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Pathogenesis of Inflammation and Repair in Advanced COPD

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Abstract

Chronic obstructive pulmonary disease is characterized by an abnormal persistent inflammatory response to noxious environmental stimuli, most commonly cigarette smoke. Although cigarette smoking elicits airway inflammation in all of those who smoke, persistent inflammation and clinically significant COPD occurs in only a minority of smokers. The pathogenesis of COPD involves the recruitment and regulation of neutrophils, macrophages, and lymphocytes to the lung, as well as the induction of oxidative stress, all of which result in lung parenchymal destruction and airway remodeling. Recent research has generated a greater understanding of the mechanisms responsible for COPD development, including new concepts in T cell biology and the increasing recognition that the processes governing lung cell apoptosis are upregulated. We are also starting to understand the reasons for continued inflammation even after smoking cessation, which accelerates the rate of lung function decline in COPD. Herein we review our current knowledge of the inflammatory pathways involved in COPD pathogenesis, as well as newer concepts that have begun to unfold in recent years.

Keywords

Chronic obstructive pulmonary disease; oxidative stress; apoptosis; inflammatory cells; cytokines

Chronic obstructive pulmonary disease (COPD) is characterized by abnormal and persistent inflammation in response to a noxious environmental insult.¹ Cigarette smoking has been firmly established as the most important risk factor for the development of COPD. Studies have found that smokers have a two-to threefold increase in the rate of decline in lung function compared with nonsmokers.^{2,3} However, although cigarette smoking elicits airway inflammation in all of those who smoke, persistent inflammation and clinically significant COPD occurs in only a minority of smokers.⁴ This observation has led to the concept that an

abnormal inflammatory response to cigarette smoke leads to the development of COPD in the susceptible individual.

The clinical and pathological spectrum of COPD is broad, with many patients demonstrating a combination of both emphysema and airway disease to varying degrees. Why these two significantly different pathological processes develop as a result of the same environmental exposure is unclear and continues to occupy the attention of COPD investigators. Therefore, the pathogenesis of COPD, as might be expected, is a complex and evolving area of research. Fortunately the last several years have generated a greater understanding of the mechanisms responsible for COPD development. We will review our current knowledge of the inflammatory pathways involved in COPD pathogenesis, as well as newer concepts that have begun to unfold in recent years.

IMMUNOLOGICAL COMPONENTS IN DISEASE DEVELOPMENT

The impairment in lung function that is associated with COPD is the result of chronic inflammatory processes, many of which are initiated years before the initial symptoms are apparent. In most cases these inflammatory processes are initiated as a response to persistent exposure to tobacco smoke, and there is a complex interplay between lung epithelial cells, endothelial cells, neutrophils, macrophages, and multiple subpopulations of both CD8⁺ and CD4⁺ T cells. Figure 1 demonstrates some of these interactions involved with COPD pathogenesis. The combination of tissue damage, the release of various inflammatory mediators and cytokines, and chemokines leads to the activation of epithelial cells, and these cells serve as a substantial source of chemoattractant cytokines, including the chemokines CXCL1, CXCL8, CXCL10, CCL2, and CCL5.⁵ These cytokines act to promote the activation of endothelial cells in the lung tissue, resulting in an upregulation of several adhesion molecules, including both intercellular adhesion molecules (ICAM)-1 and E-selectin.⁶ The expression of adhesion molecules and chemokines drives the accumulation of leukocytes, which serve as an additional source of chemoattractant cytokines, and additional leukocytic infiltration. The predominant inflammatory infiltrate is a combination of neutrophils, macrophages, and CD8⁺ T cells,^{5,7} and the biochemical mechanisms that are responsible for the accumulation of these cells are distinct. It is commonly believed that these cells contribute to the progression of disease in the lung tissue. However, it is most likely that these cells function in a complex fashion to provide both beneficial and detrimental activities, which may include protection against infectious agents, on the one hand, and the attenuation of tissue repair processes, on the other. A more detailed description of these inflammatory cell populations is presented here.

THE NATURE OF INFLAMMATORY AND CELLULAR INFILTRATION IN COPD

Neutrophils

Neutrophils are brought into the lung in COPD primarily in response to the generation of CXCL8, and to a lesser extent, to the production of CXCL1, CXCL5, and leukotriene B₄.^{8–10} In addition to its chemoattractant activity, CXCL8 also stimulates neutrophil bactericidal activity through the activation of its receptors, CXCR1 and CXCR2.¹¹ The

expression of these receptors is upregulated in the lung mucosa in COPD patients during acute exacerbation.¹² During periods of bacterial infection, neutrophil immigration is also stimulated by the release of bacterial formylated peptides, such as fMLF, because neutrophils express the high affinity fMLF receptor, FPR.

The accumulation of neutrophils in the lung is believed to act as a double-edged sword in the sense that these cells are believed to provide beneficial antibacterial activity but also serve as a potential source of intracellular activation products such as myeloperoxidase and proteases such as the matrix metalloproteinases and neutrophil elastase. There is increasing evidence that the release of these proteases by inflammatory cells is a significant source of tissue destruction in COPD. In addition, recent work by Hartl et al¹¹ suggests that elevated levels of elastase lead to the cleavage of neutrophil CXCR1, and the loss of this receptor reduces the antibacterial activity of these phagocytic cells. The activated neutrophils in the lung can also provide an additional source of several chemokines, including CXCL8 as well as the interferon-inducible chemokines CXCL9, 10, and 11.⁷ The production of these chemoattractant cytokines promotes the sustained traffic of inflammatory cells into the diseased lung tissue.

CD8⁺ T Cells

There are thousands of xenobiotic compounds found within cigarette smoke (CS) that possess inflammatory capacities. Chronic exposure to CS causes significant alterations in the responses of immune cells and epithelial cells within the lung, and these can ultimately result in COPD.¹³ It has been well documented that CD8⁺ T cell numbers are increased in the lungs of COPD patients and this increase correlates with the disease severity.¹⁴ The CD8⁺ cells have been shown to exhibit a Tc1 cytokine secretion pattern that includes expression of interferon (IFN)-gamma. Because of this, COPD has been thought of as a Th1- (or Tc1-) mediated disease. Additionally, these CD8⁺ cells have been shown to be activated in COPD as measured by the production of granzyme B and perforins, which may be responsible in part for the local tissue destruction observed within the lung.¹⁵ Because CD8⁺ cells play a significant role in the clearance of viral infections and transformed cells, the pulmonary inflammation and cellular destruction observed in COPD may be a result of chronic and/or frequent viral or bacterial lung infections or the attempt of the immune system to eliminate damaged cells due to long-term exposure to CS. COPD patients can experience events of acute exacerbation characterized by greatly restricted air flow, which often requires hospitalization. It is thought that bacterial or viral lung infections may induce these events of acute exacerbation in COPD patients. Patients with frequent events of acute exacerbation tend to have increased disease progression. It is likely that a combination of these events over a period of years serves to perpetuate elevated levels of activated CD8⁺ T cells in the COPD lung.

Recently, activated CD8⁺ cells in the lungs of COPD patients have also been shown to produce Th2- (or Tc2-) type cytokines such as interleukin (IL)-4.¹⁶ The production of this cytokine may substantially alter macrophage function given that monocytes and macrophages can polarize to an “alternatively activated” form in response to IL-4 or IL-13. There is microarray evidence in cells obtained during bronchoalveolar lavage (BAL), which

suggests that there are increased levels of transcripts that are consistent with the accumulation of alternatively activated macrophages.¹⁷ These data also imply that COPD may not be strictly a Th1-mediated disease but may vary with time, types of microbial infections, or location of disease within the lung.

CD4⁺ T Cells

CD4⁺ T cells have also been observed to be elevated in the lungs of COPD patients.^{18,19} These CD4⁺ cells are activated and appear to be of a Th1 subtype because they express IFN-gamma and CXCR3.^{20,21} Like CD8⁺ cells, CD4⁺ cell numbers in the lung correlate directly with disease severity.²² This may be due in part to the increased amount of IFN-gamma, which can stimulate macrophages to assist in tissue destruction. The activated CD4⁺ cells also express cytokines and chemokines, which cause additional inflammatory cells to infiltrate the lung. This process may be self-propagating given that a chronic immune response is observed within the lungs of former smokers for many years after cessation of smoking.^{23,24}

T Regulatory Cells

Considering the thousands of toxic compounds in CS and the degree of tissue damage that can occur, it is surprising that it takes decades for the development of COPD, and yet not all smokers develop COPD. This suggests that there is an aberrant or possibly enhanced immune response occurring in those individuals that develop COPD. Some have suggested that there is an autoimmune influence to the disease. However, another viewpoint can be taken in which there may be an altered regulation of how or when the immune response should be dampened or suppressed. Studies of T regulatory (Treg) cells have provided some evidence to clarify this issue. For example, Treg cells are characterized by the surface expression of CD4 and CD25 and by the expression of a transcriptional factor, FoxP3, and these cells function to regulate immune responses.²⁵ Indeed when examining the CD4⁺ T cells in lungs of either never-smokers, smokers without COPD, and smokers with COPD, it has been observed that there are differences in the numbers of Treg cells. Barceló et al²⁶ found many more Treg cells present in the lungs of smokers without COPD as compared with smokers with COPD. And the numbers of Treg cells in smokers without COPD were significantly higher than in nonsmokers. This observation may explain the lengthy time to develop COPD and why some smokers never develop COPD.

Th17 Cells

Th17 cells are another CD4⁺ T cell subset that appears to be involved in several autoimmune diseases, including psoriasis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and asthma.²⁷ These cells are characterized by several surface markers, and the expression of a restricted set of cytokines, including CD4, IL-21R, IL-23R, IL-17, IL-21, IL-22, and the transcription factor RORC.²⁷ The Th17 cell subpopulation develops following stimulation in the presence of the cytokines TGF- β , IL-1, IL-6, IL-21, and IL-23. Th17 cells have not yet been specifically identified in the lungs of COPD patients, but Th17-related cytokines have been observed in bronchial mucosa.²⁸ In addition, IL-17, IL-22, and IL-23 positive cells correlate with the numbers of CD4⁺ and CD8⁺ cells in the mucosa. Additionally, IL-17 has been shown to induce neutrophil infiltration in the lung in murine

models of mycoplasma infection.²⁹ This may contribute to the higher numbers of neutrophils observed in the COPD lung. Finally, overexpression of IL-17 in lungs of mice induce many of the same characteristics of COPD such as recruitment of CD4⁺ cells, mucus hypersecretion, small airways fibrosis, and induction of MMP-9.³⁰

Interestingly, there are reports that Treg cells can polarize to become Th17 cells, and vice versa, demonstrating plasticity in at least these CD4⁺ T cell subtypes.³¹ Several questions remain to be addressed, including the mechanisms responsible for the traffic of Th17 cells into the lungs during COPD. Are the Th17 cells derived from circulating Th17 cells, or do Treg cells which are in high numbers in the lungs of smokers without COPD polarize into Th17 cells? Finally, if this is the case, what event(s) trigger this shift to a Th17 phenotype?

Macrophages

Macrophages are important first-responding cells in the innate immune system. They serve multiple roles, including the destruction of pathogen-infected cells, clearance of debris and foreign matter, presentation of antigens for the development of acquired immune responses, and wound and tissue repair.^{32,33} Macrophages are derived from monocytes and are classified into two major types. Classically activated macrophages (M1) are induced by IFN-gamma plus stimulation via the Toll-like receptors. These cells produce nitric oxide and have enhanced phagocytic activity. They are capable of eliminating infected cells and apoptotic cells. More recently, it has been found that macrophages can have an alternatively activated form (M2), which is induced by IL-4 and/or IL-13, and they are involved in wound and tissue repair, fibrosis, and immune responses to parasites.³² These macrophages are characterized by increased expression of arginase and fibronectin and are well suited for wound and tissue repair.

An early response of alveolar macrophages to CS is to attempt to remove these toxins from the body. Macrophage numbers have been shown to increase two-to threefold and actively begin the process of clearing the debris from lungs following exposure to CS.³⁴ Chronic exposure to CS results in increased cytokine and chemokine expression as well as MMP expression by the macrophages. However, these macrophages appear to be less mature and functionally impaired.³⁵ Classically activated macrophages are assumed to play a role in tissue destruction given that CD4 and CD8 cells within the lung are a source of IFN-gamma. However, gene expression analysis of cells found in the BAL fluid of COPD patients suggest that alternatively activated macrophages are present.¹⁷ This may explain why fibrotic lesions can be found in the lungs of some COPD patients. The alternatively activated macrophages may sense the damage induced by the CS and be attempting to repair the tissue not unlike events that occur in wound healing.

Dendritic Cells

A role for dendritic cells (DCs) in COPD is not well defined. This is due in part to the relatively small numbers of DCs found in the lung. For example, less than 1% of the cells in BAL are DCs.^{36,37} It is also complicated by which surface markers are used to identify DCs (i.e., langerin (CD207), CD1a, CD1c) and by the localization within the lung of the DCs (i.e., large airway, small airway, or alveoli). Because of these factors, there are mixed

reports regarding whether DC numbers are altered due to chronic exposure to CS.^{36–39} However, some in vitro studies with human monocytes–derived DCs have been performed as well as in vivo animal studies. Exposure of DCs to smoke extract results in a dose-dependent impairment of DC function. Human monocyte–derived DCs treated with CS have a reduced capacity to induce T cell proliferation and Th1 differentiation.⁴⁰ Interestingly, these DCs can induce Th2 differentiation. In murine models, a low dose of CS results in fewer myeloid DCs, whereas higher doses result in increased numbers in the lung.^{41,42} These in vitro and in vivo data suggest that CS can affect DCs in multiple ways. However, the role of DCs in the development and pathogenesis of COPD remains unresolved.

INFLUENCES OF CIGARETTE SMOKING

Cigarette smoking has been recognized as the most important causative factor of COPD.⁴³ Cigarette smoking causes airway inflammation and remodeling that primarily occur at the level of the small airways, defined as bronchioles that are less than 2 mm in diameter. This process begins early in the natural history of COPD, often significantly prior to the development of symptoms. Inflammatory changes were first demonstrated in the peripheral airways of young smokers in the 1970s, indicating that small airway pathology starts to develop prior to the diagnosis of COPD.⁴⁴ This inflammatory infiltrate is composed of macrophages, CD8⁺ lymphocytes, and neutrophils.^{45–48} In addition, goblet cell hyperplasia, squamous metaplasia, peribronchial fibrosis, and smooth muscle hypertrophy are seen with increased frequency in smokers compared with nonsmokers.^{24,49–52} These pathological changes can improve with smoking cessation; studies have shown that small airway function is better and inflammation is lower in ex-smokers compared with smokers.^{53,54}

Smoking cessation can also slow the progressive decline in lung function in COPD. In a longitudinal cohort study, the subjects who continued to smoke had a greater decline in lung function than those who had stopped smoking.⁵⁵ The Lung Health Study showed a similar result, following nearly 6000 adult smokers with early COPD for 5 years.⁵⁶ The mean annual rate of forced expiratory volume in 1 second (FEV₁) decline was smallest for those who quit during the first year ($-0.33 \pm 0.05\%/year$), intermediate for those who smoked intermittently ($-0.58 \pm 0.05\%/year$), and greatest for those who continued to smoke ($-1.18 \pm 0.03\%/year$).⁵⁷

However, smoking cessation cannot totally halt the inflammatory progress in COPD. In the subset of smokers who develop COPD, inflammation is amplified and persists even after the initiating event of smoking has been removed.^{58–60} Why this occurs is incompletely understood. It is hypothesized that cigarette smoking impairs lung host defenses, which leads to microbial colonization, airway epithelial injury from the inflammatory response, and the subsequent vicious circle of further reduction of innate lung defense mechanisms, increased microbial colonization, and more lung destruction.⁶¹ This hypothesis is supported by data showing that an increase in airway inflammation is perpetuated by latent adenovirus infection¹⁹ and by *Haemophilus influenzae* infection.⁶² Other infectious agents that have been isolated with increased frequency in COPD patients include *Chlamydia pneumoniae* and *Pneumocystis jiroveci*.⁶³ Human immunodeficiency virus infection also predisposes to the development of emphysema. Whether the presence of these organisms

represents innocent colonization or low-grade infection causing tissue damage is a matter of debate. There are some data that change in strain type of *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and *Pseudomonas aeruginosa* may cause exacerbations of COPD,⁶⁴ and numerous bacteria and viruses have been isolated from sputum during COPD exacerbations,^{65–67} supporting their role in at least disease activity.

OXIDANT/ANTIOXIDANT IMBALANCE

An imbalance between oxidative stress and antioxidative capacity contributes to the development and progression of COPD. The lung is a unique organ that is directly exposed to high levels of oxygen and other reactive compounds such as cigarette or biomass smoke. In COPD, the airway or alveolar epithelium inflammation causes its oxidative stress. The accumulated activated phagocytes in the tissue produce both reactive oxygen species and reactive nitrogen species, which can damage host tissues.⁶⁸ To balance the oxidative stress, the major antioxidative system includes multiple components: enzymes such as superoxide dismutase (SOD), catalase (CT), thioredoxin/peroxiredoxin and glutathione peroxidase (GPx), and metabolites such as L-ascorbic acid (vitamin C), tocopherols (vitamin E), melatonin, thioredoxin, and glutathione (GSH).

Clinical evidence has showed that the antioxidative capability is reduced in COPD. Plasma lipid peroxide (malondialdehyde, MDA, a marker for oxidative stress) levels are high and antioxidants (α -tocopherol and SOD) are low in patients with COPD.⁶⁹ The levels of glutathione-S-transferase-omega in alveolar macrophages, extracellular fluids, and airway secretions are decreased in COPD.⁷⁰ In a study of 79 consecutive patients, erythrocyte GPx activity was significantly lower, and serum MDA levels were significantly higher in the severe COPD patients compared with those with moderate COPD. A recent study also showed that red cell antioxidative enzyme activities were altered, with GPx having lower, SOD having greater, and catalase having similar activity in COPD patients compared with healthy controls.⁷¹ These findings suggest that antioxidant capacity is inversely related to COPD severity.⁷² Production of peroxynitrite, an extremely potent oxidant, is increased in the airways of patients with COPD. Reduced peroxynitrite inhibitory activity and increased levels of nitrogen oxides are found in induced sputum from patients with COPD. An imbalance in nitrogen oxides and antioxidant defense may also contribute to the pathogenesis of COPD.⁷³

Oxidative stress may also be a critical contributor to COPD exacerbation because evidence of oxidative stress is elevated and the antioxidant enzymes and melatonin values are reduced.⁷⁴ The use of cigarettes has shown an increase in oxidative stress by causing plasma lipid peroxidation and imbalance in erythrocyte antioxidant capacity. A significant difference has been observed in each of three parameters between nonsmokers and patients with COPD and between smokers and nonsmokers.⁷⁵

Antioxidants suppress the oxidative stress in COPD, and a clinical trial study of erdosteine, a thiol agent with antioxidant activity, showed a beneficial effect in COPD. In clinically stable COPD, long-term treatment is associated with a reduction in acute exacerbation and hospitalization rate and a significant improvement of quality of life.⁷⁶ A clinical trial study

of the effect of zinc, which is required for enzymes such as SOD, on oxidant stress showed that administration of zinc picolinate supplementation demonstrates favorable effects on oxidant–antioxidant balance in patients with COPD.⁷⁷ Moreover, exogenous supplementation with vitamin E has been shown to bring down the levels of MDA in COPD, suggesting attenuation of further damage.⁶⁹ Treatment with N-acetylcysteine (NAC), a mucolytic drug with antioxidant properties, decreases inflammatory parameters.⁷⁸ The use of antioxidants demonstrates the beneficial effect of inhibiting oxidant pathways in patients, and the long-term therapeutic effect of antioxidant agents offers a promising avenue for further investigation.

NEW CONCEPTS IN COPD PATHOGENESIS

Without question there are several complex and dynamic interactions between inflammatory mediators that cause tissue damage and remodeling. It is believed that the alveolar destruction in emphysema is irreversible, but recent studies in the last decade challenge this concept. Alveolar regeneration has been demonstrated in elastase-induced emphysema rodent models after treatment with all-trans-retinoic-acid,⁷⁹ granulocyte stimulating factor,⁸⁰ adrenomedullin,⁸¹ and hepatocyte growth factor.⁸² The most enthusiasm for pharmacotherapy surrounds the use of retinoic acid, despite conflicting animal data^{83,84} and a lack of efficacy in a human trial.⁸⁵ The effects of a gamma selective retinoic agonist on amount of emphysema and lung function in humans are currently being studied in a large randomized, placebo-controlled, multicenter trial.

In addition to protease/antiprotease imbalance, derangement of normal lung homeostasis also contributes to COPD pathogenesis. The maintenance of lung architecture depends upon the interaction between different cell types and lung matrix. Alveolar epithelial and pulmonary vascular endothelial cells routinely undergo cell death and are replaced by newly generated cells. Imbalance in the processes governing cell death may lead to dysregulation of the overall maintenance of lung structure, and therefore lung destruction. Supporting this notion is a growing body of evidence that increased or accelerated apoptosis of alveolar and pulmonary vascular endothelial cells results in the development of emphysema.^{86–88} Similarly, these apoptotic cells may not be cleared efficiently from the lung and may serve as an antigenic stimulus that activates the immune system.⁸⁹

It is becoming increasingly apparent that vascular endothelial growth factor (VEGF), a ligand that governs the cellular processes of growth and programmed cell death, is involved with COPD pathogenesis. Blockade of VEGF receptors or reduction in gene expression has been shown to cause alveolar cell apoptosis and airspace enlargement in animal models.^{90–92} VEGF and VEGF receptor protein expression have also been shown to be lower in emphysema patients compared with those without emphysema.⁹³

Ceramide, a second messenger lipid crucial to the processes involved in alveolar destruction, may also play an important role in COPD development. Supporting this hypothesis are observations that inhibition of ceramide synthesis prevents the VEGF receptor blockade–induced alveolar cell apoptosis and emphysema in mice, and the intratracheal administration of ceramide resulted in the development of emphysema.⁹⁴ Other mediators involved with

alveolar cell efferocytosis include hepatocyte growth factor, transforming growth factor β , and β catenin,⁸⁹ and increased levels of these proteins may swing the balance between cell death and replacement toward apoptosis.

The mechanisms by which alveolar cell apoptosis is increased in COPD are not completely understood. It may be the result of cigarette exposure itself, cell destruction from proteases secreted by CD8⁺ lymphocytes and neutrophils, or increasing oxidative stress. As mentioned earlier, there are a significant number of oxidants and free radicals in cigarette smoke.⁹⁵ Cell death has been demonstrated in a dose- and time-dependent manner when exposed to cigarette smoke extract in human lung fibroblasts as well as in animal models.^{96,97} This appears to be mediated through the induction of numerous proapoptotic proteins such as caspase-3 and caspase-8.²⁹ It is likely that this process escalates in response to cigarette smoke-induced increases in oxidative stress.⁹⁸ Alternatively, cell death may be a consequence of the increased protease activity that results in emphysematous destruction of the alveoli, as opposed to being a cause. Figure 2 displays the potential interactions between oxidant stress, protease/antiprotease imbalance, and lung cell apoptosis.

Some investigators postulate that COPD has an autoimmune component, based on observations that airway inflammation in COPD persists despite smoking cessation. One study revealed that human umbilical vein endothelial cells injected into rats resulted in antibodies not only to these cells but also to lung capillary endothelial cells.⁹⁹ Interestingly, the animals also developed emphysema, providing evidence that autoimmune attack against vascular endothelial cells can result in alveolar destruction. Similarly, transfer of CD4⁺ cells or serum from emphysematous animals to wild-type animals also resulted in the development of emphysema.⁹⁹ Another study found more antiepithelial cell antibodies in the plasma of COPD patients compared with smokers without lung disease,¹⁰⁰ which builds a greater case for autoimmunity as a potential pathogenetic mechanism of COPD. These data propose a novel mechanism for COPD pathogenesis and will require further investigation.

AREAS FOR FUTURE RESEARCH COPD

COPD pathogenesis involves complex interactions between proinflammatory stimuli and recruitment and upregulation of neutrophils, macrophages, and lymphocytes, leading to the destruction of lung parenchyma and airway remodeling. Although the inflammatory processes involved are becoming clearer, the reasons why individuals develop different clinical phenotypes are not. The answer may lie in genetic polymorphisms that confer not only disease susceptibility but also phenotypic expression. As our understanding of lung inflammation improves, future research will focus on how the inflammatory responses to cigarette smoke interact in the susceptible individual to cause various aspects of COPD pathology.

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Figure 1.

Diagram of some of the inflammatory pathways involved with the development of chronic obstructive pulmonary disease.

Figure 2.

Proposed interactions between oxidative stress, inflammation, apoptosis, and protease/antiprotease imbalance. (Reproduced from Park JW, et al. Functional significance of apoptosis in chronic obstructive pulmonary disease. *J COPD* 2007;4:347–353. With permission.)