Summary
Jian-Qing He, Scott J. Tebbutt and Peter D. Paré
Genetics of COPD

There is convincing evidence that chronic obstructive pulmonary disease (COPD) is a complex genetic disease in which multiple susceptibility genes and environmental factors interact to contribute to its development. In this chapter we discuss the different phenotypes that can be used in genetic studies of COPD and the two major approaches that can be used to identify disease-causing genes: genomic scans and association studies. Whole genome scans using classical linkage analysis have the advantage that they allow the identification of novel genes for disease susceptibility. However, few such studies have been carried out in COPD due to the difficulty of ascertaining large families with multiple-affected individuals and the lack of large cohorts of exposed and affected sib-pairs. Case-control or cohort-based association studies, in which candidate polymorphisms in biologically plausible candidate genes are tested, is the most frequently employed strategy. Although association studies are easier to conduct, they are limited by our knowledge of disease pathogenesis and are subject to a number of potential confounding influences which may lead to false positive or negative results. Despite these difficulties there is accumulating evidence to implicate a number of specific genes in COPD pathogenesis in addition to the well recognized contribution of alpha-1-antitrypsin. Larger sample size, better study design (including family studies), more robust phenotypes, as well as the use of genomic controls and haplotype blocks will accelerate the identification of COPD-causing genes in the future.

Key Words: COPD, genetics, polymorphisms, haplotypes, population admixture, genomic scans, association studies, alpha-1-antitrypsin, candidate gene, phenotype.

Summary
Simonetta Baraldo, Renzo Zuin and Marina Saetta
The pathology of COPD

Chronic obstructive pulmonary disease (COPD) is a complex disease characterised by irreversible airflow limitation. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases, the most common of which is tobacco smoke. The pathological hallmarks of COPD include both small airway abnormalities and destruction of lung parenchyma or emphysema, which would contribute to the development of airflow limitation through distinct mechanisms. When pathological changes involve the small airways, they will contribute to airflow limitation by narrowing and obliterating the lumen and by actively constricting the airways, therefore increasing the resistance. When pathological changes are localised in lung parenchyma, they will contribute to airflow limitation by reducing the elastic recoil of the lung, through parenchymal destruction, as well as by reducing the elastic load applied to the airways through destruction of alveolar attachments. This, therefore, reduces the driving pressure. A chronic inflammatory response is present throughout the entire bronchial tree of patients with COPD and has an important role in the development of chronic airflow limitation. This inflammatory response is characterized by an infiltration of CD8 T-lymphocytes, macrophages and neutrophils, which can secrete a wide range of cytokines and mediators that can be crucial in the development of airway wall remodelling and parenchymal destruction. Despite the progress in the understanding of COPD, no therapy has yet managed so far to halt the progression of the disease or to reverse its pathological lesions. Nevertheless, there are
encouraging indications for future research since elucidation of the molecular mechanisms involved in COPD pathogenesis may lead to identification of new potential treatments.

**Key Words:** Airflow limitation, cigarette smoking, inflammation, emphysema.

**Summary**

Frances Gilchrist, Onn Min Kon and Michael I. Polkey

**Lung function in COPD**

This chapter reviews classical and recent aspects of lung function testing and physiology in COPD. The aim of the chapter is to enable the reader to select the most appropriate test for their clinical or academic need and to guide them how to perform the test.

**Key Words:** COPD, lung function, FEV1.

**Summary**

Rachel C. Tennant, Trevor T. Hansel and David M. Hansell

**Computed tomography (CT) scans in COPD**

Computed tomography (CT) scanning permits the imaging of the large and small airways as well as lung parenchyma of patients with chronic obstructive pulmonary disease (COPD). CT scans are increasingly employed in routine clinical practice in COPD, and are required prior to considering the surgical procedures of bullectomy, lung volume reduction surgery (LVRS) and lung transplantation. Emphysema may usefully be assessed by CT scans coupled to computerised density mask methods of analysis, and CT scans have been found useful in monitoring the effects of $\alpha_1$-antitrypsin replacement in patients with emphysema due to inherited deficiency of this anti-protease. CT scans can demonstrate a variety of lung pathology in smoking-related lung disease: including bronchial wall thickening in chronic bronchitis, respiratory bronchiolitis with interstitial lung disease (RBILD), tubular bronchiectasis, lung fibrosis, and malignant lesions. Furthermore, in a group of heavy smokers studied over 15 years, it has been demonstrated that the “ground glass” appearance of a macrophage infiltration of the alveoli occurs in regions that later become affected by emphysema. It may be possible to study the effects of anti-inflammatory therapy by performing serial low radiation CT scan protocols, in an effort to document effects on this macrophage infiltration. The relationship between CT scan appearances and the pathophysiology of COPD requires further analysis, and CT scans are likely to play an expanding role in clinical practice and also in assessment of the effects of new drugs for patients with COPD.

**Key Words:** Computed tomography (CT), chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, respiratory bronchiolitis with interstitial lung disease (RBILD).

**Summary**

Peter J. Barnes

**Oxidative stress in COPD**

Reactive oxygen species (ROS) are generated by inflammatory cells in chronic obstructive pulmonary disease (COPD) airways and may have several effects on airway function and the inflammatory process. There is increased endogenous production of ROS by neutrophils and macrophages in COPD patients and cigarette smoke is rich in oxidants. ROS may have direct
effects on target cells in the airways, causing bronchoconstriction, plasma exudation, mucus secretion, neural activation, as well as decreasing antiproteases. There may be indirect effects, including the formation of isoprostanes, and the activation of the transcription factors NF-κB and AP-1, and histone acetylation, which switches on multiple inflammatory genes. In addition, oxidative stress may impair the anti-inflammatory action of corticosteroids. There are several new non-invasive techniques for monitoring oxidative stress in COPD, including exhaled carbon monoxide, ethane and pentane as well as markers in exhaled breath condensate, including hydrogen peroxide, isoprostanes and 3-nitrotyrosine. These markers are increased in COPD and are related to disease severity. Antioxidants should have a beneficial effect in COPD, but more potent antioxidants need to be developed.

**Key Words:** Reactive oxygen species COPD, hydrogen peroxide, superoxide anions, 8-isoprostane, antioxidant, histone acetylation, NF-κB.

**Summary**

Anita L. Sullivan and Robert A. Stockley

**Proteinases in COPD**

It is generally accepted that a proteinase-antiproteinase imbalance plays an important role in the pathophysiology of COPD. In this chapter the historical background to proteinase research in COPD is outlined, and the role of neutrophil elastase is then discussed in detail. The potential role of other proteinases such as cysteine proteinases and matrix metalloproteinases and how these may interrelate in COPD is covered in the later sections.

**Key Words:** Chronic obstructive pulmonary disease, neutrophil, neutrophil elastase, serine proteinase, cysteine proteinase, matrix metalloproteinase, macrophage metalloelastase, alpha-1-antitrypsin, tissue inhibitor of metalloproteinases, chemotaxis, bacterial infection.

**Summary**

Duncan F. Rogers

**Mucus hypersecretion in COPD**

Patients with chronic obstructive pulmonary disease (COPD) invariably exhibit characteristics of airway mucus hypersecretion, including sputum production, increased luminal mucus, goblet cell hyperplasia and submucosal gland hypertrophy. These features are inconsistent between patients and their impact on morbidity and mortality is variable. However, current evidence indicates that airway hypersecretion has clinical significance in COPD, particularly in those who are prone to respiratory infections. This suggests that it is important to develop drugs that inhibit mucus hypersecretion in these patients. A number of drugs are available that may have therapeutic benefit in the ‘bronchitic’ component of COPD, for example cyclooxygenase inhibitors and anticholinergics. Novel compounds are in development, including inhibitors of epidermal growth factor receptor tyrosine kinase. Lomucin, a putative inhibitor of calcium-activated chloride channels, is in clinical trial. However, COPD may have a specific phenotype that differs from other hypersecretory conditions of the airways. Consequently, we need to determine if there is an intrinsic abnormality specific to mucus in COPD. Based upon this information, appropriate suppressors of mucus hypersecretion in COPD can be developed.
Key Words: Airway, chronic bronchitis, chronic obstructive pulmonary disease, COPD, goblet cell, mucin, mucolytic, respiratory tract, sputum, submucosal gland.

Summary

Vera Keatings and Clare M. O’Connor
Induced sputum and BAL analysis in COPD

Elucidation of the contribution of inflammation to the pathophysiology of chronic obstructive pulmonary disease (COPD) requires evaluation of the inflammatory cells and mediators present in the airways. The two techniques most widely used to sample the airways are bronchoalveolar lavage (BAL) and, more recently, induced sputum. Induced sputum samples the upper airways and, as the less invasive technique, is best suited to evaluation of inflammatory changes in this compartment over time. It is also a more acceptable method of sampling for control subjects and ‘healthy’ smokers, the comparator groups against which airway inflammation in COPD need to be evaluated. A significant practical problem with this technique is the interference of dithiothreitol (DTT), used to solubilise mucus plugs, with the measurement of many inflammatory mediators. For evaluation of inflammation in the more distal airways, BAL is the sampling method of choice and presents few methodological problems in analysing inflammatory mediators. However, this procedure is not well tolerated in patients with moderate to severe disease nor is it suitable for studies involving repeated sampling over time. This chapter reviews the information on airway inflammation obtained by both procedures to provide a basis for selection of sampling method for research studies.

Key Words: Induced sputum, bronchoalveolar lavage, airway inflammation, chronic obstructive pulmonary disease.

Summary

Sergei A. Kharitonov and Peter J. Barnes
Exhaled breath markers in COPD

Exhaled nitric oxide (NO) has been measured in exhaled air in patients with chronic obstructive pulmonary disease (COPD). More recently, novel multiple exhalation flow approach has been successfully developed that allows assessing NO derived from small vs. larger airways in COPD. Several non-volatile markers and mediators (hydrogen peroxide, reactive nitrogen species and nitrotyrosine, prostanoids, leukotrienes and 8-isoprostanes) have been detected in exhaled breath condensate. Exhaled breath temperature and bronchial blood flows measurements have been also developed. There is a strong rationale to use these non-invasive markers to monitor airway inflammation and oxidative stress in COPD, as well as during treatment with corticosteroids in combination with long-acting β2-agonists and novel therapies.

Key Words: Airway inflammation; oxidative stress; chronic obstructive pulmonary disease; exhaled nitric oxide; exhaled breath condensate; hydrogen peroxide; reactive nitrogen species; nitrotyrosine; prostanoids; leukotrienes; 8-isoprostanes; exhaled breath temperature; bronchial blood flow; metabolomics; proteomics.
Summary
Alvar G.N. Agustí
Systemic features of COPD

Chronic obstructive pulmonary disease (COPD) is associated with several systemic (i.e., extra-pulmonary) effects. These include, among others, the presence of systemic inflammation, unexplained weight loss and skeletal muscle dysfunction. These systemic features of COPD have clinical relevance because they jeopardize the quality of life and, importantly, the prognosis of patients with COPD. This chapter reviews the characteristics and mechanisms of the currently accepted systemic features of COPD and anticipates some others of potential future relevance with the hope that this may stimulate research in this field and eventually contribute to develop new therapeutic alternatives for this devastating disease.

Key Words: Cachexia, chronic bronchitis, emphysema, hypoxia, inflammation, skeletal muscle.

Summary
Annemie M.W.J. Schols and Emiel F.M. Wouters
Pulmonary rehabilitation

Pulmonary rehabilitation refers to the whole spectrum of non-pharmacological intervention strategies, directed to improve health and functional status of patients with chronic respiratory diseases. It is now clearly established that these multidisciplinary programs improve exercise capacity, reduce symptoms, improve quality of life and reduce medical consumption in COPD patients. Exercise training, peripheral muscle training and nutritional support are evidence-based components of an integrated management approach of COPD when adequately targeted and implemented.

Key Words: COPD, rehabilitation, exercise, nutrition, education.

Summary
Trevor T. Hansel, Rachel C. Tennant, Edward M. Erin, Andrew J. Tan and Peter J. Barnes
New drugs for COPD based on advances in pathophysiology

A characteristic inflammatory infiltrate consisting of macrophages, neutrophils and CD8+ T cells occurs in the large and small airways, lung parenchyma and lung vasculature of patients with chronic obstructive pulmonary disease (COPD). In response to irritants in cigarette smoke, cycles of inflammation and resolution are associated with excess mucus production, fibrosis, and proteolysis. A range of new drugs are being developed to target this inflammatory process: the phosphodiesterase-4 (PDE-4) inhibitors cilomilast and roflumilast now being in phase III development for COPD. Alternative approaches are to give antioxidants, inhibitors of nitric oxide synthase (iNOS), and leukotriene B4 receptor antagonists. More specific therapy includes adhesion molecule- and chemokine-directed drugs, as well as therapies to combat tumour necrosis factor-α (TNF-α) and augment interleukin-10 (IL-10). Drugs that inhibit cell signalling include inhibitors of p38 mitogen-activated protein (MAP) kinase, nuclear factor-κB (NF-κB) and phosphoinositol-3 (PI-3) kinase-γ. When considering agents that act on structural cells, epidermal growth factor (EGF) receptor kinase inhibitors and calcium activated chloride channel (CACC) inhibitors have
potential to combat mucus overproduction. Therapy to combat fibrosis is being developed against transforming growth factor-β1 (TGF-β1), fibroblast growth factors (FGF), tryptase and protease activated receptor-2 (PAR-2). There are also efforts to develop elastase and matrix metalloprotease (MMP) inhibitors to prevent proteolysis and the development of emphysema, as well as drugs such as retinoids that could reverse the process of lung destruction. There is a major need to have reliable decision making in early clinical studies when assessing new drugs in COPD; this is aided by recent advances in CT scanning, lung function and exercise testing methodology, and non-invasive biomarkers.

**Key Words:** Anti-inflammatory, COPD, adhesion molecule, chemokine, cytokine, tumour necrosis factor-α (TNF-α), phosphodiesterase-4 (PDE-4), p38 mitogen-activated protein (MAP) kinases, nuclear factor-κB, fibrosis, elastase, matrix metalloprotease (MMP), retinoic acid.
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