parenchyma destruction and the loss of alveolar attachments is the major reason for small airway obstruction in COPD. It is widely accepted that both bronchiolitis and the loss of alveolar attachments contribute to the small airway obstruction.[13,18]

Emphysema

Emphysema is defined by permanent air space enlargement involving the distal to terminal bronchioles, respiratory bronchioles and occasionally the alveoli.[13] The mechanism of the disease involves unregulated inflammation associated with release of large amounts of proteolytic enzymes. However, the exact mechanism that results in parenchyma destruction, fibrosis and remodeling is not well understood.

Two distinct forms of emphysema are described in the literature.[22] Centrilobular emphysema is common in cigarette smokers. The main site of inflammation and destruction is the respiratory bronchioles but in advanced disease the capillary bed can also be involved. The enlargement and confluence of respiratory bronchioles is most frequent in the 3rd order respiratory bronchioles, however, alveolar ducts and sacs may also be involved (*Figure 2a*). This form of emphysema is more frequently observed in the upper lobes in its mild form. The reason for the localization is not known. Panacinar emphysema is typically seen

in α_1-antitrypsin (α_1-AT) deficiency. This quite rare genetic disease counts for approximately 1% of all emphysema cases. In panacinar emphysema respiratory bronchioles, alveolar ducts and sacs are equally involved in the disease process (*Figure 2b*). Panacinar emphysema is mostly localized to the lower lung lobes.

Protease/antiprotease imbalance is blamed for pulmonary emphysema. Inflammation is dominated by $CD8^+$ T lymphocytes in emphysema, however, macrophages and neutrophils produce excessive amounts of proteases including leukocyte elastase, cathepsin G, proteinase 3, MMPs, cystein proteinases and plasminogen activator. All of these enzymes are capable of destroying the elastin and other components of the alveolar wall.[54] Counterbalancing antiproteases are α_1-AT, α_1-antichymotripsin, secretory leukocyte protease inhibitor (SLPI), tissue inhibitors of metalloproteinases (TIMPs) and cystatins.

At the same time, this concept does not fully explain the mechanism of emphysema. In the majority of smokers or in many other diseases where inflammation is observed, e.g. pneumonia or acute respiratory distress syndrome), emphysema is not present. There is cumulating evidence that accelerated epithelial and endothelial cell apoptosis interacts with inflammation and proteolysis in tissue destruction in emphysema.[1,20,62] Kasahara et al experimentally demonstrated that the blockade of vascular endothelial growth factor (VEGF) induces alveolar septal cell apoptosis and emphysema.[19]

Alveolar attachments, interacinar septa and airspace walls are destroyed in the late phase of emphysema. However, there is scientific data that despite septal destruction there is collagen fibrosis in the alveolar wall in advanced emphysema.[65]

In emphysema, alveolar wall and attachment destruction leads to the loss of elastic recoil followed by decline in lung function and FEV_1. However, the picture is complicated by the fact that the commonly observed obstructive bronchiolitis in emphysema also results in airflow limitation observed in COPD. Snider and colleagues suggested that in advanced emphysema the loss of elastic recoil may be the principal cause of airflow limitation while in milder forms of emphysema peripheral airway abnormalities predominate.[59]

Pulmonary vascular disease

Secondary pulmonary hypertension is common in very severe COPD. Tobacco smoke itself can cause endothelial dysfunction in pulmonary vessels, most likely mediated through endothelial-derived relaxing factor.[41,56] Furthermore, patients with mild to moderate COPD have increased pulmonary vascular pressure following exercise.[18] Intimal thickening, smooth muscle hypertrophy and inflammation was detected in patients with COPD.[41,52] Intimal thickening occurs first when lung function is still normal and pulmonary vascular pressure is physiological. Later increase in smooth muscle hypertrophy follows which is moderate, but may expand to small vessels where the smooth muscle layer normally is not present.[11] $CD8^+$ T lymphocytes and macrophages dominate pulmonary vessel inflammation. Pulmonary vessel remodeling is also noticed in advanced COPD. Proteoglycan and collagen deposition further reduces vessel lumen and fibrosis may obliterate smaller vessels. Endothelin-1 (ET-1) shows increased expression in pulmonary vessels exposed to hypoxia.[11] ET-1 levels are also increased during extracerbations. ET-1 acts through ET_A receptors and promotes smooth muscle hyperplasia and fibrosis in pulmonary vessels.

Hypoxemia was once believed to be the cause of pulmonary hypertension. Chronic hypoxia can cause pulmonary hypertension. However, there is no reversibility of pulmonary hypertension when applying normoxia. There is cumulating evidence that inflammation and vascular remodeling can contribute to this effect.[49]

Right heart failure (cor pulmonale) is the most severe complication of COPD. Although pulmonary hypertension and cor pulmonale are common consequences of COPD, the direct mechanism remains unclear.

Muscular wasting in COPD

Progressive muscle weakness, wasting and cachexia are prominent in late stages of COPD. Weight loss has been linked to increased TNF-α production and soluble TNF-α receptors.[5] It is suggested that TNF-α mediates muscular wasting, at least by 3 different mechanisms. 1. It directly induces protein loss in the muscles. 2. TNF-α-induced apoptosis via TNF receptors on muscle cells. FAS ligands, jun-N terminal kinases (JNK) and nuclear factor-κB (NFκB) intercellular pathways are known to be involved in this process.[24,29] 3. It is hypothesized that cell loss can also occur due to changes in TNF-α/NFκB signaling by reactive oxygen species (ROS). However, this last mechanism remains unclear.[29]

The loss of respiratory muscles can further deteriorate lung gas exchange contributing to the progression of dyspnea.

Exacerbations

Exacerbations are frequent in COPD and largely contribute to health expenses, since most patients seek medical care due to the acute exacerbation of the disease. Despite intensive investigation, the mechanisms of acute exacerbations in COPD are not known, and it is hard to link any of the major symptoms to acute pathologic changes in the lung. As described above, it is debated whether increased large airway secretion affects the course of the disease. Once it was believed that bacterial infection

is the major cause of exacerbations, however, now it is clear that viral infections and inhaled environmental pollution contribute to hospitalization more often.[54] Approximately 50% of exacerbations results from viral infections or noninfectious causes.[3,12] Based on virus serology findings, viruses that often provoke exacerbations are influenza, parainfluenza, corona and rhinoviruses.[46] Besides viruses, noninfectious causes contribute to exacerbations, such as allergens, toxic inhalation, noncompliance with medical treatment, thickening of bronchial secretion, congestive heart failure and pulmonary embolism. Tracheal aspirate fluid culture shows the frequent colonization of lower airways with bacteria in stable COPD. The most common colonizers are Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis and α-hemolytic streptococci.[28] Changes either in concentration or in location of these pathogens were not observed during acute episodes of COPD, providing further evidences that bacterial infection/reinfection is not the principal cause of exacerbations. [12] However, a recent clinical investigation showed that exacerbations may correlate with the appearance of a new strain of the above mentioned bacteria in the lower airways.[58] Due to the conflicting clinical findings, the therapeutic role of antibiotics in acute exacerbation remains controversial.[32,55] There are only few changes in inflammation observed in acute exacerbation. Sputum cytology and bronchial biopsy data show continuously high levels of inflammatory cells in both airway mucus and the bronchial wall in COPD, and acute exacerbations did not lead to significant change in cell involvement.[3,50] In mild exacerbation, prominent eosinophilia was detected in the airway wall and lumen.[51] The reason for eosinophilia is not known, but it may be a result of eotaxin production by viral agents. Eotaxin is an eosinophil chemoattractant. Interestingly, in severe exacerbations increased neutrophil chemoattractant gene expression, including interleukin-8, and increased levels of myeloperoxydase, a neutrophil marker were detected.[42,47] These data suggest a role for neutrophils is the acute exacerbation of chronic bronchitis/COPD.

Inflammatory mediators in COPD

Inflammation, as discussed above, is a key component of the disease, and involves many cell types and a variety of proinflammatory mediators. Neutrophil- and macrophage-mediated inflammatory reactions are seen in the lung of smokers even before COPD is established.[36] However, only a small portion, 15-20% of all smokers develop the disease. In smokers with COPD, the inflammatory response is further augmented when compared to "normal smokers" (without COPD), assessed by inflammatory cell count and proinflammatory cytokine measurements in the bronchoalveolar lavage fluid (BALF) and the airway tissue.[15,42] This finding supports the theory that besides inflammation, genetic factors, viral infections, oxidative stress and other unknown factors are necessary to be present to develop COPD. Ning and colleagues in a genome-wide gene expression analysis found 327 genes that were differently expressed in patients with normal lung function results (GOLD stage 0) when compared to moderate COPD (GOLD stage 2).[37] Among them, many coded for important transcription and growth factors involved in inflammation and lung development, but not yet described in the disease.

Proinflammatory mediators and chemoattractants released by inflammatory cells and activated epithelial cells contribute to further augmented inflammation. Here we discuss the role of leukotriene-B_4 (LTB_4), IL-8 and other chemokines, TNF-α, interleukin-13 and ET-1. LTB_4 is measured in increased quantities in the sputum of patients with COPD.[17] It is secreted by activated macrophages and neutophils and it is a potent leukocyte chemoattractant. There is evidence that increased amounts of LTB_4 are secreted by macrophages in α_1-antitrypsin deficiency. IL-8 (CXCL8) is another potent neutrophil chemoattractant found in high concentrations in the induced sputum of COPD patients. IL-8 may be secreted by macrophages and neutrophils. Qiu and colleagues found increased IL-8 gene expression in bronchial biopsies from patients with severe acute exacerbations. The level of IL-8 may correlate with neutrophil involvement in severe COPD extracerbation.[42] IL-8 activates macrophages and neutrophils through CXCR-1 and 2 receptors. Other CXC chemokines, growth-related oncogene (GRO-α, -β and -γ), epithelial-derived neutrophil-activating peptide (ENA78) and CC chemokine macrophage chemotactic factor-1 (MCP-1), a macrophage chemoattractant, are also increased in COPD. These cytokines also have affinity to CXCR2.[42] TNF-α is measured in large quantities in COPD, especially during exacerbations. Cigarette smoke can activate macrophages to produce TNF-α.[22] TNF-α induces the gene expression of many pro-inflammatory cytokines (including IL-8 and more TNF-α) via NF-κB transcription factor activation. TNF-α may induce skeletal muscle wasting directly as explained above. Interleukin-13 and γ-interferon are overexpressed in emphysema, mediated by the increased expression of MMPs and cathepsins during parenchyma destruction.[67] ET-1 levels are also increased in COPD. As detailed above, they are important in pulmonary vascular remodeling.

Inflammatory cells (macrophages and neutrophils) secrete reactive oxygen species (ROS) that play a major role in pathology of COPD. Besides endogenous production, cigarette smoke contains large quantities of ROS (10^{17} molecules/puff of smoke). This finding further emphasizes the pathogenic role of smoking in COPD. Excessive ROS production inactivates antiproteases (α_1-AT, SLPI) and overwhelms endogenous antioxidant sys-

tems (glutathione, uric acid, bilirubin). Drost and colleagues found reduced glutathione levels in the bronchoalveolar lavage fluid (BALF) of patients with severe exacerbations of COPD.[8] Oxidants contribute to mucus hypersecretion. ROS can directly activate NF-κB transcription factor and lead to proinflammatory cytokine (IL-8 and TNF-α) production.[8] Furthermore, inducible nitric oxide synthase (iNOS) and inducible cyclooxygenase (COX2) is activated via the same mechanism by oxidants.[13] Hydrogen peroxide (H_2O_2) can directly cause bronchoconstriction. Increased levels of H_2O_2, ethane, isoprostanases (directly oxidized arachidonic acid) and peroxynitrite (superoxide anion combined with nitric oxide, which can generate hydroxyl anion) are measured in patients with COPD. [13]

There are over 20 different MMPs identified. Their role in elastolysis and parenchyma destruction is well described in the literature.[4] Increased MMP-1, -2, -8 and -9 levels were described in the BALF of patients with COPD.[57] Proinflammatory cytokines TNF-α and interleukin-1β can release MMP-9 from epithelial cells following 1-day exposure. Furthermore, there is recent evidence that macrophage-produced MMP-9 is involved in elastolysis and small airway fibrosis at the same time. MMP-9 increased the release of neutrophil chemotactic peptide, leading to neutrophil activation and elastase release. MMP-9 also inactivates α_1-AT and contributes to transforming growth factor-β_1 (TGF-β_1) activation.[23] TGF-β_1 overproduction leads to fibrosis in the lung.[4] Protease-activated receptor-2 (PAR-2), a transmembrane receptor, plays an important role in matrix remodeling, cell migration, proliferation and inflammation. PAR-2 expression is increased on vessel smooth muscles cells in COPD.[34] PAR-2 induces proliferation of human airway smooth muscle cells and lung fibroblast, and increases MMP-9 release from the airway epithelium.[66] Together MMP-9, TGF-β_1 and PAR-2 can enhance remodeling and fibrosis in COPD.

Conclusion

For a long time, COPD was considered the disease of poor and socially disadvantaged people. Because of neglect from both patients and medical caregivers, not enough attention was paid to its therapy. Definitive structural changes in the lung tissue were discovered only with autopsy, often in the most severe form. In the last 30 years, due to major advances in spirometry techniques, lung function changes can be accessed in depth. However, the three different morphological findings, chronic bronchitis, obstructive bronchiolitis and emphysema, were only recently linked to one common lung function finding (GOLD criteria 2001, 2003).

Despite intensive investigation, the pathology of COPD is not fully understood. Indeed, there is a lot to be done in this field. Smoking is the best-described causative risk factor in COPD, however, only a small proportion of smokers develop the disease. Genetic factors are often blamed for "COPD susceptibility". The discovery of molecular mechanisms of COPD is a key to find new and specific drugs for the treatment of disease. There are at least two new fields where this approach can be used. Recent evidences are provided that ROS released from tobacco smoke or from inflammatory cells can provoke proinflammatory cytokine production via the activation of intracellular inflammatory pathways NF-kB and MAP kinases. Therapeutic targeting of inflammatory pathways can reduce inflammation in the early phases of the disease. On the other hand, matrix metalloproteinase blockade can be used to reduce lung remodeling. The pathology of COPD needs to be investigated in further details now to reduce morality and health care costs for the future generations.

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