Handbook of Experimental Pharmacology 237

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Pharmacology and Therapeutics of Asthma and COPD

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We have dedicated this volume to Dr Dom Spina who sadly passed away on December 5, 2016. Dr Spina had made major contributions to the field of Pulmonary Pharmacology throughout his career, not least in the area of xanthines and phosphodiesterase inhibitors, the subject of his contribution to this volume. He will be sorely missed by all who knew and had the privilege of working with him.

Preface

In 2004 we edited Volume 161 on the *Pharmacology and Therapeutics of Asthma and COPD* as part of this prestigious series. Over the last decade there have been substantial increases in our understanding of the mechanisms underlying asthma and COPD, as well as in the treatment of these important diseases. We have brought together internationally recognized authorities to review the most important new information on the advances in our understanding of the pathogenesis and treatment of these diseases, including the substantial advances in the topical delivery of inhaled medicines. It is hoped that this book will be invaluable for research scientists and clinicians involved in research into asthma and COPD, and that this volume will be a major reference resource for chest physicians and those involved in the development of novel pharmaceutical entities for these diseases.

Each chapter is extensively referenced, generously illustrated with clear diagrams and photographs, and represents a state-of-the-art review of this important area of respiratory medicine.

London, UK
December 2016

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Pathogenesis of COPD and Asthma

Clive Page, Blaze O'Shaughnessy, and Peter Barnes

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Abstract

Asthma and COPD remain two diseases of the respiratory tract with unmet medical needs. This review considers the current state of play with respect to what is known about the underlying pathogenesis of these two chronic inflammatory diseases of the lung. The review highlights why they are different conditions requiring different approaches to treatment and provides a backdrop for the subsequent chapters in this volume discussing recent advances in the pharmacology and treatment of asthma and COPD.

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1 Pathology of COPD

The major pathological features of COPD are obstructive bronchiolitis, emphysema and, in many cases, mucus hypersecretion (chronic bronchitis) (Fig. 1), but the relative contributions of each of these pathologies to COPD vary between patients (Hogg and Timens 2009). Even in early or mild COPD, there is evidence of airflow obstruction and a significant loss (disappearance) of small airways (McDonough et al. 2011). A novel CT imaging technique for quantifying small airway disease shows that this small airways loss is an early feature of disease and might account for the initial progression of airway obstruction in COPD (Galban et al. 2012). Structural changes in small pulmonary arterioles are also common in patients with COPD, with increased intimal thickening and vascular smooth muscle proliferation, perhaps resulting from inflammation in these vessels, as well as hypoxic

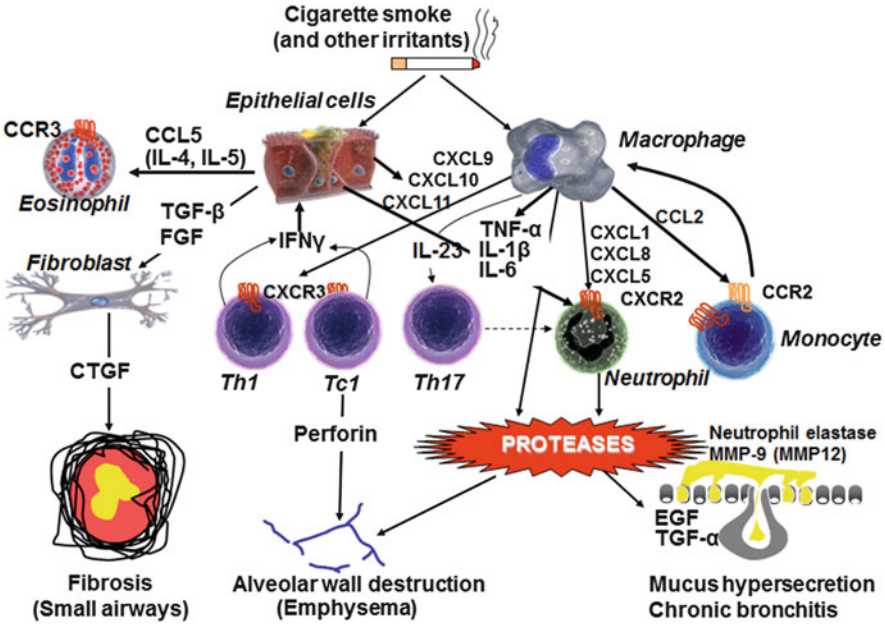

Fig. 1 Pathogenesis of COPD. Cigarette smoke (and other irritants) activate macrophages in the respiratory tract that release chemotactic factors that attract inflammatory cells from the circulation and fibrogenic factors such as transforming growth factor-β (TGF-β) and connective tissue growth factor (CTGF) which stimulate fibrosis in peripheral airways. Various cells release proteases in the airways, including matrix metalloproteinases (MMPs) that break down connective tissue in the lung parenchyma, resulting in emphysema, and stimulate mucus hypersecretion (chronic bronchitis). T cells play an important role in the persistence of inflammation

vasoconstriction (Peinado et al. 2008). However, pulmonary hypertension is usually not marked in COPD, except for a small group of patients with disproportionate pulmonary hypertension who can develop right heart failure (Seeger et al. 2013).

2 Chronic Inflammation

COPD is associated with chronic inflammation that predominantly affects peripheral airways and lung parenchyma, although large airways also show inflammatory changes (Barnes 2014). The degree of inflammation increases – with increased numbers of neutrophils, macrophages and lymphocytes in the lungs – as the disease progresses (Hogg and Timens 2009). Chronic inhalation of irritants, including cigarette smoke, biomass fuel smoke and air pollutants, activates pattern recognition receptors, such as Toll-like receptors (TLRs), resulting in an innate immune response, which leads to increased numbers of neutrophils and macrophages in the lungs as well as activation of airway epithelial cells and mucus secretion (Brusselle et al. 2011). Activation of adaptive immunity occurs later in the course of the disease and leads to increased numbers of T lymphocytes and B lymphocytes in the lungs. These cells might be organized into lymphoid follicles, which involves an increase in the number and activation of dendritic cells. During this adaptive immune response there is also an increase in the number of $CD8^+$ cytotoxic T (Tc1) and $CD4^+$ T helper (Th)1 cells in lung tissue (Barnes 2008a). The number of $CD4^+$ Th17 cells is also increased in the lungs and might further amplify neutrophilic inflammation (McAleer and Kolls 2014). Some patients with COPD have increased eosinophils in their airways and sputum and share some features of asthma, such as reversibility of the airway obstruction and a greater response to corticosteroids compared with patients with typical COPD (Barrecheguren et al. 2015). This has led to the description "Overlap Syndrome" to describe such patients, which has recently been reviewed elsewhere (Postma and Rabe 2015).

The levels of many different inflammatory mediators are increased in the lungs of patients with COPD, including lipid and peptide mediators, as well as a network of cytokines and chemokines that maintain inflammation and recruit circulating cells into the lungs (Barnes 2008b). Many of these proinflammatory mediators are regulated through the activation of the pro inflammatory transcription factor, nuclear factor-kB (NF-kB), and mitogen-activated protein kinases (MAPK), particularly p38 MAPK (Di Stefano et al. 2002; Renda et al. 2008). In addition, several proteases that degrade elastin fibres are secreted from airway resident neutrophils, macrophages and epithelial cells in patients with COPD. In larger airways, elastase from neutrophils might be an important stimulator of mucus hypersecretion, whereas matrix metalloproteinases (MMP9 and MMP12) in the lung parenchyma might be more important in the elastolysis that is observed in those patients having emphysema.

Even cigarette smokers with normal lung function have increased airway inflammation, suggesting this might be the normal response of the respiratory mucosa to inhaled irritants. However, this inflammation seems to be amplified in COPD

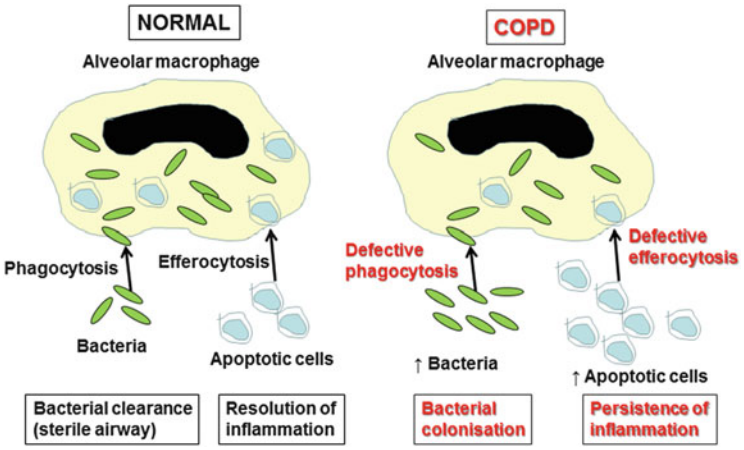

Fig. 2 Defective phagocytosis in COPD. Normally, macrophages phagocytose bacteria in the lung periphery and respiratory tract to maintain lung sterility. These macrophages also phagocytose apoptotic cells (efferocytosis) resulting in resolution of inflammation. In chronic obstructive pulmonary disease (COPD), macrophages are defective at phagocytosing bacteria, which results in chronic bacterial colonization of the lower airways. In addition, these macrophages have an impaired ability to carry out uptake (efferocytosis) of apoptotic cells, which results in failure to resolve inflammation

patients, particularly during acute exacerbations. The amplified inflammatory response in COPD might be explained by reduced expression of the nuclear enzyme histone deacetylase 2 (HDAC2, encoded by *HDAC2*) in macrophages and epithelial cells found in the lungs of those with COPD, resulting in activation of multiple inflammatory genes (Ito et al. 2005). The lung inflammation in COPD patients persists even after smoking cessation, suggesting that it is maintained by some autonomous mechanism that is not yet understood.

The lower respiratory tract of patients with COPD is often colonized with bacteria, such as *Haemophilus influenzae* and *Streptococcus pneumoniae*. This chronic bacterial colonization has been linked to a defect in the uptake (phagocytosis) of bacteria by macrophages (Taylor et al. 2010; Donnelly and Barnes 2012), and, particularly with *H. influenzae*, might be a factor driving chronic airway and systemic inflammatory responses in these patients (Fig. 2) (Singh et al. 2014). This defect in phagocytosis might also apply to defective uptake of apoptotic inflammatory cells (efferocytosis) and so might contribute to the impairment in resolution of lung inflammation observed in patients with COPD (Donnelly and Barnes 2012; Mukaro and Hodge 2011). Autoimmune mechanisms might also have a role in the persistence of bacterial infections in the lungs of such patients as there is evidence for the presence of autoantibodies, such as endothelial cell antibodies and antibodies against carbonyl modified proteins, in the lungs of those with COPD, at least in patients with severe disease (Kirkham et al. 2011). Finally, the peripheral lung inflammation might also 'spill over' into the systemic circulation and contribute to the systemic inflammation in COPD that is associated with various

comorbidities, such as cardiovascular disease and metabolic diseases (Barnes 2010). However, not all patients with COPD have evidence of systemic inflammation (Agusti et al. 2012) and comorbidities might be part of multimorbidity with similar mechanisms, such as accelerated ageing, affecting several organs at the same time.

3 Accelerated Ageing

COPD is largely a disease of the elderly and there is increasing evidence that emphysema is caused by accelerated ageing of the lung parenchyma due to defective endogenous anti-ageing mechanisms, such as those that involve sirtuins (Ito and Barnes 2009), with the activation of pathways leading to telomere shortening and cellular senescence (Fig. 3) (Mercado et al. 2015; Mitani et al. 2015). Cellular senescence and decreased sirtuin-1 have also been found in circulating endothelial progenitor cells of COPD patients, which are less effective at vascular repair than cells from age-matched normal individuals, which predisposes these individuals to cardiovascular disease and other comorbidities (Paschalaki et al. 2013). Indeed, stem cell senescence might be a common mechanism in COPD and its comorbidities, with consequent failure to repair tissue damage (Barnes 2015). Autophagy is a process whereby cells keep their cytoplasm clean by removing damaged organelles and proteins which is impaired with ageing (Madeo et al. 2015). There is increasing evidence that autophagy is defective in COPD, so that the accumulation of damaged proteins and organelles, such as mitochondria, result in accelerated cellular senescence and death (Mizumura et al. 2012).

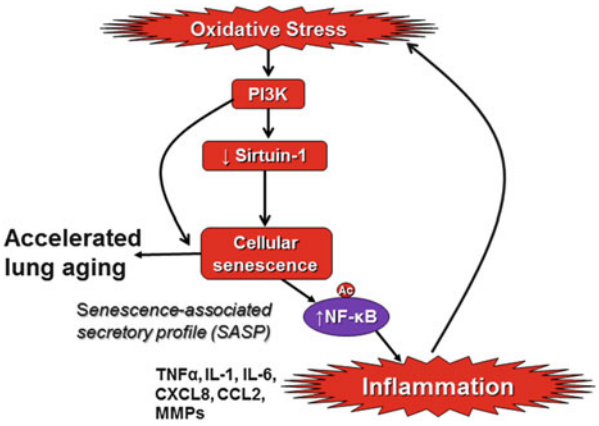

Fig. 3 Accelerated ageing and inflammation in COPD. Oxidative stress drives accelerated ageing though activation of phosphoinositide-3-kinase (PI3K) and reduction in sirtuin-1 which leads to cellular senescence and the release of inflammatory proteins (SASP), which further increase oxidative stress

4 Oxidative Stress

Increased oxidative stress is a key driving mechanism in the pathophysiology of COPD and accounts for many of the features of the disease (Kirkham and Barnes 2013). Oxidative stress is increased in patients with COPD from cigarette smoke exposure, but also endogenously from the activation of inflammatory cells, particularly neutrophils and macrophages. Reactive oxygen species (ROS) contribute to the pathophysiology of COPD in several ways (Fig. 4). For instance, ROS activate NF-kB and p38 MAPK, resulting in increased expression of inflammatory genes and proteases. ROS also inhibit endogenous antiproteases, such as α1-antitrypsin, resulting in increased elastolysis. Oxidative stress also leads to DNA damage, which is normally repaired by the efficient DNA repair machinery, but there might be a failure to repair double-stranded DNA breaks in COPD patients, which might also lead to increased risk of developing lung cancer (Caramori et al. 2011). ROS induce carbonylation of proteins, which, particularly in severe COPD, might lead to the generation of circulating autoantibodies that might perpetuate inflammation and lung injury (Kirkham et al. 2011). ROS also activate transforming growth factor β (TGF-β), leading to fibrosis. In addition, oxidative stress reduces corticosteroid responsiveness through a reduction in HD2 activity

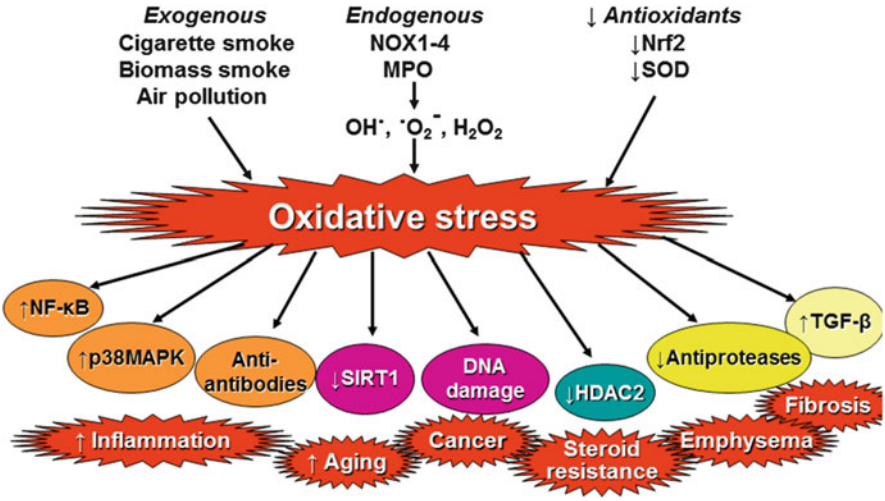

Fig. 4 Increased oxidative stress in COPD. Oxidative stress might be increased in chronic obstructive pulmonary disease (COPD) by a reduction in the expression of transcription factor NRF2, NADPH oxidases (NOX), myeloperoxidase (MPO) and superoxide dismutase (SOD) and other antioxidants, which might be triggered by inflammatory stimuli. Oxidative stress is a key mechanism that drives the development and progression of COPD through activation of the proinflammatory transcription factor nuclear factor-kB (NF-kB), p38 mitogen-activated protein kinase (MAPK), generation of autoantibodies to carbonylated proteins, reduced expression of sirtuin-1 (SIRT1), DNA damage, reduced histone deacetylase 2 (HDAC2) expression, reduced activity of antiproteases and increased release of transforming growth factor (TGF)-β