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Inflammation in COPD and New Drug Strategies

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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 lung¹. The abnormal inflammatory response is usually triggered by smoking², or other environmental irritant exposures³ which interact with genetic factors⁴, 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 features⁵. 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 walls⁶.

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 COPD⁷ and mortality can be high as many patients with an acute exacerbation of COPD may not fulfil the criteria for admission to intensive care⁸ 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 worldwide¹¹ 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 met¹². 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 antitrypsin¹⁵ 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 exchange¹⁶. 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 tests¹⁷. 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-smokers¹⁸. 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 attachments²¹. 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 limitation²². 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 disease²³ and recurrent exacerbations can accelerate this process with progressive loss of lung function²⁴. 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 markers²⁵. COPD is associated with important comorbidities including cardiac failure, metabolic syndrome and the combination of these comorbidities 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 diseases²⁷ such as rheumatoid arthritis, atherogenesis, multiple sclerosis, and systemic lupus erythematosus²⁸.

On the basis of current evidence, it has been suggested that the immunological inflammatory / repair pathway in COPD comprise of three stages²⁹.

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 macrophages³⁰.

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- γ positive T-lymphocytes which has a direct link with disease activity³¹. The role of tissue specific chemokines driving an ongoing inflammatory influx becomes more evident by this time³².

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 parenchyma³³. The function of these cells involves apoptosis and eventual tissue destruction³⁴. 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 fibroblasts³⁷.

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 extent³⁸. 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 airway³⁹. 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 smokers⁴². These macrophages also produce oxidants and pro-inflammatory cytokines and proteases which collectively potentially drive lung parenchymal destruction⁴³.

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 COPD⁴⁴. 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 proteases⁴⁵. The action of the proteases is inhibited by anti-proteases like, α -1antitrypsin (α -AT), α 1- 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 emphysema⁴⁷. 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 heterogeneous⁴⁸.

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 upregulated⁴⁹. Both IL-8 and TNF α promote neutrophil chemotaxis and activation of adhesion molecules. In parallel, a reduction of the anti-inflammatory cytokine IL-10 promotes a pro-inflammatory environment⁵⁰. Many of the pro-inflammatory abnormalities identified in induced sputum and lung biopsies of COPD patients persist even after smoking cessation⁵¹, 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 patients⁵². 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 COPD⁵³.

Oxidative stress

Increased oxidative stress has been suggested to be an important piece in the inflammatory jigsaw of chronic obstructive pulmonary disease⁵⁴. Cigarette smoke causes increased oxidative stress⁵⁵. 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 process⁵⁶ 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 COPD⁵⁷.

Oxidative stress may increase mucous secretion, enhance elastase activity and reduce activity of protease inhibitors⁵⁸. Moreover, oxidative stress activates nuclear factor- κ B (NF- κ B) which increase transcription of important pro-inflammatory genes like, IL-8, Inducible nitric oxide synthase and cyclooxygenase (COX-2) are possible factors⁵⁹. 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 smoke⁶⁰.

Systemic inflammation in COPD

As well as an inflammatory response in the airways, chronic obstructive pulmonary disease is characterised by systemic inflammation⁶¹. 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 COPD⁶⁴. 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- α cytokines⁶⁵. Higher concentrations of these markers have been observed in the cases of severe COPD⁶⁶. 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 obstruction⁶⁷. This rise of plasma fibrinogen in patients with COPD can be of further clinical importance since it has been implicated in coronary heart disease⁶⁸. 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 effect⁷⁴. 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 lung⁷⁵.

Obesity and the metabolic syndrome⁷⁶ have been identified as risk factors for COPD, but, their relationship with inflammation and COPD needs further explanation⁷⁷. 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 lipopolysaccharide⁷⁸. It is profoundly increased in the sputum of COPD patients and correlates with sputum CRP and TNF- α levels⁷⁹. 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 inflammation⁸⁰. 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 important⁸¹. 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 theory⁸². Many other inflammatory mediators including tissue factor, FVIIa⁸³, 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 COPD⁸⁶. Reduced bone density, resulting in fractures in COPD patients is common and increases as the disease progresses⁸⁷. 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 mortality⁹². There are multiple extra-pulmonary manifestations, which are related to the disease and other systemic effects⁹³, 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 morbidity⁶⁶. Depression is common in COPD and correlates with reduced exercise tolerance, muscle weakness and fatigue⁹⁷. 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-morbidities⁹⁸.

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 goal¹⁰².

6. Current treatment of COPD

Whilst COPD is a complex disease, current treatments are largely symptomatic and do not significantly alter the natural disease progression¹⁰³. 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 advocates¹⁰⁴.

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 modalities¹⁰⁷. Bronchodilators, anti-cholinergic, thioxanthines, steroids and antibiotics for bacterial exacerbation and oxygen therapy are the medical therapeutic options¹⁰⁸. Smoking cessation and long term home oxygen¹⁰⁹ are the only two treatments which have been demonstrated to improve mortality¹¹⁰. The remaining treatments provide symptom control and some improvement in quality of life¹¹¹. Short and long acting beta adrenoceptor agonists have been the gold standard of airways disease in COPD and asthma, and in COPD¹¹² 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 available¹¹³.

Treatment of inflammation in COPD

The concept of targeting inflammation to treat COPD has largely been neglected until relatively recently¹¹⁴. The mainstay of current anti-inflammatory therapy is steroid therapy,

however it is now recognised that these drugs have a minimal effect in established COPD¹¹⁵. As stated above, there is a pressing need for a better understanding of the key pathophysiological 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 life¹¹⁶. Inhaled steroids reduce exacerbations in COPD and this has been demonstrated in a number of studies examining long-acting β -agonists / inhaled steroid combination therapies¹¹⁷. Despite, the predominant neutrophilic and lymphocytic involvement of cells in the pathogenesis of COPD, the presence of some eosinophils¹¹⁸ 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 COPD¹²¹. 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 cough¹²². Roflumilast is an oral preparation which inhibits pulmonary inflammation through the selective inhibition of the iso-enzyme PDE4, which hydrolyses cyclic AMP¹²³, which is expressed in structural cells of the lung such as, smooth muscle cells, airway epithelium and inflammatory cells such as neutrophils, lymphocytes or macrophages¹²⁴. Despite the concerns regarding dose dependant side effects such as headache, nausea and diarrhoea¹²⁵, 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 function¹²⁸.

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 COPD¹²⁹ targeting pulmonary and systemic inflammation, will prove effective. There are a number of specific therapeutic targets against the influx of inflammatory cells into the lung¹³⁰, including inhibitors of p38 mitogen-activated protein kinase (MAPK), nuclear factor- κ B (NF- κ B), 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 COPD¹³².

Cytokines and chemokines inhibitors

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 COPD¹³³ but its use has failed to show any change in sputum neutrophils, FEV1, FEV1/FVC or IL-6¹³⁴. There is also significant toxicity and cost issues and further attempts to use it in COPD have been halted¹³⁵.

Antibody against human IL-8

A fully humanised monoclonal IgG₂ 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 elastase¹³⁷. 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 neutrophils¹³⁹. Using agents which are CXCL1 and CXCL8 (IL8) receptor antagonists blocks the neutrophilic inflammatory response in the lungs and may help to control COPD¹⁴⁰ 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-smokers¹⁴¹ 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 agents¹⁴². The study of such products in humans is in the early phase and clinical preparations are probably a long way off currently¹⁴³.

5-Leukotriene B₄/Lipoxygenase inhibitors

Leukotriene B₄ (LTB₄), a pro-inflammatory derivative of arachidonic acid, is both a chemoattractant and activator of neutrophils and may be important in COPD¹⁴⁴. 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 studied¹⁴⁵. 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 inhibition¹⁴⁶. The potential clinical benefits of both of these approaches remain under investigation¹⁴⁷.

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 setting¹⁴⁹. NAC treatment of patients with stable, moderate-to-severe COPD has a beneficial effect on physical performance, probably due to a reduction in air trapping¹⁵⁰. NAC probably exhibits an anti-inflammatory effect by influencing neutrophils and macrophage function¹⁵¹.

p38 mitogen-activated protein kinase (MAPK) inhibitors

p38 MAPK inhibitors are another novel drug strategy proposed for targeting inflammation in COPD¹⁵². The p38 MAPK pathway is activated by stress and it regulates a wide variety of inflammatory cytokines including IL-8, TNF- α and MMPs¹⁵³. 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 controls¹⁵⁶. Another study has demonstrated that SB-681323 is a potent p38 MAPK inhibitor that potentially suppresses inflammation in COPD¹⁵⁷. But further clinical trials with this class of molecule are starting and are eagerly awaited.

Nuclear factor- κ B (NF- κ B) inhibitors

Nuclear factor- κ B (NF- κ B) has been implicated in inflammation in COPD by causing propagation of cytokines and neutrophils¹⁵⁸. Therefore, this pathway has been targeted to overcome inflammation and airways injury in COPD patients. One approach is to inhibit the I κ B kinase (IKK) using glucocorticoids, such as dexamethasone or prednisolone which downregulates the pro-inflammation¹⁵⁹. Experiments have also been performed using resveratrol, one of the flavonoids naturally occurring in red wine. It inhibits this pathway of inflammation¹⁶⁰ 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 asthma¹⁶¹. Targeting this pathway has a potential therapeutic role and this may be one of the actions of theophylline⁶⁵². The idea for development of PI3K inhibitors would be to ensure greater efficacy in severe steroid-insensitive asthma and COPD where corticosteroids are of limited¹⁶³ 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 yet¹⁶⁴. 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 inflammation¹⁶⁵. Recent work on the relatively newer compounds like Sivelestat sodium hydrate has not proved to be very encouraging¹⁶⁶.

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-9¹⁶⁷. 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 established¹⁶⁸.

HDAC modifiers

There are 11 classic human HDACs that regulate histone acetylation¹⁶⁹. HDAC2 is involved in suppression of NF- κ B-mediated inflammatory gene expression by corticosteroids¹⁷⁰ and HDAC2 mRNA and protein expression is significantly reduced in tissue specimens of the peripheral lung and in alveolar macrophages from patients with COPD¹⁷¹. 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 corticosteroids¹⁷². It has been reported that theophylline¹⁷³ 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 persistent¹⁷⁴. 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 COPD¹⁷⁵. 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 effects¹⁷⁶, through reducing lower airway bacterial colonization may also be beneficial¹⁷⁷. Macrolides in COPD decrease neutrophil counts and inflammatory markers and reduce the number of exacerbations¹⁷⁸. The role of regular macrolides in COPD¹⁷⁹ 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 care¹⁸¹. There is compelling evidence of the role of systemic inflammation in decreasing muscle mass, weakness and loss of function in COPD patients¹⁸² 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 interventions¹⁸³. Targeting patients with multiple co-morbidities and provision of early pulmonary rehabilitation and physiotherapy can have a major impact on improving morbidity and decreasing mortality¹⁸⁴. 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 pathophysiological 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

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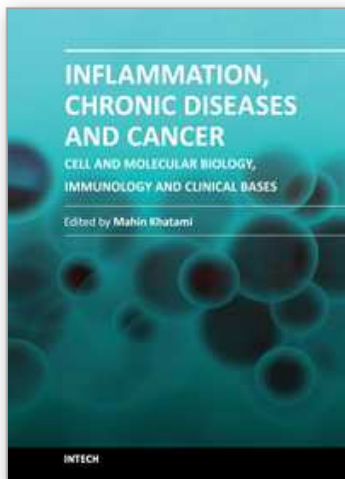
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This book is a collection of excellent reviews and perspectives contributed by experts in the multidisciplinary field of basic science, clinical studies and treatment options for a wide range of acute and chronic inflammatory diseases or cancer. The 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.

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