IS CHRONIC OBSTRUCTIVE PULMONARY DISEASE AN INFLAMMATORY DISORDER?

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ABSTRACT
Chronic obstructive pulmonary disease (COPD) is an inflammatory disorder and which aspects of inflammation can be inhibited with current and potential drugs. This paper reviews the evidence for an inflammatory basis for COPD and the potential interventions. Once established, COPD is progressive and characterised by a neutrophilic inflammation of the Airways, even after smoke exposure ceases. Further, there is upregulation of pro-inflammatory cytokines that are chemotactic for neutrophils and their activation. The ensuing destruction of the respiratory tract is mediated by activation of several proteolytic mechanisms that are able to overcome antiproteolytic defences. Investigation continues to explain the weak effects of corticosteroids in this condition, and the observation that there is inhibition of histone deacetylase is plausible. There appears to be a genetic predisposition for the development of severe COPD.

INTRODUCTION
Chronic obstructive pulmonary disease (COPD) is an underdiagnosed and consequently undertreated illness. Recent data propose that COPD will emerge as one of the major causes of morbidity and mortality the world over.1,2 The therapeutic nihilism was, at least, partly due to the dismal outlook and the lack of relatively effective therapeutic interventions in the past. This has fortunately changed and we are currently experiencing a revolution in clinical research and management of COPD.

The most effective weapon against COPD is prevention. This is achieved by avoiding cigarette smoking as the major contributing factor to the burden of COPD, reducing reliance on biomass fuel combustion (in developing regions) by provision of electricity, and reduction in industrial and atmospheric pollution.3 It is obvious that control of these personal and environmental factors remains a pipe dream and clinicians will be faced with an ever-burgeoning morbidity from COPD for many decades to come. There is a need for effective therapeutic interventions that is further emphasised by the fact that COPD progresses despite removal of causative agents once the disease has gained a foothold.

Research into the pathogenesis of COPD and its complications has lagged behind that of asthma. Recent data have revealed several pathogenic mechanisms with the promise of targeted treatment. We present the thesis that COPD is an inflammatory disorder. Acknowledgement of this will lead to a more positive clinical approach and the development of novel treatments for an incurable disease, where previously the patient was allowed to progress to respiratory failure and death, unless co-morbidity superseded this event.

Several factors have contributed to a renewed interest in COPD research, including:
1. The explosion in cell and molecular biology technology.
2. The ease of sampling the respiratory tract in vivo utilising fibre-optic bronchoscopy.
3. Sampling of the respiratory tract relatively non-invasively utilising the technique of sputum induction, which also facilitates more rapid and frequent sampling.
4. Measurements of constituents of exhaled air such as nitric oxide.
5. Application of research in asthma to COPD.

DEFINITION
The modern definition of COPD is that of an obstructive airways disease characterised by progressive airflow limitation that is not fully reversible.4 The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases.5 The term COPD is a rubric to accommodate two common diseases, namely chronic bronchitis and emphysema, associated with the same aetiological agents. Of importance in this revised definition is the inflammatory nature of COPD.

INFLAMMATION IN COPD
It is apparent that inflammation is an important component of COPD, and this coupled with the fact that COPD is a major global health problem has resulted in renewed interest in understanding cellular and molecular mechanisms in COPD.6 Current therapy is mainly symptomatic and directed to improve airflow limitation; there is, as yet, no defined treatment that reduces the inevitable progression of the disease. Definition of the inflammatory mechanisms holds promise for the development of novel therapeutic interventions and the identification of those at particular risk in whom preventive measures may be reinforced.

The following questions should be answered to determine whether COPD is an inflammatory disease:
1. Do the agents known to cause COPD operate through defined inflammatory pathways?
2. Are pro- and anti-inflammatory markers present in the regions of the lungs affected in COPD?

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3. Do agents, known to inhibit specific inflammatory pathways, interfere with the pathogenesis of COPD?

Clinical research in the last two decades provides definite answers to questions 1 and 2. Question 3 is a challenge to clinical scientists. In this respect, the lack of a systemic response to corticosteroids (agents that have a universal inhibitory effect on pulmonary inflammation) remains an enigma. Unravelling this puzzle should result in the development of targeted interventions in COPD.

1. Pathogenic mechanisms of COPD

Exposure to cigarette smoke, biomass fuels and atmospheric pollution are known causes for COPD and account for the vast majority of cases. A small number of cases are due to alpha-antitrypsin deficiency. Endobronchial disease due to tuberculosis may account for a larger proportion of cases in regions such as sub-Saharan Africa than is currently acknowledged. The mechanisms by which these agents induce damage to the lungs are well defined using molecular biological studies. These are beyond the scope of this review. Briefly, the noxious agents cause a local inflammatory response that is amplified by cytokines that act locally and systemically. There is chronic neutrophilia in the airways and the neutrophils are in an activated state. This is sustained by elevation of neutrophil chemo-attractants such as leukotriene B4 (LTB4), interleukin-8 (IL-8) and tumour necrosis factor-alpha (TNF-α). The activated neutrophils then release proteases. This results in elastolysis. These processes result in the pathological features of COPD, namely bronchiitis and emphysema.

2. Pro-inflammatory markers in the lungs of patients with COPD

One of the early studies that demonstrated that COPD is an inflammatory disease confirmed the observation that induced sputum showed a neutrophil predominance compared with that of healthy controls. What was particularly interesting in this study was that COPD patients who had stopped smoking for some time also had sputum neutrophilia. This suggests that once the inflammation in COPD has set in it continues unabated. This is very much like occupational asthma, where prolonged exposure to a trigger in the work environment can result in chronic asthma despite removal from exposure.

The fact that chemical mediators are increased in COPD may also explain the systemic manifestations of COPD such as loss of weight, malaise and other constitutional symptoms. Activation of apoptotic mechanisms may also explain the loss of the muscle bulk in COPD. The mechanisms by which these agents induce damage to the lungs are well defined using molecular biological studies. These are beyond the scope of this review. Briefly, the noxious agents cause a local inflammatory response that is amplified by cytokines that act locally and systemically. There is chronic neutrophilia in the airways and the neutrophils are in an activated state. This is sustained by elevation of neutrophil chemo-attractants such as leukotriene B4 (LTB4), interleukin-8 (IL-8) and tumour necrosis factor-alpha (TNF-α). The activated neutrophils then release proteases. This results in elastolysis. These processes result in the pathological features of COPD, namely bronchiitis and emphysema.

3. Do agents, known to inhibit specific inflammatory pathways, interfere with the pathogenesis of COPD?

It is logical to expect that if COPD is an inflammatory condition, and based on the pro-inflammatory markers, corticosteroids should be beneficial. Unlike in asthma, the response to corticosteroids in COPD is disappointing. Few observations may be made in respect of corticosteroids in COPD: (a) high-dose inhaled corticosteroids reduce the frequency of exacerbations in more advanced COPD; (b) pulse oral corticosteroids during an exacerbation of chronic bronchitis are effective in shortening the duration and reducing the relapse rate; and (c) inhaled corticosteroids may be effective in improving lung function in some patients with very mild COPD with more reversible disease. Much research is devoted towards understanding why corticosteroids are not more effective in COPD. It is an oversimplification to attribute the lack of efficacy solely to the neutrophilic inflammation. This is discussed later.

It is possible that leukotriene blockers that inhibit LTB4 synthesis may inhibit neutrophil chemotaxis. Also, research is focused on other inhibitors of neutrophil action.

ASPECTS OF INFLAMMATION IN COPD

Although many studies have attempted to characterise the inflammation in COPD, the issue is far from resolved because the results of these studies vary according to the severity of the disease (mild, moderate or severe), the type of controls studied (never smokers, smokers with normal lung function, patients with stable COPD compared with those studied during exacerbations of the disease), the compartments of the lung sampled (central airways, peripheral airways, alveolar space) and/or the bias of the study towards the role of a given cell type. Agusti et al. summarised the salient features pertinent to the inflammation in COPD as follows:

1. All smokers develop this inflammatory response.
2. The inflammatory response is accentuated in patients with COPD.
3. The extent of the inflammatory response correlates with the severity of the disease.
4. The inflammation persists after smoking cessation.

A number of inflammatory cell types and mediators are involved in the inflammatory process and these will be discussed below. However, there are several unanswered questions:

1. Why do only some smokers develop COPD?
2. What perpetuates the inflammation despite smoking cessation?
3. What makes the inflammation steroid-resistant?

Some of these questions become clearer when the pathogenesis of COPD is reviewed.

Pathogenesis of COPD

Most of the inflammation in COPD occurs in the peripheral airways and lung parenchyma, as opposed to asthma where the inflammatory changes are concentrated in the bronchi and bronchioles. The inflammatory infiltrate is:

- the lung parenchyma involves macrophages and T lymphocytes which are predominantly CD8+ (cytotoxic) T cells
- the bronchial wall consists of increased numbers of macrophages, CD8+ T cells and an increased number of neutrophils
- the broncho-alveolar lavage and induced sputum samples comprise macrophages and neutrophils.

Compared with asthma, eosinophils are not prominent except during exacerbations. The high numbers of neutrophils in the lavage fluid from subjects with COPD are not seen in the sub-epithelial zone of the bronchi as noted in bronchial biopsy specimens. The chief inflammatory mediators involved in COPD are LTB4, TNF-α and IL-8. There is a complex interplay between inflammatory cells and mediators and this is summarised in Figure 1. Macrophages play a critical role in COPD inflammation. Cigarette smoke and other irritants activate macrophages and epithelial cells, which then release neutrophil chemotactic factors (IL-8 and LTB4). The neutrophils and macrophages release proteases, which break down the connective tissue in...
the lung parenchyma, resulting in emphysema, and also increased secretion of mucus. The actions of the proteases are normally counteracted by antiproteases but for various reasons the activity of these antiproteases is impaired. Cytotoxic T lymphocytes may be involved in apoptosis and destruction of alveolar wall epithelial cells through the release of perforins and TNF-α.3

**Protease/antiprotease imbalance in the lung**

A number of proteases are released which are involved in the breakdown of connective tissue in the lungs resulting in emphysema. The ones that have been studied are neutrophil elastase, proteinase 3, cathepsins and matrix metalloproteinases.3,7 The serine proteases are also potent stimulants of mucus secretion. Normally, these proteases are inhibited by antiproteases such as α1-antitrypsin, secretory leukoprotease inhibitor and tissue inhibitors of matrix metalloproteinases (TIMP).

It is thought that in smokers who develop COPD, the production of these antiproteases may be inadequate as a result of genetic polymorphisms. This would then result in unopposed action of the proteases and resultant tissue destruction.3

**Oxidative stress**

There is increasing evidence that oxidative stress plays an important role in the pathogenesis of COPD.1,7 Reactive oxygen species such as superoxide anion, hydrogen peroxide, hydroxyl radical and peroxynitrate are produced by the various inflammatory cells discussed above, and are also contained in cigarette smoke. Oxidative stress may exacerbate COPD through various mechanisms, viz:

- Activation of the transcription factor nuclear factor-kB (NF-κB) which then switches on the genes for TNF-α, IL-8 and other inflammatory proteins, and
- Oxidative damage of antiproteases; this results in unopposed action of the proteases.

The inflammatory mechanisms discussed above occur to a lesser extent in cigarette smokers without COPD and are amplified in smokers who develop COPD.7 It is hypothesised that this amplification may be as a result of increased production of inflammatory proteins and enzymes, or defective anti-inflammatory proteins and enzymes, or defective anti-inflammatory or antiprotease mechanisms as a result of genetic polymorphisms.7 Recent work demonstrates that highly activated oligo-clonal T cells perpetuate the inflammation in COPD patients.19 Another hypothesis is that an autoimmune process may be responsible for perpetuation of the inflammation seen in these patients. However, at this stage of our knowledge it is not exactly clear why inflammation persists despite smoking cessation.

The inflammation in COPD is poorly responsive to corticosteroids and this is in contrast to the favourable effects of corticosteroids in treating asthma. The exact reason for unresponsiveness has not been clearly defined. A novel molecular mechanism has been suggested by some workers.20 Multiple inflammatory genes are activated as a consequence of acetylation of core histones around which DNA is wound. This acetylation results in unwinding of the chromatin structure allowing gene transcription and production of a number of inflammatory proteins. Corticosteroids work via histone deacetylase 2 (HDAC 2) to reverse this process, thus shutting off gene transcription and hence production of inflammatory proteins.

It is proposed that in patients with COPD there is impaired function of HDAC 2 as a direct result of cigarette smoking and oxidative stress, with consequent loss of responsiveness to corticosteroids. This is an attractive theory, which needs to be confirmed by ongoing studies. If proven, this will open up the possibility of anti-inflammatory drugs that work via this mechanism in COPD (and perhaps other diseases).
It is highly likely that genetics has a very important role to play in COPD. There is epidemiological evidence that genetic factors influence the development of COPD. There is an increased prevalence of COPD in relatives of patients with COPD. Twin studies also suggest a genetic basis to the development of COPD. To date, alpha-antitrypsin deficiency remains the only proven genetic risk factor for COPD but this accounts for a very small percentage of patients. Polymorphism in the promoter region of the gene for TNF-α has been shown to increase the risk for COPD by about 10 times in a Taiwanese population but these results were not reproducible in a British population. Other genetic polymorphisms have been described but awaits confirmation in further studies. Newer techniques (gene chips and proteomics) are being used to study the genetics involved in COPD and hopefully this will provide answers to some of the questions raised earlier in this article. These techniques may identify markers of risk and also novel molecular targets for future treatment modalities.

CONCLUSION

COPD presents a huge burden to our health care resources. Current therapeutic strategies based on exploiting bronchodilator responses alone are inadequate in reducing the disease morbidity. The view that COPD is an inflammatory disease is well supported by current clinical research into the pathogenesis and progression of the disease. The mechanisms for relative corticosteroid resistance need to be unravelled and may result in novel therapeutic approaches in the near future. Cell and molecular biology research technology and relative ease of sampling of the respiratory tract in vivo has promoted COPD research. Further insights may yield therapeutic interventions that target specific inflammatory mechanisms. There is no justification for therapeutic nihilism in COPD in the third millennium. We must not lose sight of the fact that this is a preventable disease.

REFERENCES