15

Inflammation in COPD and New Drug Strategies

Liam Heaney and Izhaq Masih
Queens University, Belfast, Northern Ireland, United Kingdom

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a disease characterized by poorly reversible airflow limitation of the airways that is usually progressive and associated with an abnormal inflammatory response in the lung[1]. The abnormal inflammatory response is usually triggered by smoking[2], or other environmental irritant exposures[3] which interact with genetic factors[4], leading to both airway and systemic inflammation resulting in airway injury and lung damage.

The term COPD is a descriptive term encompassing a heterogeneous subset of clinical syndromes, specifically chronic bronchitis, emphysema and asthma and it is now recognised that there is significant overlap between the previously described clinical syndromes. The term 'overlap syndrome' is often used to describe a patient with fixed airflow obstruction (COPD), but having some asthmatic features[5]. Chronic bronchitis is clinically defined as a cough productive of sputum lasting at least three months for two consecutive years and emphysema is a pathological entity characterised by destruction of the lung parenchyma with resultant enlarged alveolar spaces and loss of alveolar walls[6].

Morbidity and mortality due to COPD are significant and there remains a significant unmet clinical need. Many acute medical admissions to hospital are due to exacerbations of COPD[7] and mortality can be high as many patients with an acute exacerbation of COPD may not fulfil the criteria for admission to intensive care[8] and ward based management including non-invasive ventilation may not be appropriate in all cases due to intolerance or in the terminal stage of the disease[9, 10]. Globally, COPD is on the rise and currently it is ranked as the fifth largest disease to cause death worldwide[11] and estimation by the World Health Organisation is that by 2020, it will be the third largest cause of mortality. Despite this significant level of morbidity, many of the management and prevention targets outlined in the 1998 Global strategy for the diagnosis, management and prevention of Obstructive pulmonary Disease (GOLD) have not been met[12]. A better understanding of the inflammatory pathophysiological mechanisms in COPD is essential to developing novel effective therapies.

2. Pathogenesis

The major risk factors for COPD are tobacco smoking; occupational dust exposure, industrial fumes, and indoor pollution from biomass cooking with inadequate ventilation in poor living conditions and all of these have been directly implicated in the abnormal inflammatory response in the airways[13, 14]. However, not all smokers get COPD, so clearly

there are genetic factors which define the 'susceptible smoker'. The best characterised genetic susceptibility factor is homozygous deficiency of α-1 antitrypsin[15] but there are clearly other factors which are poorly understood.

The pathophysiology of COPD involves inflammation of the proximal and peripheral airways and destruction of lung parenchyma with emphysema. The airway damage results in significant physiological derangement with expiratory airflow limitation and abnormal gas exchange[16]. Emphysema contributes to the 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 inflammation is present in smokers before airflow obstruction is evident with pulmonary function tests[17]. Persistent and progressive inflammatory changes in the large and smaller airways are the hallmark of the disease process and once established, these changes persist even in ex-smokers[18]. The pathophysiology of COPD involves inflammation of the proximal and peripheral airways and destruction of lung parenchyma with emphysema[19, 20].The airway damage results in significant physiological derangement with expiratory through destruction of alveolar attachments[21]. Inflammation of peripheral airways contributes to the airflow limitation by increasing the thickness of the airway wall which, together with fibrosis and smooth muscle hypertrophy, may cause airway narrowing. The presence of increased quantities of purulent sputum in the airways also contributes to airflow limitation[22]. Functionally, the decrement of FEV1 is due to both the small airways narrowing and mechanical effects of emphysema while the decrease in gas transfer arises from the parenchymal destruction of emphysema. Whilst the inflammatory changes are present in stable COPD, they become more evident in exacerbations of the disease[23] and recurrent exacerbations can accelerate this process with progressive loss of lung function[24]. Recent data has also demonstrated systemic inflammation is also present in COPD, and there is a strong association of increased cardiopulmonary mortality in COPD patients with exaggerated systemic inflammatory markers[25]. COPD is associated with important comorbidities including cardiac failure, metabolic syndrome and the combination of these co-morbidities combined with a systemic inflammatory response has led to the term of 'chronic systemic inflammatory syndrome' [26].

3. Stages of inflammation in COPD

The precise immunological inflammatory mechanisms in COPD have not been totally elucidated but there is mounting evidence to suggest that there is a cascade of evolutionary events involved in the development of disease. Many of the steps in this cascade are similar to those proposed in other chronic inflammatory diseases[27] such as rheumatoid arthritis, atherogenesis, multiple sclerosis, and systemic lupus erythematosus [28].

On the basis of current evidence, it has been suggested that the immunological inflammatory / repair pathway in COPD comprise of three stages[29].

Stage 1: Initial response to the smoke and noxious stimuli

The constant insult due to inhaled irritants to the airways kick starts both innate and adaptive immunological responses. The innate response is a non-selective response while the adaptive response is more selective to specific antigenic stimulation. The innate response results in a non-specific inflammatory response in the airways and lung parenchyma with recruitment and activation of inflammatory cells such as neutrophils and macrophages[30].

Stage 2: T-cell proliferation

There is migration of dendritic cells to regional lymph nodes with resultant significant proliferation of T-lymphocytes during this phase which results in the expression of pro-inflammatory cytokines and interferon-Y positive T-lymphocytes which has a direct link with disease activity[31]. The role of tissue specific chemokines driving an ongoing inflammatory influx becomes more evident by this time[32].

Stage 3: Adaptive immune response

The adaptive response of immunity is the hallmark of this step which leads to the dominance of CD8+ cytotoxic lymphocytes in all parts of the airways and lung parenchyma[33]. The function of these cells involves apoptosis and eventual tissue destruction[34]. However, the CD4 lymphocytes and B lymphocytes are also found abundantly in the airways of patients with COPD[35, 36].

4. Cellular inflammatory response in COPD

The inflammatory process in COPD occurs due to a persistent airways insult (commonly tobacco smoke exposure) and is characterised by abnormal activation of both the innate and adaptive immune responses of the airway tract. The cells which have been most implicated in the pathogenesis of COPD have been the $CD8^+$ T lymphocyte and the macrophage, however, other cells, in both the innate immune system and the adaptive immune response are also likely to have important roles, including neutrophils, airway epithelial cells, endothelial cells, eosinophil and fibroblasts[37].

Cells involved in inflammation in COPD (innate and adaptive immune response)

CD8+ lymphocytes
Macrophages
Neutrophils
CD4+ lymphocytes
Epithelial cells
Endothelial cells
Eosinophil
Fibroblasts

Cytokines and chemokines of inflammation

Interleukin 8(IL-8)
Tumour necrosis factor (TNF-α)
Interleukin 6(IL-6)
Leukotriene-B4 (LTB4)
GRO alpha (GRO- α)
Interleukin 1(IL-1)

Sampling the airway using induced sputum, has demonstrated an airway neutrophilia in patients with COPD, which is also seen in sputum samples of non-obstructed smokers, but to a lesser extent[38]. Bronchial biopsies demonstrate an infiltration of $CD8^+$ T lymphocytes and recent data suggests reduced apoptosis of these $CD8^+$ cells in the airway, which may explain one of the mechanisms of their persistence in the airway[39]. These $CD8^+$ T lymphocytes infiltrate the lung and pulmonary vasculature and it has been hypothesised that this reflects an underlying auto-immune process specifically that lung

injury in COPD may occur due to an auto-antigen recognised by the CD8 cytotoxic T cells causing airway damage[40, 41]

In the case of emphysema, alveolar macrophages have been implicated and in bronchoalveolar lavage samples, the numbers of activated macrophages are 5 to 10 fold higher than non-obstructed smokers [42]. These macrophages also produce oxidants and pro-inflammatory cytokines and proteases which collectively potentially drive lung parenchymal destruction[43].

Protease / anti-protease imbalance

As a consequence of activated inflammatory cells in the airway and alveolar compartment, proteases including neutrophil elastase, cathepsins and matrix metalloproteinases (MMP) are released and have been implicated in the patho-physiology of COPD[44]. Bronchoalveolar lavage macrophages from patients with emphysema express more MMP-9 and MMP-1 than cells from control subjects, suggesting that these cells, rather than neutrophils, may be the major cellular source of these proteases[45]. The action of the proteases is inhibited by anti-proteases like, α-1antitrypsin (α-AT), α1- anti-chymotrypsin, secretory leukocyte protease inhibitor (SLPI), and tissue inhibitors of metalloproteinases (TIMPs) [46]. A decrease in anti-protease activity is considered as a potential factor in airway wall and parenchymal destruction causing emphysema[47]. However, given that many smokers with airway inflammation do not develop COPD and those who do develop COPD have varying degrees of emphysematous change, the interaction between protease and anti-protease activity is likely to complex and heterogeneous[48].

Cytokine / chemokine response

As a consequence of the abnormal cellular activation in the airway, pro-inflammatory cytokines including interleukin 8 (IL-8) and tumour necrosis factor (TNF-α) are upregulated[49]. Both IL-8 and TNFα promote neutrophil chemotaxis and activation of adhesion molecules. In parallel, a reduction of the anti-inflammatory cytokine IL-10 promotes a pro-inflammatory environment[50]. Many of the pro-inflammatory abnormalities identified in induced sputum and lung biopsies of COPD patients persist even after smoking cessation[51], suggesting that once the inflammatory process has been activated, and removal of the original inciting insult does not stop a progressive process.

In COPD, the inflammatory process is also augmented by the important chemotactic mediators such as leukotriene-B4 (LTB4) and GRO alpha (GRO-α). Both GRO-α and IL8 recruit neutrophils to the airway and IL8, TNF-α and LBT4 are increased in the sputum of COPD patients[52]. Some patients show evidence of eosinophil recruitment to the airway and increased eosinophil basic proteins (eosinophil cationic proteins and eosinophil peroxidase) have been observed in induced sputum of COPD patients. This may reflect 'overlap' syndrome as described above, and sputum eosinophilia has been shown to predict a better response to steroid treatment in COPD[53].

Oxidative stress

Increased oxidative stress has been suggested to be an important piece in the inflammatory jigsaw of chronic obstructive pulmonary disease[54]. Cigarette smoke causes increased oxidative stress[55]. Smoking produces exogenous stress to the epithelial cells of the airways due to the presence of harmful oxidants in the smoke. Endogenous stress occurs due to the inflammatory process[56] provoked by the increased production of alveolar neutrophils and

macrophages and endogenous oxidants like, hydrogen peroxide, ethane, and isoprostane in the exhaled breath condensates from patients with COPD[57].

Oxidative stress may increase mucous secretion, enhance elastase activity and reduce activity of protease inhibitors[58]. Moreover, oxidative stress activates nuclear factor-κB (NF-κB) which increase transcription of important pro-inflammatory genes like, IL-8, Inducible nitric oxide synthase and cyclooxygenase (COX-2) are possible factors[59]. An increase in endothelial dysfunction of peripheral blood vessels together with haemostatic and coagulation markers have also been reported after inhalation of cigarette smoke and particulate matter, again supporting the profound systemic effects of inhaled tobacco smoke[60].

Systemic inflammation in COPD

As well as an inflammatory response in the airways, chronic obstructive pulmonary disease is characterised by systemic inflammation[61]. Evidence exists to support the fact that the systemic inflammation is seen in stable COPD and when there is an exacerbation, systemic inflammatory markers get worse[, 62, 63].

The precise interaction between systemic inflammation and COPD pathogenesis is unclear. In smokers, increased serum levels of CRP relate to a higher risk of developing COPD[64]. As well as CRP, other serum biomarkers are elevated in COPD including fibrinogen, TNF-α, IL-6 and IL-8. In general, acute phase reactants are strongly induced by IL-6 or TNF-alpha cytokines[65]. Higher concentrations of these markers have been observed in the cases of severe COPD[66]. Plasma CRP and fibrinogen are acute phase proteins which are produced in the liver and are released in the bloodstream and fibrinogen is under the control of IL-6. Raised levels are present in the blood of stable COPD patients but significantly higher levels have been described during exacerbation of COPD which strongly suggest its systemic inflammatory link to airway obstruction[67]. This rise of plasma fibrinogen in patients with COPD can be of further clinical importance since it has been implicated in coronary heart disease[68]. An inverse relationship between systemic inflammatory biomarkers and pulmonary function tests (FEV1) has been described, which may be of a diagnostic value and helpful to determine prognosis[69, 70].

The concept of systemic inflammation in COPD is based upon the theory of 'spill-over'[71]. According to this theory, pulmonary inflammation stimulates the haematopoietic system, releasing increased numbers of leucocytes and platelets into the bloodstream[72, 73]. Lung-derived inflammatory cytokines and other mediators circulate in the bloodstream and then cause a systemic inflammatory effect[74]. However whilst systemic inflammation certainly co-exists with lung inflammation, it has not been proven in studies using the surfactant marker-D (SP-D,) that the inflammatory mediators present in the systemic circulation are actually derived from the lung[75].

Obesity and the metabolic syndrome[76] have been identified as risk factors for COPD, but, their relationship with inflammation and COPD needs further explanation[77]. Hormones including adiponectin and most notably leptin may have a role in mediating systemic inflammation. Leptin has effects on adipose tissue and on the hypothalamus to regulate food intake by satiety but it is also a T-cell modulator and influences inflammation. Leptin levels are influenced by IL-6 and lipopolysaccharide[78]. It is profoundly increased in the sputum of COPD patients and correlates with sputum CRP and TNF-α levels[79]. Conversely, it is well known that cachexia in COPD is a marker of increased mortality and may be due to an increase in lipolysis due to persistent inflammation[80]. Half of COPD patients die with

cardiovascular events in hospital and as the role of systemic inflammation in heart disease is proven, the relationship between COPD and ischaemic heart disease may be important[81]. It has been proposed that systemic inflammation in COPD affects the vascular endothelium causing arterial stiffness and atherosclerosis. The presence of increased CRP and circulating leukocytes in patients with COPD and cardiovascular events supports this theory [82]. Many other inflammatory mediators including tissue factor, FVIIa[83], and nitric oxide have been studied to explore involvement of the coagulation system and oxidative stress in causing systemic inflammation in COPD[84, 85].

Osteoporosis and osteopenia are important disease co-morbidities of COPD[86]. Reduced bone density, resulting in fractures in COPD patients is common and increases as the disease progresses[87]. This is very notable in patients with alpha antitrypsin-1 deficiency. A number of studies have suggested that systemic inflammation is implicated in reduced bone density[88, 89]. Bone remodelling due to increased osteoclastic activity may be related to systemic inflammation, skeletal muscle loss and reduced physical activity, poor nutritional status, hypovitaminosis D, nutritional calcium deficiency and glucocorticoid treatment[90, 91].

Comorbidities in COPD

COPD has significant morbidity and mortality[92]. There are multiple extra-pulmonary manifestations, which are related to the disease and other systemic effects[93], such as weight loss, muscle wasting, osteoporosis, cachexia, atherosclerosis and co-morbid associations such as congestive cardiac failure, depression & chronic fatigue, dementia and cancer. More than 50% of deaths among COPD patients are from the cardiovascular causes[94, 95]. Chronic obstructive pulmonary disease progression not only has important physical effects but also has significant psychological morbidity[66]. Depression is common in COPD and correlates with reduced exercise tolerance, muscle weakness and fatigue[97]. Studies have demonstrated that as COPD gets worse, fatigue and depression leads to a decline in quality of life and ultimately a worse prognosis. TNF-α has also been implicated in the depression seen in COPD patients and an association between systemic markers of inflammation and depression whilst modest, is statistically significant, in comparison to the other co-morbidities[98].

5. COPD and related co-morbidities

Lung:

Pneumonia
Lung cancer
Obstructive sleep apnoea

Heart:

Pulmonary hypertension
Cor-pumonale
Coronary heart disease
Congestive cardiac failure

CNS:

Anxiety
Depression
Stroke

Musculo-skeletal:

Peripheral muscle deconditioning
Peripheral muscle wasting
Steroid myopathy
Osteoporosis and bone fractures

Blood and circulation:

Peripheral vascular disease
Normocytic anaemia

Metabolic and endocrine:

Diabetes
Metabolic syndrome

Degenerative:

Cognitive impairment
Parkinson's disease

Miscellaneous:

Arthritis
Glaucoma
Bowel and prostate cancer

In summary, there is a consensus now that both airway and systemic inflammation play a key role in the pathogenesis of chronic obstructive pulmonary disease[99, 100, 101]. The underlying mechanisms and interactions are likely to be complex and need better description which is an important future research goal[102].

6. Current treatment of COPD

Whilst COPD is a complex disease, current treatments are largely symptomatic and do not significantly alter the natural disease progression[103]. Many countries have formulated their own guidelines and most national and international respiratory societies have taken initiatives to provide training and knowledge to their professionals and act as patient advocates[104].

Conventionally, COPD is treated with both pharmacological and non-pharmacological interventions[105, 106]. Smoking cessation, regular exercise, adequate nutritional support, weight reduction and pulmonary rehabilitation are the important non-pharmacological treatment modalities[107]. Bronchodilators, anti-cholinergic, thioxanthines, steroids and antibiotics for bacterial exacerbation and oxygen therapy are the medical therapeutic options[108]. Smoking cessation and long term home oxygen[109] are the only two treatments which have been demonstrated to improve mortality[110]. The remaining treatments provide symptom control and some improvement in quality of life[111]. Short and long acting beta adrenoceptor agonists have been the gold standard of airways disease in COPD and asthma, and in COPD[112] there has been a move to the earlier introduction of long-acting bronchodilators, and it is probable that multiple combinations of long-acting bronchodilator therapies will become available[113].

Treatment of inflammation in COPD

The concept of targeting inflammation to treat COPD has largely been neglected until relatively recently[114]The mainstay of current anti-inflammatory therapy is steroid therapy,

however it is now recognised that these drugs have a minimal effect in established COPD[115]. As stated above, there is a pressing need for a better understanding of the key patho-physiological mechanisms in this disease to allow more targeted therapy.

Steroids

A number of clinical trials in COPD demonstrated that high dose inhaled steroid treatment had no effect in disease progression, measured by progressive loss of FEV1, however there was some improvement in disease specific quality of life[116]. Inhaled steroids reduce exacerbations in COPD and this has been demonstrated in a number of studies examining long-acting β-agonists / inhaled steroid combination therapies[117]. Despite, the predominant neutrophilic and lymphocytic involvement of cells in the pathogenesis of COPD, the presence of some eosinophils[118] in the airways of such patient have provoked a great interest in the non-invasive, easy and reproducible measurement of biomarkers such as the of fractional exhaled nitric oxide (FENO) to identify patients who may respond better to steroid therapy[119, 120]however FeNO is reduced by smoking

Phosphodiesterase 4 (PDE4) inhibitors

There are other therapies which have been investigated to target inflammation in COPD[121]. Roflumilast is the first selective PDE4 inhibitor which has recently been licensed for COPD in Europe and America. It has been advocated in subjects with frequent exacerbations and symptomatic severe COPD patients with productive cough[122]. Roflumilast is an oral preparation which inhibits pulmonary inflammation through the selective inhibition of the iso-enzyme PDE4, which hydrolyses cyclic AMP[123], which is expressed in structural cells of the lung such as, smooth muscle cells, airway epithelium and inflammatory cells such as neutrophils, lymphocytes or macrophages[124]. Despite the concerns regarding dose dependant side effects such as headache, nausea and diarrhoea[125], it may offer some benefit in COPD patients with frequent exacerbations. Recent data have demonstrated that the use of roflumilast decreased the exacerbations and the need for adjuvant steroid therapy. Its use showed improvement in pulmonary function tests and when compared with the placebo, it showed improvement in functional capacity[126, 127]. Further longitudinal studies are warranted to measure the real benefit and effectiveness. However the clinical use of roflumilast has been encouraging so far in reducing exacerbations and improving lung function[128].

Novel treatment strategies for COPD

With better understanding of the pathophysiology of COPD disease process and recognition of inflammation as an important feature, it is anticipated that disease modifying therapy for COPD[129] targeting pulmonary and systemic inflammation, will prove effective. There are a number of specific therapeutic targets against the influx of inflammatory cells into the lung[130]. including inhibitors of p38 mitogen-activated protein kinase (MAPK), nuclear factor-κB (NF-κB), and phosphoinositide-3-kinase (PI3K) [131]. There is also a search for inhibitors of proteinases and matrix metalloproteinases (MMPs) which could prevent lung destruction and emphysema. The immunomodulatory role of macrolides is also one of the potential novel treatments for COPD[132].

Cytokines and chemokines inhibitors

TNF-α TNF-α plays a key role in COPD and acts as a catalyst for chemokine interleukin-8 (IL-8). Infliximab is a monoclonal antibody which neutralizes TNF-α by binding it. Its role

has been evaluated in COPD[133] but its use has failed to show any change in sputum neutrophils, FEV1, FEV1/FVC or IL-6[134]. There is also significant toxicity and cost issues and further attempts to use it in COPD have been halted[135].

Antibody against human IL-8

A fully humanised monoclonal IgG_2 antibody directed against human IL-8 (ABX-IL8) blocks binding to IL-8 receptors on neutrophils and neutralizes IL-8–mediated neutrophil activation *in vitro*[136]. It has been shown that pretreatment of sputum supernatant of 20 patients with COPD with an anti–IL-8 antibody led to a concentration-dependent inhibition of neutrophil chemotaxis. Moreover, ABX-IL8 is proposed to block IL-8–induced neutrophil activation and degranulation, preventing release of neutrophil elastase[137].However in a clinical trial, whilst well tolerated and shown to be beneficial in reducing dyspnoea, there was no real added benefits were noted in secondary outcomes (lung function, health status and inflammatory markers) [138].

CXCL1, CXCL8 receptor antagonists

CXCL1 (GRO-α) is produced by structural and inflammatory cells and is chemotactic for neutrophils[139]. Using agents which are CXCL1 and CXCL8 (IL8) receptor antagonists blocks the neutrophilic inflammatory response in the lungs and may help to control COPD[140] and clinical trial data is awaited

CCL2 (MCP-1) and CCR2 antagonists

Bronchoalveolar lavage from patients with COPD contains increased MCP-1 (CCL2) in comparison to healthy non-smokers[141] and it has also been postulated that in COPD, the MCP-1 receptor, CCR2, shows increased expression. These findings relate to disease severity and FEV1. Therefore targeting of CCL2 and its receptor could provide potentially potent and novel anti-inflammatory agents[142]. The study of such products in humans is in the early phase and clinical preparations are probably a long way off currently[143].

5-Leukotriene B_4 / Lipoxygenase inhibitors

Leukotriene B_4 (LTB_4), a pro-inflammatory derivative of arachidonic acid, is both a chemoattractant and activator of neutrophils and may be important in COPD[144]. LTB4 is synthesized by neutrophils and alveolar macrophages, where the conversion of arachidonic acid to the intermediate compound 5-hydroperoxyeicosatetraenoic acid requires both the enzyme 5-lipoxygenase (5-LO) and 5-lipoxygenase activating protein (FLAP). In a preliminary double-blind, randomized, placebo-controlled trial the effects of the FLAP antagonist, BAYx1005, on sputum LTB4 and myeloperoxidase (a marker of sputum neutrophil number and activation) concentrations, and on the chemotactic activity of the secretions in patients with COPD and chronic bronchitis was studied[145]. A modest but significant reduction in sputum LTB4 concentrations in the patients in this trial was observed. However, the reductions in LTB4 concentration were comparable in magnitude to those seen during the resolution of purulent exacerbations of chronic bronchitis. This study have established that a leukotriene synthesis inhibitor may affect neutrophilic bronchial inflammation in patients with stable COPD and chronic bronchitis, and that this class of drug merits further investigation in a larger number of patients. Another Possible way to inhibit leukotriene synthesis pathway is to target is 5-lipoxygenase inhibition[146]. The potential clinical benefits of both of these approaches remain under investigation[147].

Anti-oxidants including N-Acetylcysteine

N-Acetylcysteine is an anti-oxidant which is most commonly used in paracetamol overdose. It targets oxidative stress and causes activation of anti-proteases and reduces expression of IL-8 and TNF-α [148]. Recent data demonstrated an improvement in vital capacity and inspiratory capacity of patients with COPD in an ICU setting[149]. NAC treatment of patients with stable, moderate-to-severe COPD has a beneficial effect on physical performance, probably due to a reduction in air trapping[150] NAC probably exhibits an anti-inflammatory effect by influencing neutrophils and macrophage function[151].

p38 mitogen-activated protein kinase (MAPK) inhibitors

p38 MAPK inhibitors are another novel drug strategy proposed for targeting inflammation in COPD[152]. The p38 MAPK pathway is activated by stress and it regulates a wide variety of inflammatory cytokines including IL-8, TNF-α and MMPs[153]. Corticosteroids partially suppress cytokine production by COPD alveolar macrophages [154, 155] but p38 MAPK activation in alveolar macrophages is corticosteroid insensitive. One study investigated the dose-sparing and efficacy-enhancing effects of combined treatment with a corticosteroid and a p38 MAPK inhibitor, and showed the combination synergistically enhances the anti-inflammatory effects on cytokine production by alveolar macrophages in COPD patients and controls[156]. Another study has demonstrated that SB-681323 is a potent p38 MAPK inhibitor that potentially suppresses inflammation in COPD[157]. But further clinical trials with this class of molecule are starting and are eagerly awaited.

Nuclear factor-κB (NF-κB) inhibitors

Nuclear factor-κB (NF-κB) has been implicated in inflammation in COPD by causing propagation of cytokines and neutrophils[158]. Therefore, this pathway has been targeted to overcome inflammation and airways injury in COPD patients. One approach is to inhibit the IκB kinase (IKK) using glucocorticoids, such as dexamethasone or prednisolone which downregulates the pro-inflammation[159]. Experiments have also been performed using resveratrol, one of the flavonoids naturally occurring in red wine. It inhibits this pathway of inflammation[160] however, there is no evidence of clinical benefit currently.

Phosphoinositide 3-kinases (PI3K) inhibitors

The components of the PI3K pathway play a crucial role in the expression and activation of inflammatory mediators, inflammatory cell recruitment, immune cell function, airway remodelling and corticosteroid insensitivity in COPD and asthma[161].Targeting this pathway has a potential therapeutic role and this may be one of the actions of theophylline[652] The idea for development of PI3K inhibitors would be to ensure greater efficacy in severe steroid-insensitive asthma and COPD where corticosteroids are of limited[163] with a better side effect profile.

7. Anti-proteinases

Neutrophil elastase inhibitors

For nearly two decades, there has been a pursuit to find safe oral inhibitors of neutrophil elastase. Many of the compounds developed have had poor pharmacokinetics and a low therapeutic index. Tripeptidyl trifluoromethyl ketones were the first developed with an improved profile but they have not been fully optimized for oral use yet[164]. Targeting

neutrophil elastase may be very useful in COPD since it can cause direct activation of MMPs such as MMP-9, which play a crucial role in airway inflammation[165]. Recent work on the relatively newer compounds like Sivelestat sodium hydrate has not proved to be very encouraging[166].

Matrix metalloproteinases (MMPs) inhibitors

MMPs are a major class of proteolytic enzymes potentially involved in COPD. Bronchoalveolar lavage of patients with emphysema shows high levels of MMP-1 and MMP-9[167]. Drugs such as BMS-561392 and gw3333 which could inhibit the MMPs and TNF-α are in the pre-clinical stage. Their development and potential efficacy in targeting inflammation in COPD has yet to be established[168].

HDAC modifiers

There are 11 classic human HDACs that regulate histone acetylatio[169]. HDAC2 is involved in suppression of NF-κB–mediated inflammatory gene expression by corticosteroids[170] and HDAC2 mRNA and protein expression is significantly reduced in tissue specimens of the peripheral lung and in alveolar macrophages from patients with COPD[171]. This speculated link may have therapeutic implications, because reductions in HDAC activity may be reversible. Theophylline is an activator of HDAC157, and there is evidence to suggest that low concentrations of theophylline completely restore HDAC activity in alveolar macrophages from patients with COPD, with reduced production of inflammatory cytokines and restoration of responsiveness to corticosteroids[172]. It has been reported that theophylline[173] and PI3K inhibitor (LY294002) have a similar effect in lung macrophage cells, increasing HDAC2 expression and re-sensitizing the cells to steroids. Whether this is a mechanism of the therapeutic action of theophylline in COPD is not known.

Macrolides

The hallmark of COPD is the airways inflammation which is primarily neutrophilic in nature and low grade neutrophilic inflammation is often persistent[174]. Treatment with macrolides has been shown to reduce the number of neutrophils and the levels of interleukin-8 (IL-8) protein in bronchoalveolar lavage fluid in COPD[175]. The mechanisms by which macrolides exert a beneficial effect on chronic inflammatory airway disease are thought to be independent of their antibiotic effects but rather due their anti-inflammatory effects[176], through reducing lower airway bacterial colonization may also be beneficial[177] Macrolides in COPD decrease neutrophil counts and inflammatory markers and reduce the number of exacerbations[178]. The role of regular macrolides in COPD[179] needs to be defined more clearly, and there remain concerns about widespread use of these drugs particularly with regard to antibiotic resistance and superadded infections like MRSA and C.difficile[180].

Non-pharmacological treatments – novel strategies

Non-pharmacological treatments will remain important in the future management of COPD and will continue to involve more integrated care[181]. There is compelling evidence of the role of systemic inflammation in decreasing muscle mass, weakness and loss of function in COPD patients[182]and tests to detect early markers of muscle involvement may be clinically beneficial to target patients of greatest risk of losing muscle mass with early rehabilitation interventions[183]. Targeting patients with multiple co-morbidities and provision of early pulmonary rehabilitation and physiotherapy can have a major impact on improving morbidity and decreasing mortality[184]. Identifying which smokers are at risk of

development of COPD and which patients will develop more progressive disease may also be important advances in the future[185, 186, 187].

8. Summary

Chronic obstructive pulmonary disease (COPD) is a disease characterized by poorly reversible airflow limitation which is usually progressive and associated with an abnormal inflammatory response in the lung. Cigarette smoking is the major risk factor responsible for the development of COPD, however other environmental exposures, such as combustion of biomass fuels, are major causes in certain countries. A decade since the introduction of the Global strategy for the diagnosis, management and prevention of Obstructive pulmonary Disease (GOLD), the incidence of COPD continues to rise and the World Health Organisation and the World Bank predict that by the 2020, it will be the third leading cause of mortality in the world.

The term chronic obstructive pulmonary disease is a descriptive term encompassing a heterogeneous subset of clinical syndromes, specifically chronic bronchitis, emphysema and asthma and it is now recognised that there is significant overlap between the previously described clinical syndromes. The term 'overlap syndrome' is often used to describe a patient with fixed airflow obstruction (COPD), but having some asthmatic features. Chronic bronchitis is clinically defined as a cough productive of sputum lasting at least three months for two consecutive years and emphysema is a pathological entity characterised by destruction of the lung parenchyma with resultant enlarged alveolar spaces and loss of alveolar walls.

The patho-physiology of COPD involves inflammation of the proximal and peripheral airways and destruction of lung parenchyma with emphysema. The airway damage results in significant physiological derangement with expiratory airflow limitation and abnormal gas exchange. Emphysema contributes to the 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. Inflammation of peripheral airways contributes to the airflow limitation by increasing the thickness of the airway wall which, together with fibrosis and smooth muscle hypertrophy, may cause airway narrowing.

The inflammatory process in COPD usually starts with a persistent airways insult (commonly tobacco smoke exposure) which leads to abnormal activation of both the innate and adaptive immune responses of the airway tract. Pathologically, epithelial squamous cell metaplasia, goblet cell hyperplasia, parenchymal destruction (emphysema) and small airway are all consequences of this persistent inflammatory environment. Both, innate and adaptive immune responses are involved in the inflammatory process in COPD. There is evidence that airways inflammation is present in smokers before airflow obstruction is evident with pulmonary function tests. The cells which have been mostly implicated in this inflammatory process $CD8^+$ T lymphocytes and macrophages which through the production of LTB4, TNF-α, IL-8, GRO-α recruit neutrophils to the airway, with resultant injury. Increased neutrophils are seen in bronchoalveolar lavage and induced sputum of the patients with COPD compared to smokers without airflow obstruction. Neutrophil myeloperoxidase and human neutrophil lectin are also elevated consistent with neutrophil activation and degranulation. Some patients show evidence of eosinophil recruitment to the airway and increased eosinophil basic proteins (eosinophil cationic proteins and eosinophil peroxidase) have been observed in induced sputum of COPD patients. This may reflect 'overlap' syndrome as described above, and sputum eosinophilia has been shown to predict

a better response to steroid treatment in COPD. Exacerbations are significant events in patients with COPD as they cause increased breathlessness and purulent sputum production. In patients with frequent exacerbations, there is accelerated lung function decline, as a consequence of augmented inflammation and injury during exacerbations.

Bronchial biopsies in COPD have shown infiltration of mononuclear cells and $CD8^+$ T lymphocytes. Macrophages are activated by cigarette smoke and other inhaled irritants and may play an important role in driving the inflammatory process in COPD through the release of neutrophil chemotactic factors as well as proteolytic enzymes. More recently, it has been suggested that COPD may represent an 'auto-immune' disease, with failure to regulate the adaptive response to auto-antigens produced as a consequence of tobacco smoke exposure. A subtype of regulatory CD4+ T-cells expressing CD25 (Tregs) are upregulated in COPD, which supports an auto-immune aetiology.

Protease / anti-protease imbalance excessive oxidative stress have also been linked to progressive airway injury in COPD. Neutrophil elastase, cathepsins and matrix metalloproteinases have all been implicated in the patho-physiology of COPD. Bronchoalveolar lavage macrophages from patients with emphysema express more MMP-9 and MMP-1 than cells from control subjects in COPD, suggesting that these cells, rather than neutrophils, may be the major cellular source. There is also evidence for increased oxidative stress in COPD, evidenced by an increase in oxidized or nitrated proteins and peroxidised polyunsaturated fatty acids and their degradation products. Increase in endothelial dysfunction of peripheral blood vessels together with haemostatic and coagulation markers have also been reported after inhalation of cigarette smoke and particulate matter, again supporting the profound systemic effects of inhaled tobacco smoke.

There is growing evidence to suggest that as well as an inflammatory response in the airways, chronic obstructive pulmonary disease is characterised by systemic inflammation. Recent evidence has demonstrated systemic 'spill-over' of this pulmonary inflammation with evidence of elevated systemic inflammatory markers, pro-inflammatory cytokines and lipopolysaccharide binding protein.

Systemic manifestations of COPD may significantly affect patients' quality of life and prognosis of the disease. It has been well recognised that systemic effects may be related to systemic inflammation in COPD. COPD is associated with cachexia, weight loss, osteoporosis, muscle wasting, heart failure, atherosclerosis, dementia, depression, and cancer and these extra- pulmonary manifestations of COPD account for much of the morbidity and mortality in COPD patients. Depression is also a major co-morbidity in COPD and patients with more systemic inflammation as well as more depression or fatigue have been shown to be less physically active and more exercise intolerant. There is evidence to suggest that certain age related conditions like, arthritis, Parkinson's disease and cancer of the prostate and bowel have links with COPD. The risk of developing arthritis, anaemia and glaucoma increases in COPD patients with growing age.

Current anti-inflammatory therapies, particularly steroid therapy, have a minimal effect in established COPD. There is a significant need for a better understanding of the key patho-physiological mechanisms in this disease to allow more targeted therapy. Novel pharmacological strategies are still in the developmental stage. Cytokine and chemokine inhibitors, for example antibodies against human IL-8, CXCL1, CXCL8 antagonists, CCL2, CCR2, lipoxygenase and LB4 inhibitors have shown some promise but there remain issues around safety and efficacy and cost effectiveness. The role of anti-oxidants, MAPK-inhibitors and PI3k inhibitors is still under investigation. The use of macrolides has been the focus of recent attention and recent data has suggested a role in exacerbation prevention.

9. References

[1] Celli BR, MacNee W, ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004; 23: 932- 946

[2] Willemse BWM, Postma DS, Timens W, Ten Hacken NHT: The impact of smoking cessation on respiratory symptoms, lung function, airway hyperresponsiveness and inflammation. *Eur Respir J* 2004; 23:464-476

[3] Govender N, U G Lalloo, Naidoo R N. Occupational exposures and chronic obstructive pulmonary disease: a hospital based case-control study. *Thorax* 2011; 66: 597e601

[4] Singh D, Fox S M, Singer R T, Plumb J, Bates S, Broad P, Riley J H,Celli B. Induced sputum genes associated with spirometric and radiological disease severity in COPD ex-smokers. *Thorax* 2011; 66: 489-495

[5] Gibson, PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it? *Thorax* 2009 Aug; 64: 728-35

[6] Puente-Maestu L, Stringer W W. Hyperinflation and its management in COPD. *Int J Chron Obstruct Pulmon Dis* 2006; 1: 38-400

[7] Connolly MJ, Lowe D, Anstey K, et al. Admissions to hospital with exacerbations of chronic obstructive pulmonary disease: effect of age related factors and service organisation. *Thorax* 2006; 61: 843e8

[8] Groarke JD, Gallagher J, Stack J, et al. Use of an admission early warning score to predict patient morbidity and mortality and treatment success. *Emerg Med J* 2008; 25: 803e6

[9] Heitz CR, Gaillard JP, Blumstein H, et al. Performance of the maximum modified early warning score to predict the need for higher care utilization among admitted emergency department patients. *J Hosp Med* 2010; 5: E46e52

[10] Mitchell IA, McKay H, Van Leuvan C, et al. A prospective controlled trial of the effect of a multi-faceted intervention on early recognition and intervention in deteriorating hospital patients. *Resuscitation* 2010; 81: 658e66

[11] Pauwels RA, Rabe KF, Burdon and clinical features of chronic obstructive pulmonary disease (COPD). *Lancet* 2004; 364: 613-620

[12] Rabe K, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2007; 176: 532-55

[13] Peacock J L, Anderson H R, Bremner S A, Marston L, Seemungal T A, Strachan D P, Wedzicha J A. Outdoor air pollution and respiratory health in patients with COPD. *Thorax* 2011; 66: 591e596

[14] Po JY, FitzGerald JM, Carlsten C. Respiratory disease associated with solid biomass fuel exposure in rural women and children: systematic review and meta-analysis. *Thorax* 2011; 66: 232-9

[15] Denden S, Khelil A H, Knani J, Lakhdar R, Perrin P, Lefranc G, Chibani J B. Alpha-1 antitrypsin gene polymorphism in Chronic Obstructive Pulmonary Disease (COPD) *Genet Mol Biol* 2010; 33(1): 23-26

[16] Rodríguez-Roisin R, Drakulovic M, Rodríguez DA, Roca J, Barberà JA, Wagner PD. Ventilation-perfusion imbalance and chronic obstructive pulmonary disease staging severity. *J Appl Physiol* 2009 Jun; 106: 1902-8

[17] Anthonisen NR, Connett JE, Murray RP. Smoking and lung function of Lung Health Study participants after 11 years. *Am J Respir Crit Care Med* 2002 ;16: 675-679

[18] Rutgers SR, Postma DS, ten Hacken NH, et al. ongoing airway inflammation in patients with COPD who do not currently smoke. *Thorax* 2000; 55: 12-18

[19] Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350:2645–2653

[20] Hurst JR, Wilkinson TMA, Perera WR, Donaldson GC, Wedzicha JA. Relationships among bacteria, upper airway, lower airway, and systemic inflammation in COPD. *Chest* 2005; 127: 1219-1226

[21] Lindberg A, Jonsson AC, Ronmark E, Lundgren R, Larsson LG, Lundback B: Prevalence of chronic obstructive pulmonary disease according to BTS, ERS, GOLD and ATS criteria in relation to doctor's diagnosis, symptoms, age, gender, and smoking habits. *Respiration* 2005; 72: 471-9

[22] Vestbo J, Prescott E, Lange P, and the Copenhagen City Heart Study Group. Association of chronic mucus hypersecretion with FEV1 decline and chronic obstructive pulmonary disease morbidity. *Am J Respir Crit Care Med* 1996; 153: 1530-1535

[23] Hurst JR, Perera WR, Wilkinson TM, Donaldson GC, Wedzicha JA. Exacerbation of chronic obstructive pulmonary disease: pan-airway and systemic inflammatory indices. *Proc Am Thorac Soc* 2006 Aug; 3: 481-2

[24] Donaldson GC, Seemungal TAR, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002; 57: 847-852

[25] Marquis K, Maltais F, Duguay V et al. "The metabolic syndrome in patients with chronic obstructive pulmonary disease" *Journal of Cardiopulmonary Rehabilitation* 2005; 25: 226- 232

[26] Fabbri L M, K F Rabe. From COPD to chronic systemic inflammatory syndrome? *Lancet* 2007; 370: 797-99

[27] Rose N, Afanasyeva M. Autoimmunity: busting the atherosclerotic plaque. Nat *Med* 2003; 9: 641-2

[28] Steinman L. State of the art: four easy pieces: interconnections between tissue injury, intermediary metabolism, autoimmunity and chronic degeneration. *Proc Am Thorac Soc* 2006; 3: 484-6

[29] Cosio MG, Saetta M, Agusti A. Immunologic aspects of chronic obstructive pulmonary disease. *N Engl J Med* 2009; 360: 2445-54

[30] Barnes PJ, Cosio MG. Cells and mediators of chronic obstructive pulmonary disease. *Eur Respir Monogr* 2006; 38: 130-58

[31] Di Stefano A, Caramori G, Capelli A, et al. STAT4 activation in smokers and patients with chronic obstructive pulmonary disease. *Eur Respir J* 2004; 24: 78-85

[32] Freeman CM, Curtis JL, Chensue SW. CC chemokine receptor 5 and CXC chemokine receptor 6 expression by lung CD8+ cells correlates with chronic obstructive pulmonary disease severity. *AmJ Pathol* 2007; 171: 767-76

[33] Retamales I, Elliott WM, Meshi B, et al. Amplification of inflammation in emphysema and its association with latent adenoviral infection. *Am J Respir Crit Care Med* 2001; 164: 469-73

[34] Calabrese F, Giacometti C, Beghe B, et al. Marked alveolar apoptosis/proliferation imbalance in end-stage emphysema. *Respir Res* 2005; 6: 14

[35] Turato G, Zuin R, Miniati M, et al. Airway inflammation in severe chronic obstructive pulmonary disease: relationship with lung function and radiologic emphysema. *Am J Respir Crit Care Med* 2002; 166: 105-10

[36] van der Strate BW, Postma DS, Brandsma CA, et al. Cigarette smoke-induce emphysema: a role for the B cell? *Am J Respir Crit Care Med* 2006; 173: 751-8

[37] Barnes PJ, Shapiro SD, Pauwels RA: Chronic obstructive pulmonary disease: molecular and cellular mechanisms. *Eur Respir J* 2003; 22:672-688

[38] Cowburn AS, Condliffe AM, Farahi N, Summers C, Chilvers ER. Advances in neutrophil biology: clinical implications. *Chest* 2008; 134: 606-12

[39] Siena L, Gjomarkaj M, Elliot J, Pace E, Bruno A, Baraldo S, Saetta M, Bonsignore MR, James A. Reduced apoptosis of CD8+ T-Lymphocytes in the airways of smokers with mild/moderate COPD. *Respir Med* 2011 May 23: (Epub)

[40] Agustí A, MacNee, W, Donaldson, K, Cosio, M. Hypothesis: Does COPD Have an autoimmune component? *Thorax.* 2003; 58: 832-834

[41] Saetta M, Turato G, Maestrelli P, Mapp CE, and Fabbri LM. Cellular and structural bases of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2001; 163: 1304-1309

[42] Cowburn AS, Condliffe AM, Farahi N, Summers C, Chilvers ER: Advances In neutrophil biology: clinical implications. *Chest* 2008; 134:606-12

[43] Barnes P J. Mediators of Chronic Obstructive Pulmonary Disease. *Pharmacol Rev* 2004; 56:515-548

[44] Stockley RA. Proteases and antiproteases. *Novartis Found Symp* 2001; 234: 189-199

[45] Belvisi MG, Bottomley KM. The role of matrix metalloproteinases (MMPs) in the pathophysiology of chronic obstructive pulmonary disease (COPD): a therapeutic role for inhibitors of MMPs. *Inflamm Res* 2003; 52: 95-100

[46] Chapman HA Jr. Shi GP. Protease injury in the development of COPD. Thomas A Neill lecture. *Chest* 2000; 117: 2955-95

[47] Turino G M. The origins of a concept: the protease antiprotease imbalance hypothesis. *Chest* 2002; 122: 1058-1060

[48] Betsuyaku T, Takeyabu K, Tanino M, Nishimura M. Role of secretory leukocyte protease inhibitor in the development of subclinical emphysema. *Eur Respir J* 2002; 19: 1051-1057

[49] Hurst J R, Perera W R, Wilkinson T M A, Donaldson G C, Wedzicha J A. Systemic and Upper and Lower Airway Inflammation at Exacerbation of Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2006; 173: 71-78

[50] Barnes PJ. Emerging targets for COPD therapy. *Curr Drug Targets Inflamm Allergy* 2005; 4: 675-83

[51] Saetta M, Turato G, Maestrelli P, Mapp CE, Fabbri LM. Cellular and structural bases of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2001; 163: 1304-1309

[52] Chung KF. Cytokines as targets in chronic obstructive pulmonary disease. *Curr Drug Targets* 2006; 7: 675-81

[53] Balzano G, Stefanelli F, Iorio C, et al. Eosinophilic inflammation in stable chronic obstructive pulmonary disease. Relationship with neutrophils and airway function. *Am J Respir Crit Care Med* 1999; 160: 1486-1492

[54] Kirkham PA, Caramori G, Casolari P, Papi A, Edwards M, Shamji B, Triantaphyllopoulos K, Hussain F, Pinart M, Khan Y, Heinemann L, Stevens L, Yeadon M, Barnes PJ, Chung KF, Adcock IM. Oxidative Stress-induced Antibodies to Carbonyl-modified Protein Correlate with Severity of COPD. *Am J Respir Crit Care Med* 2011 Jun 16 (Epub ahead of print)

[55] Lin JL, Thomas PS. Current perspectives of oxidative stress and its measurement in chronic obstructive pulmonarydisease. *COPD* 2010; 7: 291-306

[56] Bowler RP, Barnes PJ, Crapo JD. The role of oxidative stress in chronic obstructive pulmonary disease. *COPD* 2004; 1: 255-77

[57] Montuschi P, Collins JV, Ciabattoni G, Lazzeri N, Corradi M, Kharitonov SA, and Barnes PJ. Exhaled 8-isoprostane as an in vivo biomarker of lung oxidative stress in patients with COPD and healthy smokers. *Am J Respir Crit Care Med* 2000; 162: *Care Med* 162: 1175- 1177-Cavalcante AG, de Bruin PF. The role of oxidative stress in COPD: current concepts and perspectives. *J Bras Pneumol* 2009; 35: 1227-37

[58] Rahman I, Adcock M.Oxidative stress and redox regulation of lung inflammation in COPD. *Eur Respir J* 2006; 28: 219–242

[59] Sabit R, Thomas P, Shale D J, Collins P, Linnane S J. The effects of hypoxia on markers of coagulation and systemic inflammation in patients with COPD. *Chest* 2010; 138: 47-5161-Siafakas NM. "In the Beginning" of COPD: is evolution important? *Am J Respir Crit Care Med* 2007; 175: 423-4

[60] Taylor DR. Risk assessment in asthma and COPD: a potential role for biomarkers? *Thorax* 2009; 64: 261-4

[61] Vernooy JH, Kucukaycan M, Jacobs JA, Chavannes NH, Buurman WA, Dentener MA, Wouters EF: Local and systemic inflammation in patients with chronic obstructive pulmonary disease: soluble tumor necrosis factor receptors are increased in sputum. *Am J Respir Crit Care Med* 2002; 166: 1218-1224

[62] Tonstad S, Cowan J L. C-reactive protein as a predictor of disease in smokers: a review. Int J clin pract 2009; 63:1550-3

[63] Polatli M, Cakir A, Cildag O, Bolaman AZ, Yenisey C, Yenicerioglu Y. Microalbuminuria, von Willebrand factor and fibrinogen levels as markers of the severity in COPD exacerbation. *J Thromb Thrombolysis* 2007; 26: 97-102

[64] Higashimoto Y, Iwata T, Okada M, Satoh H, Fukuda K, Tohda Y. Serum biomarkers as predictors of lung function decline in chronic obstructive pulmonary disease. *Respir Med* 2009; 103: 1231-8

[65] Chung KF, Adcock IM Multifaceted mechanisms in COPD: inflammation, immunity, and tissue repair and destruction. *Eur Respir J* 2008; 31: 1334-56

[66] MacCallum PK. Markers of hemostasis and systemic inflammation in heart disease and atherosclerosis in smokers. *Proc Am Thorac Soc* 2005; 2: 34-43

[67] Donaldson G C, Seemungal TAR, Patel IS, Bhowmik A, Wilkinson TMA, Hurst JR, MacCallum PK, Wedzicha JA. Airway and Systemic Inflammation and decline in Lung Function in Patients With COPD. *Chest* 2005; 128: 1995-2004

[68] Gan WQ, Man SF, Senthilselvan A, Sin DD: Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax* 2004, 59:574-80

[69] Wouters EF, Reynaert NL, Dentener MA, Vernooy JH. Systemic and local inflammation in asthma and chronic obstructive pulmonary disease: is there a connection? *Proc Am Thoacic Soc* 2009; 6: 638-47

[70] Wouters EF. Local and systemic inflammation in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2005; 2: 26-33

[71] Han MK. Update in chronic obstructive pulmonary disease in 2010. *Am J Respir Crit Care Med* 2011; 183: 1311-5

[72] Barnes PJ. The cytokine network in chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol* 2009; 41: 631-8

[73] Lomas DA, Silverman EK, Edwards LD, Locantore NW, Miller BE, Horstman DH, Tal-Singer R. Serum surfactant protein D is steroid sensitive and associated with exacerbations of COPD. *Eur Respir J* 2009; 34: 95-102

[74] Hajer GR, van Haeften TW, Visseren FL. Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. *Eur Heart J* 2008; 29: 2959-2971

[75] Sood A. Obesity, adipokines, and lung disease. *J Appl Physiol* 2010; 108: 744-53

[76] Faggioni R, Feingold KR, Grunfeld C. Leptin regulation of the immune response and the immunodeficiency of malnutrition. *FASEB J* 2001; 15: 2565-2571

[77] Broekhuizen R, Vernooy JH, Schols AM, Dentener MA, Wouters EF. Leptin as local inflammatory marker in COPD. *Respir Med* 2005; 99: 70-4

[78] Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350: 1005e12

[79] Ramaraj R. COPD in smokers with atherosclerosis: are we missing the trail? *Am J Respir Crit Care Med* 2009; 179: 35-40

[80] Ross R. Atherosclerosis-an inflammatory disease. *N Engl J Med* 1999; 340: 115-26

[81] Borensztajn KS, von der Thüsen JH, Spek CA. The role of coagulation in chronic inflammatory disorders: a jack of all trades. *Curr Pharm Des* 2011; 17: 9-16

[82] Maestrelli P, Paska A, Saetta M, Turato G, Nowicki Y, Monti S, Formichi B, Miniati M, and Fabbri LM. Decreased haem oxygenase-1 and increased inducible nitric oxide synthase in the lung of severe COPD patients. *Eur Respir J* 2003; 21: 971-976

[83] Agusti AG, Villaverde JM, Togores B, and Bosch M Serial measurements of exhaled nitric oxide during exacerbations of chronic obstructive pulmonary disease. *Eur Respir J* 1999; 14: 523-528

[84] Jorgensen NR, Schwarz P, Holme I, Henriksen BM, Petersen LJ, Backer V. The prevalence of osteoporosis in patients with chronic obstructive pulmonary disease: a cross sectional study. *Respir Med* 2007; 101: 177-185

[85] Vrieze A, de Greef MH, Wijkstra PJ, Wempe JB. Low bone mineral density in COPD patients related to worse lung function, low weight and decreased fat-free mass. *Osteoporos Int* 2007; 18: 1197-1202

[86] Tanaka Y, Nakayamada S, Okada Y. Osteoblasts and osteoclasts in bone remodeling and inflammation. *Curr Drug Targets Inflamm Allergy* 2005; 4: 325-8

[87] Lacativa PG, Farias ML. Osteoporosis and inflammation. *Arq Bras Endocrinol Metabol* 2010; 54: 123-32

[88] Ebeling PR. Clinical practice. Osteoporosis in men. *N Engl J Med* 2008; 358:1474-1482

[89] Lam J, Takeshita S, Barker JE, Kanagawa O, Ross FP, Teitelbaum SL. TNF-α induces osteoclastogenesis by direct stimulation of macrophages exposed to permissive levels of RANK ligand. *J Clin Invest* 2000; 106: 1481-1488

[90] Barnes P J, Celli B R. Systemic manifestations and comorbidities of COPD. *Eur Respir J* 2009; 33: 1165–1185

[91] Spencer S, Calverley PM, Sherwood BP, Jones PW: Health status deterioration in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163: 122- 128

[92] Feary JR, Rodrigues LC, Smith CJ, Hubbard RB, Gibson JE. Prevalence of Major Comorbidities in Subjects with COPD and Incidence of Myocardial Infarction and Stroke *Thorax* 2010; 65: 956-962

[93] Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta analyses of prospective studies. *JAMA* 1998; 279: 1477-1482

[94] Yohannes AM, Baldwin RC, Connolly MJ. Depression and anxiety in elderly patients with chronic obstructive pulmonary disease. *Age Ageing* 2006; 35: 457-459

[95] Hill K, Geist R, Goldstein RS, Lacasse Y. Anxiety and depression in end-stage COPD. *Eur Respir J* 2008; 31: 667-677

[96] Anisman H, Merali Z, Hayley S. Neurotransmitter, peptide and cytokine processes in relation to depressive disorder: comorbidity between depression and neurodegenerative disorders. *Prog Neurobiol* 2008; 85: 1-74

[97] Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax* 2004; 59: 574-580

[98] Barnes PJ. Chronic obstructive pulmonary disease. *N Engl J Med* 2000; 343:269- 280

[99] Spencer S, Calverley PM, Burge PS, Jones PW: Impact of preventing exacerbations on deterioration of health status in COPD. *Eur Respir J* 2004; 23: 698-702

[100] Agusti A: Systemic effects of chronic obstructive pulmonary disease: what we know and what we don't know (but should). *Proc Am Thorac Soc* 2007; 4: 522-525

[101] Alifano M, Cuvelier A, Delage A , Roche N, Lamia B Molano L C , Couderc L-J, Marquette C-H, Devilliere P. Treatment of COPD: from pharmacological to instrumental therapies. *Eur Respir Rev* 2010; 19: 115, 7-23

[102] Tsoumakidou M, Tzanakis N, Voulgaraki O, Mitrouska I, Chrysofakis G, Samiou M, Siafakas NM. Is there any correlation between the ATS, BTS, ERS and GOLD COPD's severity scales and the frequency of hospital admissions? *Respir Med* 2004; 98: 178-83

[103] Sin DD, McAlister FA, Man SF, Anthonisen NR. Contemporary management of chronic obstructive pulmonary disease: scientific review. *JAMA* 2003; 290: 2301-12

[104] Quon BS, Gan WQ, Sin DD. Contemporary management of acute exacerbations of COPD: a systematic review and meta-analysis. *Chest* 2008; 133: 756-766

[105] Rafii R, Albertson TE, Louie S, Chan AL. Update on pharmaceutical and minimally invasive management strategies for chronic obstructive pulmonary disease. *Pulm Med* 2011; 2011: 257496

[106] Wilt TJ, Niewoehner D, MacDonald R, Kane RL. Management of stable chronic obstructive pulmonary disease: a systematic review for a clinical practice guideline. *Ann Int Med* 2007; 147: 639-53

[107] Stoller JK, Panos RJ, Krachman S, Doherty DE, Make B; Long-term Oxygen Treatment Trial Research Group. Oxygen therapy for patients with COPD: current evidence and the long-term oxygen treatment trial. *Chest* 2010; 138: 179-87

[108] Berry CE, Wise RA. Mortality in COPD: causes, risk factors, and prevention. *COPD* 2010; 7: 375-82

[109] Bosse G, Schmidbauer W, Spies CD, Sörensen M, Francis RC, Bubser F, Krebs M, Kerner T. Adherence to Guideline-based Standard Operating Procedures in Pre-hospital Emergency Patients with Chronic Obstructive Pulmonary Disease. *J Int Med Res* 2011; 39: 267-76

[110] Sin DD, Man SF. Corticosteroids and adrenoceptor agonists: the compliments for combination therapy in chronic airways diseases. *Eur J Pharmacol* 2006; 533: 28-35

[111] Schachter EN. New β_2-adrenoceptor agonists for the treatment of chronic obstructive pulmonary disease. *Drugs Today (Barc)* 2010; 46: 911-8

[112] Brusasco V, Crimi E. Airway Inflammation in COPD: Friend or Foe? *Am J Respir Crit Care Med* 2007; 176: 425-429

[113] Brightling CE, McKenna S, Hargadon B, et al. Sputum eosinophilia and the short term response to inhaled mometasone in chronic obstructive pulmonary disease. *Thorax* 2005; 60: 193-198

[114] Brightling CE, Wasrd R, Parker D, Morgan MD, Wardlwa AJ, Pavord AD. Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: A randomised control trial. *Lancet* 2000; 356:1480-1485

[115] Berry M, Parker D, Monteiro W, Pavord ID, *et al.* Sputum eosinophilia and the short term response to inhaled mometasone in chronic obstructive pulmonary disease. *Thorax* 2005; 60: 193-198

[116] Brightling CE, McKenna S, Hargadon B, Birring S, Green R, Siva R, Berry M, Parker D, Monteiro W, Pavord ID, *et al.* Sputum eosinophilia and the short term response to inhaled mometasone in chronic obstructive pulmonary disease. *Thorax* 2005; 60: 193- 198

[117] Lim KG, Mottram C. The use of fraction of exhaled nitric oxide in pulmonary practice. *Chest* 2008; 133: 1232-42

[118] Barnes PJ, Dweik RA, Gelb AF, Gibson PG, George SC, Grasemann H, Pavord ID, Ratjen F, Silkoff PE, Taylor DR, Zamel N. Exhaled nitric oxide in pulmonary diseases: a comprehensive review. *Chest* 2010; 138: 682-92

[119] Buckley J, Birrell MA, Maher SA et al. EP4 receptor as a new target for bronchodilator therapy. Doi: 10.1136/thx.2010.158568

[120] Rabe KF. Update on roflumilast, a phosphodiesterase 4 inhibitor for the treatment of chronic obstructive pulmonary disease. *Br J Pharmacol* 2011; 163: 53-67

[121] Martorana PA, Beume R, Lucattelli M, Wollin L, Lungarella G. Roflumilast fully prevents emphysema in mice chronically exposed to cigarette smoke. *Am J Respir Crit Care Med* 2005; 172: 848-*853*

[122] Grootendorst DC, Gauw SA, Verhoosel RM, et al. Reduction in sputum neutrophil and eosinophil numbers by the PDE4 inhibitor roflumilast in patients with COPD. *Thorax* 2007; 62:1081-1087

[123] Grootendorst DC, Gauw SA, Verhoosel RM, et al. Reduction in sputum neutrophil and eosinophil numbers by the PDE4 inhibitor roflumilast in patients with COPD. *Thorax* 2007; 62: 1081-1087

[124] Vestbo J, Tan L, Atkinson G, Ward J; UK-500,001 Global Study Team. A controlled trial of 6-weeks' treatment with a novel inhaled phosphodiesterase type-4 inhibitor in COPD. *Eur Respir J* 2009; 33:1039-44

[125] Fabbri LM, Calverley PM, Izquierdo-Alonso JL, Bundschuh DS, Brose M, Martinez FJ, Rabe KF. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with long acting bronchodilators: two randomised clinical trials. *Lancet* 2009; 374: 695-703

[126] Bateman ED, Rabe KF, Calverley PM, Goehring UM, Brose M, Bredenbröker D, Fabbri L. Roflumilast with long-acting {beta}2 agonists for COPD: influence of exacerbation history. *Eur Respir J* 2011 Jul 7 [Epub ahead of print]

[127] Donnelly LE, Rogers DF. Novel targets and drugs in inflammatory lung disease. *Curr Opin Pharmacol* 2008; 8: 219-21

[128] Hansel TT, Barnes PJ. New drugs for exacerbations of chronic obstructive pulmonary disease. *Lancet* 2009; 374: 744-55

[129] Barnes PJ. New treatments for chronic obstructive pulmonary disease. *Ann Ist Super Sanita* 2003; 39: 573-82

[130] Rubin BK, Henke MO. Immunomodulatory activity and effectiveness of macrolides in chronic airway disease. *Chest* 2004; 125: 70S-78S

[131] Dentener MA, Creutzberg EC, Pennings HJ, Rijkers GT, Mercken E, Wouters EF. Effect of infliximab on local and systemic inflammation in chronic obstructive pulmonary disease: a pilot study. *Respiration* 2008; 76: 275-82

[134] Van der Vaart H, Koeter GH, Postma DS, et al. First study of infliximab treatment in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 172: 465-469

[135] Rennard SI, Fogarty C, Kelsen S, et al. The safety and efficacy of infliximab in moderate to severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; 175: 926-34

[136] Beeh, KM, Kornmann, O, Buhl, R, et al Neutrophil chemotactic activity of sputum from patients with COPD: role of interleukin 8 and leukotriene B_4. *Chest* 2003; 123: 1240-1247

[137] Nadel, JA Role of neutrophil elastase in hypersecretion during COPD exacerbations, and proposed therapies. *Chest* 2000; 117: 386S-389S

[138] Mahler DA, Huang S, Tabrizi M, Bell GM. Efficacy and safety of a monoclonal antibody recognizing interleukin-8 in COPD: a pilot study. *Chest* 2004; 126: 926-934

[139] Dwyer MP, Yu Y, Chao J, et al. Discovery of 2-Hydroxy-N,N-dimethyl-3- {2- [[(R)-1-(5-methylfuran-2-yl)propyl]amino]-3,4-dioxocyclobut-1 enylamino} benzamide (SCH 527123): A Potent, Orally Bioavailable CXCR2/CXCR1 Receptor Antagonist. *J Med Chem* 2006; 49: 7603-7606

[140] Nicholson GC, Tennant RC, Carpenter DC, et al. A novel flow cytometric assay of human whole blood neutrophil and monocyte CD11b levels: upregulation by chemokines is related to receptor expression, comparison with neutrophil shape change, and effects of a chemokine receptor (CXCR2) antagonist. *Pulm Pharmacol Ther* 2007; 20: 52-59

[141] Capelli A, Di Stefano A, Gnemmi I, et al. Increased MCP-1 and MIP- 1beta in bronchoalveolar lavage fluid of chronic bronchitics. *Eur Respir J* 1999; 14: 160-165

[142] Butora G, Morriello GJ, Kothandaraman S, et al. 4-Amino-2-alkyl-butyramides as small molecule CCR2 antagonists with favorable pharmacokinetic properties. *Bioorg Med Chem Lett* 2006; 16: 4715-4722

[143] Pasternak A, Marino D, Vicario PP, et al. Novel, orally bioavailable gamma-aminoamide CC chemokine receptor 2 (CCR2) antagonists. *J Med Chem* 2006; 49: 4801-4804

[144] Snelgrove RJ. Leukotriene A4 hydrolase: an anti-inflammatory role for a proinflammatory enzyme. *Thorax* 2011; 66: 550-1

[145] Gompertz S, Stockley RA. A randomized, placebo-controlled trial of a leukotriene synthesis inhibitor in patients with COPD. *Chest* 2002; 122: 289-294

[146] Kilfeather S. 5-Lipoxygenase Inhibitors for the Treatment of COPD. *Chest* 2002; 121; 197S-200S

[147] Woodruff PG, Albert RK, Bailey WC, Casaburi R, *et al*. Randomized trial of zileuton for treatment of COPD exacerbations requiring hospitalization. *COPD* 2011; 8:21-9

[148] Stav D, Raz M: Effect of N-acetylcysteine on air trapping in COPD: a randomized placebo-controlled study. *Chest* 2009, 136: 381-386

[149] Bandarupalli U M, Williams G D. Recently published papers: Novel therapies in chronic obstructive pulmonary disease, cardiac chemicals and intensive care outcomes. *Critical Care* 2009; 13: 198

[150] Stav D, Raz M. Effect of N-acetylcysteine on air trapping in COPD: a randomized placebo-controlled study. *Chest* 2009; 136: 381-6

[151] Drost E, Lannan S, Bridgeman MME, *et al.* Lack of effect of *N*-acetylcysteine on the release of oxygen radicals from neutrophils and alveolar macrophages. *Eur Respir J 1991;* 4: 723-729

[152] Kumar S, Boehm J, Lee JC. p38 MAP kinases: key signalling molecules as therapeutic targets for inflammatory diseases. Nat Rev Drug Discov 2003; 2:717–726

[153] Renda T, Baraldo S, Pelaia G, et al. Increased activation of p38 MAPK in COPD. *Eur Respir J* 2008; 31: 62-69

[154] Medicherla S, Fitzgerald M, Spicer D, et al. p38a selective MAP kinase inhibitor, SD-282, reduces inflammation in a sub-chronic model of tobacco smoke-induced airway inflammation. *J Pharmacol Exp Ther* 2007; 324: 921-929

[155] Smith SJ, Fenwick PS, Nicholson AG, et al. Inhibitory effect of p38 mitogen- activated protein kinase inhibitors on cytokine release from human macrophages. *Br J Pharmacol* 2006; 149: 393-404

[156] Armstrong J, Harbron C, Lea S, Booth G, Cadden P, Wreggett K, Singh D. Synergistic effects of p38 MAPK inhibition with a corticosteroid in alveolar macrophages from COPD patients. *JPET* 2011

[157] Singh D, Smyth L, Borrill Z, Sweeney L, Tal-Singer R. A Randomized, Placebo-Controlled Study of the Effects of the p38 MAPK Inhibitor SB-681323 on Blood Biomarkers of Inflammation in COPD Patients *J Clin Pharmacol* 2010; 50: 94-100

[158] Baldwin AS Jr. The NF-kappa B and I kappa B proteins: new discoveries and insights. *Annu Rev Immunol* 1996; 14: 649-683

[159] Auphan N, DiDonato JA, Rosette C, et al. Immunosuppression by glucocorticoids: inhibition of NFkappa B activity through induction of kappa B synthesis. *Science* 1995; 270: 286-290

[160] Jazrawi E, Cosio BG, Barnes PJ, et al. Inhibition of IKK2 and JNK differentially regulates GM-CSF and IL-8 release in epithelial cells and alveolar macrophages. *Am J Respir Crit Care Med* 2003; 167: A798

[161] Thomas MJ, Smith A, Head DH, et al. Airway inflammation: chemokine- induced neutrophilia and the class I phosphoinositide 3-kinases. *Eur J Immunol* 2005; 35:1283- 1291

[162] -To Y, Ito K, Kizawa Y, Failla M, Ito M, Kusama T, Elliott W M, Hogg J C, Adcock I M, Barnes P J Targeting Phosphoinositide-3-Kinase-δ with Theophylline Reverses *Am J Respir Crit Care Med* 2010; 182: 897-904

[163] Ito K, Yamamura S, Essilfie-Quaye S, et al. Histone deacetylase 2- mediated deacetylation of the glucocorticoid receptor enables NF-kappaB suppression. *J Exp Med* 2006; 203:7-13

[164] Edwards PD, Andisik DW, Bryant CA, et al. Discovery and biological activity of orally active peptidyl trifluoromethyl ketone inhibitors of human neutrophil elastase. *J Med Chem* 1997; 40: 1876-1885

[165] Ferry G, Lonchampt M, Pennel L, et al. Activation of MMP-9 by neutrophil elastase in an in vivo model of acute lung injury. *FEBS Lett* 1997; 402: 111-115

[166] Iwata K, Doi A, Ohji G, Oka H, Oba Y, Takimoto K, Igarashi W, Gremillion DH, Shimada T. Effect of neutrophil elastase inhibitor (sivelestat sodium) in the treatment of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS): a systematic review and meta-analysis. Intern Med 2010; 49: 2423-32

[167] Belvisi MG, Bottomley KM. The role of matrix metalloproteinases (MMPs) in the pathophysiology of chronic obstructive pulmonary disease (COPD): a therapeutic role for inhibitors of MMPs? *Inflamm Res* 2003; 52: 95-100

[168] Magnussen H, Watz H, Kirsten A, Wang M, Wray H, Samuelsson V, Mo J, Kay R. Safety and tolerability of an oral MMP-9 and -12 inhibitor, AZD1236, in patients with moderate- to-severe COPD: A randomised controlled 6-week trial. *Pulm Pharmacol Ther* 2011 May 23. [Epub ahead of print]

[169] de Ruijter AJ, van Gennip AH, Caron HN, Kemp S, van Kuilenburg AB. Histone deacetylases (HDACs): characterization of the classical HDAC family. Biochem J 2003;370:737-749

[170] Ito K, Barnes PJ, Adcock IM. Glucocorticoid receptor recruitment of histone deacetylase 2 inhibits interleukin-1 beta-induced histone H4 acetylation on lysines 8 and 12. Mol Cell Biol 2000;20:6891-6903

[171] Ito K, Ito M, Elliott W M, Cosio B, Caramori G, Kon O M, Barczyk A Hayashi, S, Adcock I M, Hogg J C, Barnes P J. Decreased Histone Deacetylase Activity in Chronic Obstructive Pulmonary Disease. N Engl J Med 2005; 352: 1967-1976

[172] Rahman I, Marwick J, Kirkham P. Redox modulation of chromatin remodeling: impact on histone acetylation and deacetylation, NF-kappaB and pro-inflammatory gene expression. *Biochem Pharmacol* 2004; 68: 1255-1267

[173] Cosio BG, Tsaprouni L, Ito K, et al. Theophylline restores histone deacetylase activity and steroid responses in COPD macrophages. *J Exp Med* 2004; 200: 689-695

[174] Saraiva-Romanholo BM, Barnabé V, Carvalho AL, Martins MA, Saldiva PH, Nunes Mdo P. Comparison of three methods for differential cell count in induced sputum. *Chest* 2003; 124: 1060-1066

[175] He Z-Y, Ou L-M, Zhang J-Q, Bai J, Liu G-N, *et al*. Effect of 6 months of erythromycin treatment on inflammatory cells in induced sputum and exacerbations in chronic obstructive pulmonary disease. *Respiration* 2010; 80: 445-452

[176] van Eeden SF, Sin DD: Chronic obstructive pulmonary disease: a chronic systemic inflammatory disease. *Respiration* 2008; 75: 224-238

[177] Giamarellos-Bourboulis EJ: Macrolides beyond the conventional antimicrobials: a class of potent immunomodulators. *Int J Antimicrob Agents* 2008; 31: 12-20

[178] Patel IS, Seemungal TA, Wilks M, Lloyd-Owen SJ, Donaldson GC, Wedzicha JA: Relationship between bacterial colonisation and the frequency, character, and severity of COPD exacerbations. *Thorax* 2002; 57: 759-764

[179] Sethi S, Murphy TF: Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359: 2355-2365

[180] Kunisaki KN, Niewoehner DE. Antibiotic prophylaxis for chronic obstructive pulmonary disease. Resurrecting an old idea. *Am JRespir Crit Care Med* 2008; 178: 1098-1099

[181] Clini EM, Ambrosino N. Nonpharmacological treatment and relief of symptoms in COPD. *Eur Respir J* 2008; 32: 218-28

[182] Kuzma AM, Meli Y, Meldrum C, Jellen P, Butler-Lebair M, Koczen-Doyle D, Rising P, Stavrolakes K, Brogan F. Multidisciplinary care of the patient with chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2008 1; 5: 567-71

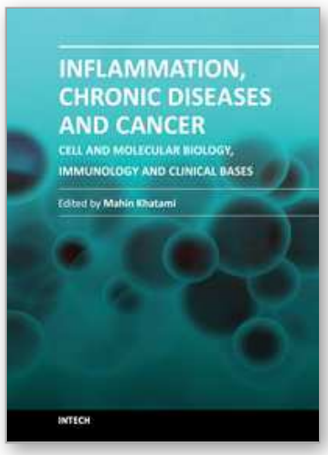
[183] Soriano J.B, Zieliński J, Price D. Screening for and early detection of obstructive pulmonary disease. *Lancet* 2009; 374: 721-732

[184] Feary JR, Rodrigues LC, Smith CJ, Hubbard RB, Gibson JE. Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care. *Thorax* 2010; 65: 956-6

[185] Rutgers SR, Postma DS, ten Hacken NH, et al. Ongoing airway inflammation in patients with COPD who do not currently smoke. *Thorax* 2000; 55: 12-18

[186] Verrills NM, Irwin JA, Yan He X, Wood LG, Powell H, Simpson JL, McDonald VM, Sim A, Gibson PG. Identification of novel diagnostic biomarkers for asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2011; 183: 1633-4

[187] Lacoma A, Prat C, Andreo F, Domínguez J. Biomarkers in the management of COPD. *Eur Respir Rev* 2009; 18: 96-104



Inflammation, Chronic Diseases and Cancer - Cell and Molecular Biology, Immunology and Clinical Bases

Edited by Dr Mahin Khatami

ISBN 978-953-51-0102-4
Hard cover, 430 pages
Publisher InTech
Published online 09, March, 2012
Published in print edition March, 2012

This book is a collection of excellent reviews and perspectives contributed by experts in the multidisciplinary field of basic science, clinical studies and treatment options for a wide range of acute and chronic inflammatory diseases or cancer. The goal has been to demonstrate that persistent or chronic (unresolved or subclinical) inflammation is a common denominator in the genesis, progression and manifestation of many illnesses and/or cancers, particularly during the aging process. Understanding the fundamental basis of shared and interrelated immunological features of unresolved inflammation in initiation and progression of chronic diseases or cancer are expected to hold real promises when the designs of cost-effective strategies are considered for diagnosis, prevention or treatment of a number of age-associated illnesses such as autoimmune and neurodegenerative diseases as well as many cancers.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Liam Heaney and Izhaq Masih (2012). Inflammation in COPD and New Drug Strategies, Inflammation, Chronic Diseases and Cancer - Cell and Molecular Biology, Immunology and Clinical Bases, Dr Mahin Khatami (Ed.), ISBN: 978-953-51-0102-4, InTech, Available from: http://www.intechopen.com/books/inflammation-chronic-diseases-and-cancer-cell-and-molecular-biology-immunology-and-clinical-bases/inflammation-in-chronic-obstructive-pulmonary-disease-implications-for-new-treatment-strategies

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen