

Future Treatment Strategies for COPD

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As the fourth leading cause of death in the United States, chronic obstructive pulmonary disease (COPD) is receiving increased attention from medical researchers. The Global Initiative for Chronic Obstructive Lung Disease now defines COPD as a progressive disease state characterized by chronic respiratory tract inflammation as well as airflow limitation that is partially reversible with appropriate treatment. The inflammatory pathway associated with COPD, although not well studied in the past, is also receiving more attention as medical researchers attempt to elucidate the cellular and molecular pathogenetic mechanisms that result in the development of COPD. Understanding the pathogenetic mechanisms will lead to new therapeutic strategies. The purpose of this review is to identify the known major therapeutic targets and the agents available to treat this devastating disease and some of the new agents that are being developed.

Chronic obstructive pulmonary disease (COPD) is defined as a disease state characterized by airflow limitation that is progressive but partially reversible with appropriate treatment. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has added chronic respiratory tract inflammation to the definition of COPD (1). The cell types involved are epithelial cells, macrophages, and CD8+ lymphocytes. The mediators that have been shown to be upregulated in COPD include cytokines and chemokines. The inflammatory pathway associated with COPD, although not well studied in the past, is now receiving more attention as researchers attempt to elucidate the cellular and molecular pathogenetic mechanisms that result in the development of COPD (**Figure 1**).

SMOKING CESSATION

Tobacco smoking is widespread and the most important risk factor for the development of COPD. Furthermore, the only therapeutic intervention

KEY POINT

An important advance in COPD treatment has been the introduction of long-acting beta-2 agonists and anticholinergics. IL-10, which decreases inflammation, may prove useful as may other agents under study that block adhesion molecules, inhibit PDE4, or reduce neutrophil elastase activity.

shown to halt the progression of COPD is smoking cessation (2). However, smoking cessation success rates using present therapeutic modalities (nicotine replacement, psychological counseling (2), and antidepressant therapy) are generally <30% over several years, even though >90% of smokers want to stop smoking. There is a family of pentameric gated ion channel receptors for acetylcholine that are also activated by nicotine. These receptors are

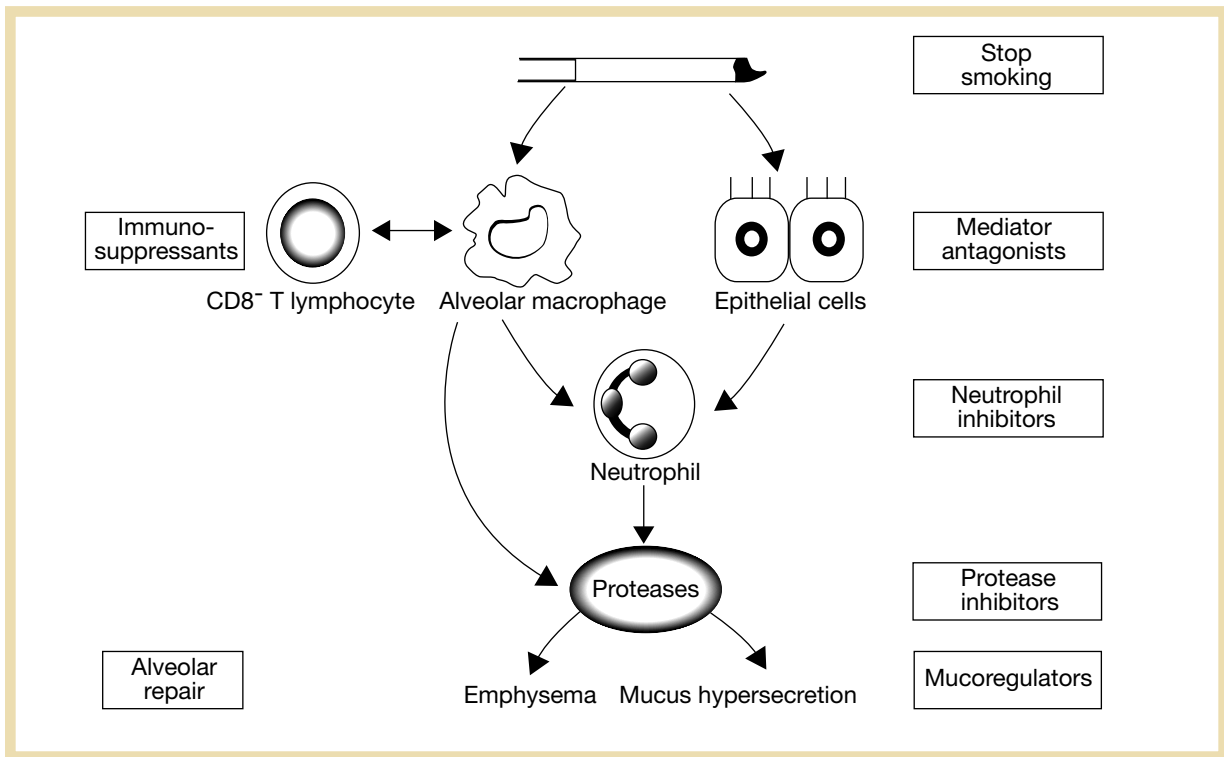


Figure 1. Targets for COPD therapy that are based on current understanding of the inflammatory mechanisms. Reprinted with permission from Barnes PJ. *New treatments for COPD.* Nat Rev Drug Discov. 2002;1:437–446. Available at: <http://www.nature.com>

composed of a variety of protein subunits (eg, α , β , γ , δ , ϵ), some of which represent the nicotine receptors. Nicotine receptor agonists and antagonists that are now under phase II and III studies may prove beneficial in smoking cessation efforts by providing relief from withdrawal symptoms and blocking the behavior-reinforcing effect of nicotine.

INHALED BRONCHODILATORS

Since airflow limitation is a hallmark of COPD, bronchodilators are the mainstay of therapy (1). Bronchodilators include beta-2 adrenergic agonists, anticholinergics, and methylxanthines. The most recent advance has been the introduction of long-acting beta-2 agonists and anticholinergics (3–6). These agents do not alter progression of the disease but they do improve airflow limitation, decrease dyspnea, improve health status, and decrease the number of exacerbations (2). Anticholinergic bronchodilators have been shown to be effective in COPD because they block the muscarinic receptors (7). In a recent review, Barnes (8) stated there are 3 different muscarinic receptors (M1, M2, and M3),

each having somewhat different functions. The M3 receptor mediates bronchoconstriction and mucus secretion and thus would be an important therapeutic target. The anticholinergic bronchodilator, ipratropium, is a relatively nonselective muscarinic receptor inhibitor. The newest anticholinergic bronchodilator, tiotropium*, is a long-acting (once-daily) inhaled drug with muscarinic receptor kinetic selectivity and half-times for dissociation from each muscarinic receptor favoring long-term blockade of the M3 receptor. Tiotropium has been used in several European countries and is now under review for approval by the US Food and Drug Administration (FDA). Other selective muscarinic inhibitors are in early-stage trials.

CORTICOSTEROIDS

Because the inflammatory pathways in COPD, unlike asthma, (which include CD 4 + lymphocytes, cysteinyl leukotrienes, eosinophils, mast

* Use not approved by the FDA. Application in process.

cells, etc.), are relatively steroid resistant, the use of either parenteral or inhaled corticosteroids has been disappointing. Although useful in treating acute exacerbations of COPD in severely ill patients, corticosteroids have not been shown to significantly alter the progression of the disease. Short-term use does not affect the inflammatory process (cells, mediators) or the expression of proteases. Although improvement in patient survival has been shown recently (9,10), a systematic review of 5 trials has demonstrated no effect on all-cause mortality. (11) Data have shown that the combination of a beta-2 agonist and a corticosteroid by the inhaled route improves function more than the individual components, suggesting an interaction between the 2 moieties that may have a positive effect in COPD. There are some patients with COPD and concomitant asthma (~10%) who may respond to the use of corticosteroids. Also patients with chronic asthma may develop airway remodeling that may appear as a fixed airway obstruction similar to COPD but due to a different inflammatory pathway.

CELLULAR COMPONENTS

The development of airflow limitation in COPD is associated with an increase in neutrophils, CD8+ lymphocytes, and macrophages. Although the exact mechanism of neutrophil accumulation in the airways is unknown, there may be an imbalance between proinflammatory and anti-inflammatory mediators (12). Interleukin (IL)-10, which decreases inflammatory responses, is reduced in COPD whereas IL-8 can induce neutrophilia in the airways. IL-10 is currently under study in clinical trials for chronic inflammatory diseases such as inflammatory bowel disease, psoriasis, and rheumatoid arthritis. Further development of this class of drugs may prove useful in treating COPD.

Various adhesion molecules (E-selectin, intercellular adhesion molecule-1) have been shown to be upregulated in COPD. The recruitment of neutrophils, as well as mononuclear cells, is dependent on these adhesion molecules. Pharmacologic agents exist that can block these adhesion molecules, and targeting these molecules may reduce the inflammation in COPD. There are also several compounds in late development that are selective

inhibitors of phosphodiesterase 4 (PDE4), for example, cilomilast, roflumilast, and BAY 19-8004 (13). PDE4 is the main phosphodiesterase expressed by neutrophils, macrophages, and CD8+ T cells, and PDE4 inhibitors have been shown to relax smooth muscle, suppress activation of inflammatory cells, and modulate the activity of pulmonary nerves (13). Although studies with these compounds have shown some lung function improvement in COPD patients, a decrease in lung inflammation in COPD has not been reported. The optimal positioning of PDE4 inhibitors will depend on demonstrating anti-inflammatory activity in the early stages of COPD.

Theophylline has been used for many years as an oral bronchodilator in COPD because of the bronchodilation effects seen when phosphodiesterase is inhibited. Given its relatively weak potency as a bronchodilator compared with the newer inhaled beta-2 agonists and anticholinergics, as well as its unfavorable side-effect profile, it is now positioned in management guidelines as a second- or third-line bronchodilator for use in COPD. Interestingly, anti-inflammatory effects with theophylline have been shown in COPD at doses lower than therapeutic levels for bronchodilation. These lower levels minimize side effects and were predominantly on neutrophil recruitment, a chemotactic activity (14).

KEY POINT

Cytokines and chemokines play a significant role in COPD. Predominant cytokines are TNF- α , IL-8, LTB₄, IL-1 β , and interferon- γ . Important chemokines include IL-8, RANTES, and growth-regulated oncogene- α . Several LTB₄ receptor antagonists are also being investigated.

Colchicine, another agent that disrupts neutrophil function, has been shown to produce some reduction in neutrophil elastase activity in COPD. IL-16, previously known as lymphocyte chemoattractant factor, has been shown to be a selective

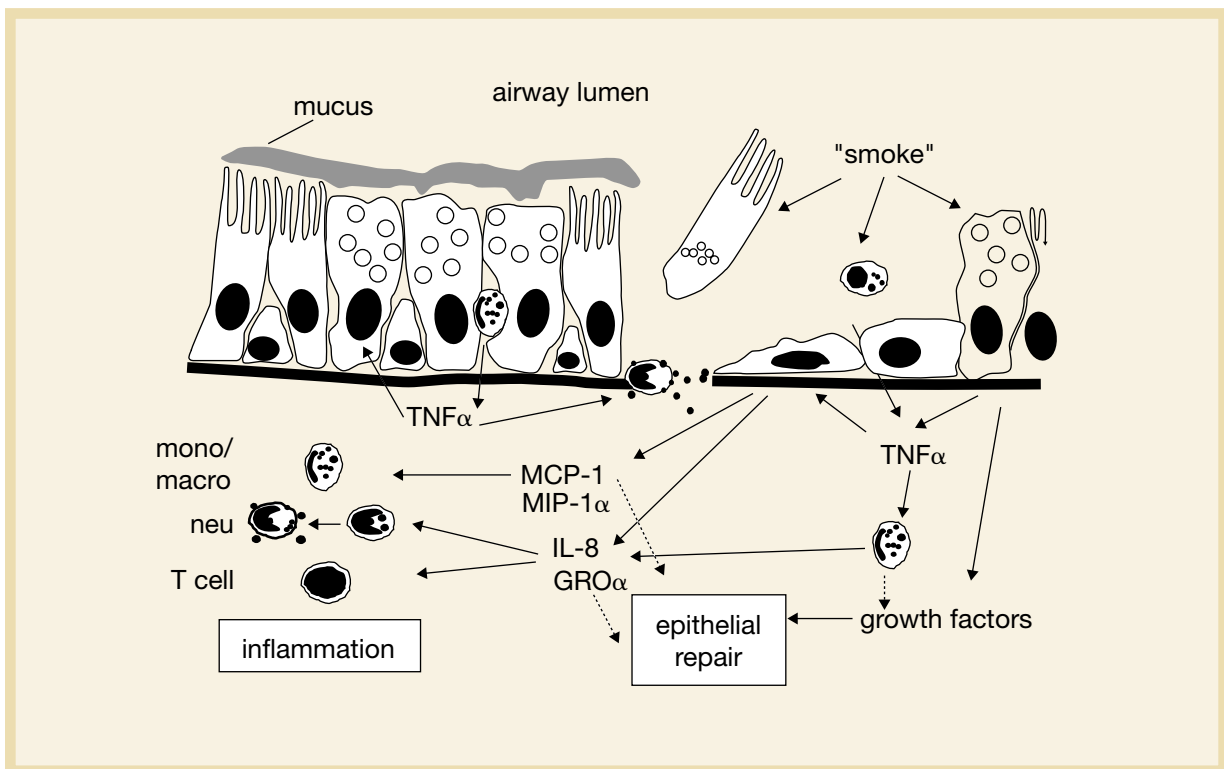


Figure 2. Simplified scheme of cytokine and chemokine actions in human lungs. Mono = monocyte; macro = macrophage; neu = neutrophil; TNF = tumor necrosis factor; MCP = monocyte chemoattractant protein; MIP = macrophage inflammatory protein; IL = interleukin; GRO = growth-regulated oncogene. Reprinted with permission from De Boer WI. Cytokines and therapy in COPD: a promising combination? *Chest*. 2002;121(Suppl 5):209S–218S.

chemoattractant for CD4+ T lymphocytes and is released by epithelial cells in response to allergen exposure; however, it is also produced in the airways by CD8+ T cells and bronchial epithelial cells. It has been also demonstrated that IL-16 increases in bronchoalveolar lavage from tobacco smokers.

INFLAMMATORY MEDIATORS

Migration and activation of inflammatory cells are regulated by cytokines and chemokines, which play a significant role in the inflammation seen in COPD (15) (**Figure 2**). The predominant mediators associated with COPD include tumor necrosis factor (TNF)- α , IL-8, and leukotriene (LT) B₄, as well as IL-1 β and interferon- γ . Raised levels of TNF- α are seen in the sputum of patients with COPD. The increase in levels may be secondary to tobacco smoke or genetic influences or both. Genetically manipulated mice that produce exces-

sive amounts of TNF- α in the lung develop lung inflammation and emphysema. Studies have also shown that TNF- α levels in COPD may be higher than in the general population, and other researchers have reported TNF- α gene polymorphisms in COPD patients. In addition, TNF- α can have a direct effect on inducing airway mucus cell hyperplasia and induction of other mediators such as IL-1 and IL-8 (15). TNF antibodies have been developed for use in other inflammatory diseases, such as rheumatoid arthritis and inflammatory bowel disease. Soluble TNF receptors are also being studied. These agents have side effects such as an increased risk of infection.

Chemokines are grouped into 4 classes based on the position of key cysteine residues: C, CC, CXC, and CX₃C. Several chemokines shown to be associated with COPD belong to the CXC family of chemokines and include IL-8, RANTES (regulated on activation, normal T cell expressed and

secreted), and growth-regulated oncogene- α . Expression of IL-8 can be upregulated by tobacco smoke and TNF- α , to name just a few, and the chemokine is elevated in the sputum and lung lavage of patients with COPD. IL-8 plays an important role in neutrophil chemotaxis, adherence, and degranulation. Blocking antibodies to IL-8 and other chemokines has been shown to be potentially useful in human diseases such as psoriasis. A phase II trial of an anti-IL-8 compound in COPD patients is currently under way. Other chemokines, including various macrophage inflammatory proteins, monocyte chemoattractant proteins (MCPs), and CC chemokine receptor 2 (CCR2), which are involved in macrophage activation and function, also may be involved in COPD. Antagonists to such molecules as MCP-1 and CCR2 may also prove useful. Studies in mice have been performed for various diseases—including airway inflammation—but no clinical trials have been reported.

The upregulation of a number of the cytokines described in COPD involves the expression of nuclear factor (NF)- κ B. Inhibitors of NF- κ B and of the kinases involved in its regulation are being studied in a nonclinical setting. Mitogen-activated protein (MAP) kinases are also important in chronic inflammation, and the p38 MAP kinase pathway involves IL-8 and TNF- α . Nonpeptide inhibitors of p38 MAP kinases have been recently developed and may have potential use in COPD.

EICOSANOIDS

Eicosanoids have a modulatory function in cells and are responsible for tissue responses such as inflammation or wound repair. The cysteinyl LTs (LTC₄, LTD₄, and LTE₄) have been shown to be involved in asthma, and several LT-modifying agents have shown some usefulness either by blocking LT synthesis or specific receptors. However, the cysteinyl LT mediators have not been shown to be important in the inflammatory pathway seen in COPD, although LTB₄ is increased in sputum and lung lavage of patients with COPD. LTB₄ is a potent chemoattractant for neutrophils. Several LTB₄ receptor antagonists are being investigated for possible use in COPD. Additionally, because LTB₄ is synthesized via the 5'-lipoxygenase path-

way, 5'-lipoxygenase inhibitors (eg, zileuton) may be useful in COPD; however, data are lacking.

Oxidative stress can form various prostanoids from arachidonic acid. These include isoprostanes, the most abundant of which is 8-iso-prostaglandin F₂ α (8). Prostaglandin E₂ can inhibit the oxidative burst in neutrophils but has not yet been studied in COPD. Various thromboxane antagonists are in development but none have been studied for COPD. Indomethacin, a cyclooxygenase inhibitor, has been shown to have no effect on sputum neutrophilia.

ANTIPROTEASES

In addition to lung inflammation, the other major component of the pathophysiology of COPD is destruction of the alveolar tissue attachments, that is, the emphysema component of COPD. Most COPD patients (~85%) exhibit both chronic bronchitis (airway inflammation) and emphysema components. The exact pathogenesis of the lung parenchymal destruction is unknown but is thought to be related to imbalance between proteases and antiproteases. It is presumed that as a result of prolonged inflammation, such as that induced by tobacco smoke, activated inflammatory cells release elastases, which overwhelm normal local antiprotease activity, resulting in lung tissue destruction. The major sources of elastases in the lung are macrophages and neutrophils. These elastases include leukocyte elastase, proteinase 3, cysteine proteinases, plasminogen activators, and matrix metalloproteinases (MMPs).

Neutrophil elastase inhibitors have been developed and show potency in inhibiting neutrophil-elastase mucus secretion in vitro. The finding in the 1960s that emphysema developed in patients with a congenital deficiency in the neutrophil elastase inhibitor, α_1 -antitrypsin inhibitor (now termed α_1 -protease inhibitor), pointed out that neutrophil elastase is an important factor in the development of COPD and emphasized the concept of unopposed elastolytic destruction of lung tissue in COPD. However, α_1 -protease inhibitor deficiency occurs in only 1% to 2% of the COPD population. Although replacement treatment with α_1 -protease inhibitor has proved beneficial in these

specific patients, it has not proved helpful in all COPD patients with a history of cigarette smoking, although cigarette smoking inactivates α_1 -antitrypsin. One oral neutrophil elastase inhibitor, MR889, was administered for 4 weeks in COPD patients but showed no overall effect on levels of elastin-derived peptides. Another oral inhibitor, ONO-6818, has proved useful in animal studies but has not yet been studied clinically. Because agents like these act extracellularly, future research in COPD may focus on whether intracellular inhibitors might be effective.

Newer inhibitors of the other proteolytic enzymes, such as cathepsin G and proteinase 3, are also under development. Although inhibitors of MMPs (BB-94, BB-2516) have been documented, they are nonselective, and research into more selective MMP inhibitors is under way. Thus, although the complete picture as to which proteases are critical to the development of tissue destruction in COPD has proved elusive, there is ample experimental evidence for the development of synthetic neutrophil elastase inhibitors and other matrix components.

MUCOREGULATORS

Excess secretion of mucus in the airways of COPD patients is associated with a more rapid decline in lung function and an increase in disease exacerbations. The release of sensory neuropeptides (tachykinins) from sensory nerve endings can induce mucus secretion from goblet cells and inflammation (neurogenic inflammation). Opiates such as morphine are effective in inhibiting mucus secretion, although their use is problematic because of their addictive properties. Other opioid agonists that do not cross the blood-brain barrier are under investigation.

The tachykinin called neurokinin (NK)-1 can induce mucus secretion in response to tobacco smoke or ozone exposure, and there are several NK-1 inhibitors in clinical development. The 9 genes that encode mucin (*MUC* genes) have been cloned, and several have been shown to be expressed in human airways. These developments may lead to drugs that inhibit the expression of these *MUC* genes.

Several mucolytic drugs also have been developed, including N-acetylcysteine and carbo-

cysteine. These drugs have potent effects in vitro but have had only marginal effects in COPD; however, N-acetylcysteine has been shown to decrease COPD exacerbations. Recombinant human deoxyribonuclease can improve mucus rheology in cystic fibrosis patients, but it has not been adequately studied in COPD patients. There are also several dopamine receptor agonists—studied thus far only in animals—that may inhibit nerve-mediated responses. These agonists include SKF 3893, AR-C68397, and quinagolide. These agents may be of therapeutic benefit in the treatment of symptoms such as cough and mucus secretion.

GENETICS OF COPD

Severe α_1 -protease inhibitor deficiency is the only proven genetic risk factor for COPD. The major environmental risk factor for the development of COPD is cigarette smoking, yet only 10% to 20% of cigarette smokers develop COPD. It is unclear whether these susceptible smokers represent a distinct subset. Several family studies and case-control studies in twins have supported the hypothesis that there are genetic factors associated with the development of COPD. Recently, it has been shown that the risk of developing COPD is increased in first-degree relatives of patients with COPD.

Several candidate genes have been suggested that might predispose a cigarette smoker to the development of COPD. These genes include antielastase polymorphisms, gene polymorphisms of proinflammatory cytokines such as TNF- α and IL-1 β , and antioxidant gene polymorphisms. A number of studies are now being undertaken to understand the genetic aspect more fully, but they require large numbers of subjects. It is likely these studies will be able to identify the genetic polymorphisms responsible for COPD, lead to identification of at-risk individuals, and target therapeutic interventions.

SUMMARY

A number of potential therapeutic targets in COPD have been reviewed. This is not an exhaustive list. Other targets, such as antioxidants, retinoids, progestational agents, and anabolic drugs, have not been reviewed. It is clear, however, that new thera-

pies are needed for this highly prevalent disease that is associated with excessive morbidity and mortality. There is also a need for developing surrogate markers that can be used to examine the clinical usefulness of newer therapeutic modalities. More research is needed to identify the cellular and molecular mechanisms responsible for the development and progression of COPD. Future treatment strategies for COPD will depend on such advances in medical knowledge.

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