



New approaches to COPD

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ABSTRACT: No currently available treatments reduce the progression or suppress the inflammation of chronic obstructive pulmonary disease (COPD). However, with a better understanding of the inflammatory and destructive process, several targets have been identified, and new treatments are now in clinical development.

Several specific therapies are directed against the influx of inflammatory cells into the airways and lung parenchyma that occurs in COPD, including adhesion molecule and chemokine-directed therapy, as well as therapies to inhibit tumour necrosis factor- α . Broad spectrum anti-inflammatory drugs are also in development, and include inhibitors of phosphodiesterase-4, p38 mitogen-activated protein kinase, nuclear factor- κ B and phosphoinositide-3 kinase- γ . More specific approaches include antioxidants, inhibitors of inducible nitric oxide synthase, and leukotriene B₄ receptor antagonists. Inhibitors of epidermal growth factor receptor kinase and calcium-activated chloride channel inhibitors have the potential to inhibit mucus hypersecretion. Other therapies are targeted at the structural changes of COPD. Therapy to inhibit fibrosis is being developed against transforming growth factor- β ₁ and protease activated receptor-2. There is also a search for serine proteinase and matrix metalloproteinase inhibitors to prevent lung destruction and the development of emphysema, as well as drugs such as retinoids that may even reverse this process.

There is the need for validated biomarkers and monitoring techniques in early clinical studies with new therapies for chronic obstructive pulmonary disease.

KEYWORDS: Adhesion molecule, anti-inflammatory, chemokine, cytokine, phosphodiesterase-4, tumour necrosis factor- α

Chronic obstructive pulmonary disease (COPD) is a major global epidemic, which is predicted to become the third most common cause of death and most common cause of chronic disability in the world by 2020 [1]. The increase in COPD is explained by increased smoking in developing countries, the failure of developed countries to effectively stop smoking and increased survival as other causes of mortality reduce. Even if smoking cessation was effective COPD would continue to increase as disease progression would not be halted. But despite the enormous global impact of COPD there are no current therapies that prevent disease progression. However, there has recently been enormous interest in COPD by researchers and the pharmaceutical industry with progress in understanding its cellular and molecular mechanisms [2, 3] and in the identification of novel targets for the discovery of new therapies [4].

THE NEED FOR NOVEL THERAPIES

There have been disappointingly few therapeutic advances in the drug therapy of COPD, in contrast to the enormous advances made in

asthma management that reflect a much better understanding of the disease [5]. Rational therapy depends on elucidating the cellular and molecular mechanisms that may be involved. There is a particular need to develop drugs that suppress the underlying inflammatory, fibrotic and destructive processes that underlie this disease (fig. 1). Many new treatments for COPD are now in development based on logical targets revealed by a better understanding of cellular and molecular mechanisms involved in disease pathogenesis. More effective smoking cessation drugs are needed. Antagonists of specific mediators, such as leukotriene B₄ (LTB₄) and chemokines such as interleukin-8 are in clinical trial, but may be too specific. Inhibition of tumour necrosis factor (TNF)- α is more likely to be successful, particularly in patients with systemic features. Other approaches include inhibiting proteases (elastases) such as neutrophil elastase, cathepsins or matrix metalloproteinases (MMP). Drugs with a broader spectrum of anti-inflammatory effects, such as phosphodiesterase (PDE)-4 inhibitors or inhibitors of signal transduction pathways, such as inhibitors of inhibitor of nuclear factor- κ B kinase (IKK-2), p38 mitogen activated protein

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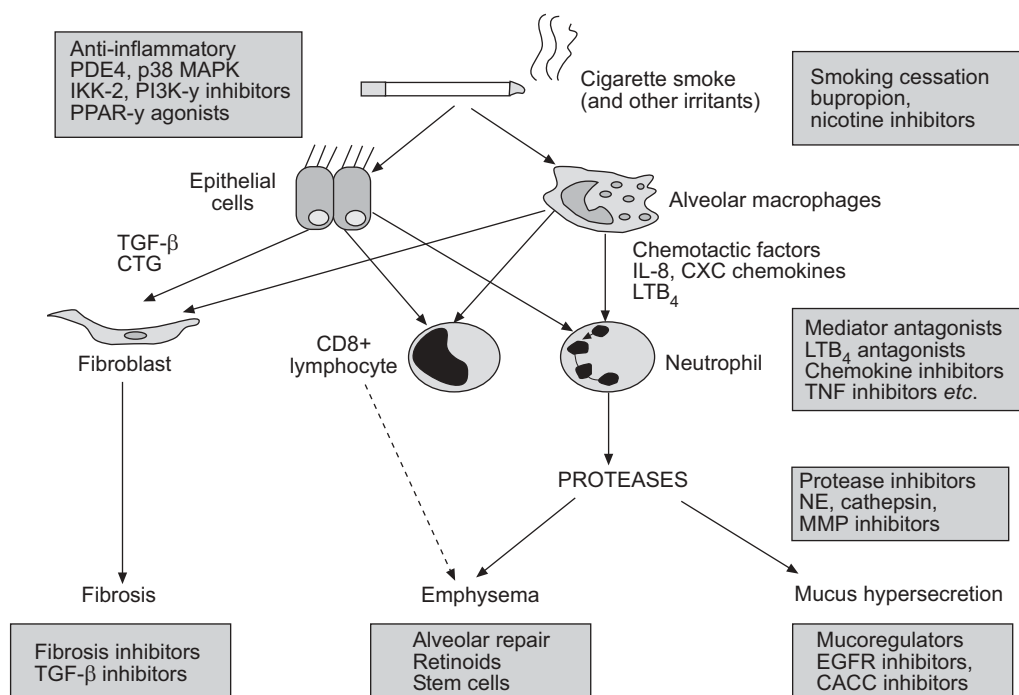


FIGURE 1. Targets for COPD therapy. PDE4: phosphodiesterase-4; p38 MAPK: p38 mitogen activated protein; IKK-2: inhibitor of nuclear factor- κ B kinase; PI3K- γ : phosphoinositide 3 inase-gamma; PPAR- γ : peroxisome proliferation activated receptor- γ ; TGF- β : transforming growth factor- β ; CTG: connective tissue growth factor; IL-8: interleukin-8; CXC: cysteine-X-cysteine; LTB₄: leukotriene B₄; TNF: tumour necrosis factor; NE: neutrophil elastase; MMP: matrix metalloproteinases; EGFR: epidermal growth factor receptors; CACC: calcium-activated chloride channels.

(MAP) kinase or phosphoinositide-3-kinase are promising. Drugs that inhibit transforming growth factor- β (TGF- β) may inhibit the fibrosis in small airways. Drugs targeted at mucus hypersecretion include inhibitors of epidermal growth factor receptors and calcium-activated chloride channels (CACC). There are also approaches to repair emphysema using retinoids (that are effective in rodent lungs) and stem cells.

COPD involves a chronic inflammation in small airways and lung parenchyma, with the involvement of neutrophils, macrophages and CD8+ T-lymphocytes [2]. This inflammation is associated with fibrosis and narrowing of small airways (obstructive bronchiolitis) and with lung parenchymal destruction (emphysema) due to the action of various proteinases, such as neutrophil elastase and matrix metalloproteinases. The inflammation of COPD is quite different from that seen in asthma, indicating that different treatments are likely to be needed [3, 6].

The challenge of drug development

There are several reasons why drug development in COPD is challenging. Only recently has there been any research interest in the molecular and cell biology of COPD in order to identify new therapeutic targets. Animal models of COPD for early drug testing are not very satisfactory [7]. There are uncertainties about how to test drugs for COPD, which may require long-term studies (over 3 yrs) in relatively large numbers of patients. Many patients with COPD may have comorbidities, such as ischaemic heart disease and diabetes, which may exclude them from clinical trials of new therapies. There is little information about surrogate markers, for example

biomarkers in blood, sputum or breath, to monitor the short-term efficacy and predict the long-term potential of new treatments. However, progress is underway and there are several classes of drug that are now in pre-clinical and clinical development [4].

SMOKING CESSATION

Cigarette smoking is the major cause of COPD in the world and smoking cessation is the only therapeutic intervention so far shown to reduce disease progression. Nicotine addiction is the major problem and treatment should be directed at dealing with this addictive state. An important advance has been the discovery that a short course of the antidepressant bupropion is an effective adjunct for smoking cessation in patients with COPD [8]. However, the relatively poor long-term quit rate (16% at 6 months) means that more effective approaches are needed. In the future these may arise from a greater understanding of the neural mechanisms involved in nicotine addiction, such as dopaminergic pathways in the nucleus accumbens [9] or the development of vaccines against nicotine [10].

NEW BRONCHODILATORS

Since bronchodilators are the mainstay of current management [11], a logical approach is to improve existing bronchodilators. Several once-daily inhaled β_2 -agonists are now in clinical development, and the once-daily inhaled anticholinergic tiotropium has recently become available in several countries [12]. Long-term studies with tiotropium bromide have demonstrated significant improvement in symptoms and improvement in the quality of life, as well as an unexpected reduction

in exacerbations [13]. Tiotropium is likely to have additive effects when combined with long-acting β_2 -agonists making once-daily combination bronchodilator inhalers a likely development.

INFLAMMATION IN COPD

Several cells and inflammatory mediators are likely to be involved in COPD (fig. 1), as many inflammatory cells and structural cells are activated and there is an on-going inflammatory process, even in patients who have given up smoking [2, 14]. The profile of mediators in COPD differs from that in asthma, so that different mediator antagonists are likely to be effective. Since COPD is characterised by inflammation with macrophages and neutrophils, attention has largely focused on inhibiting recruitment and activation of these cells, and on antagonism of their products (table 1). Many chemokines and cytokines have now been implicated in COPD and several are targets for the development of new therapies [15]. It is thought that inflammation then mediates excess mucus production, fibrosis and proteolysis; these processes contributing to mucus bronchitis, obstructive bronchiolitis and emphysema.

Corticosteroid resistance

Four large controlled trials of inhaled corticosteroids of 3-yr duration have demonstrated little effect on the loss of lung function that occurs in COPD, although there is a reduction in the number of exacerbations [16]. Neither inhaled nor oral corticosteroids suppress the inflammation in COPD lungs and alveolar macrophages appear to be steroid resistant [17]. There may be an active resistance to corticosteroids due to an inhibitory effect of cigarette smoke on histone deacetylation, which is required for corticosteroids to switch off inflammatory genes [18, 19]. Based on this insight, therapeutic strategies that unlock the molecular mechanism of resistance might be possible, since drugs that increase histone deacetylase activity may resensitise cells to the effects of corticosteroids. For example, theophylline in low concentrations increases the activation of histone deacetylases (HDAC)s and increases the responsiveness to corticosteroids, at least *in vitro* [20, 21]. A search for other drugs that activate HDAC may be another approach. Combination inhalers of a steroid and a long-acting β_2 -agonist appear to be more effective than either drug alone, and it is possible that there is some molecular synergy between these drugs [22, 23]

MEDIATOR ANTAGONISTS

Suppression of the inflammatory response with anti-inflammatory treatments is a logical approach to the treatment of COPD and may be expected to improve symptoms such as cough and mucus secretion, improve health status and reduce exacerbations. In the long-term such treatments should reduce disease progression. However, no effective anti-inflammatory therapies currently exist so it is difficult to predict what their clinical outcome will be. The easiest approach is to block the synthesis or effects of inflammatory mediators known to be generated in COPD.

Antioxidants

Oxidative stress is increased in patients with COPD [24, 25], particularly during exacerbations, and reactive oxygen species contribute to its pathophysiology [26]. This suggests that

TABLE 1 Potential new therapies for chronic obstructive pulmonary disease

Target	Candidate therapies
Smoking	Drugs acting on neural nicotine addiction
Oxidants	Antioxidants (e.g. stable glutathione analogues) Resveratrol
Leukotrienes	Inducible nitric oxide synthase inhibitors BLT1 receptor antagonists (LY 29311, SB 201146, BIL284) 5'-lipoxygenase inhibitors (zileuton, Bay x1005)
Adhesion molecules	Anti-CD11/CD18, anti-ICAM-1 E-selectin inhibitors
Chemokines	CXCR2 antagonists (SB 225002) CCR2 antagonists CXCR3 antagonists
Cytokines	TNF- α inhibitors (infliximab, etanercept) TNF- α converting enzyme (TACE) inhibitors Interleukin-10 and analogues
Phosphodiesterase-4	PDE-4 inhibitors (cilomilast, roflumilast)
Kinases and transcription factors	NF- κ B inhibitors (IKK-2 inhibitors, proteasome inhibitors, I κ B- α gene transfer) p38 MAP kinase inhibitors (SB203580, SB 239063) PI-3 kinase- γ inhibitors PPAR activators
Mucus hypersecretion	EGF receptor kinase inhibitors (gefitinib) Calcium-activated chloride channel inhibitors (niflumic acid, MSI 1956)
Fibrosis	TGF- β_1 receptor kinase inhibitors Fibroblast growth factor inhibitors PAR-2 inhibitors
Proteinases	Endogenous antiproteinases: α_1 -AT, SLPI, TIMPs, elafin Neutrophil elastase inhibitors Cysteine proteinase inhibitors Matrix metalloproteinase inhibitors
Lung regeneration agents	Retinoic acid (all-trans retinoic acid) Retinoic acid receptor- γ agonists Stem cells

BLT1: leukotriene B₄ receptor type 1; ICAM-1: intercellular adhesion molecule-1; CXCR: cysteine-x-cysteine receptor; CCR: cysteine-cysteine receptor; TNF- α : tumour necrosis factor- α ; PDE-4: phosphodiesterase-4; NF- κ B: nuclear factor- κ B; IKK: inhibitor of I κ B kinase; I κ B- α : inhibitor of NF- κ B; MAP: mitogen activated protein; PI-3: phosphoinositide-3; PPAR: peroxisome proliferation activated receptor; EGF: epidermal growth factor; TGF- β_1 : transforming growth factor- β_1 ; PAR: proteinase-activated receptor; α_1 -AT: α_1 -antitrypsin; SLPI: secretory leukoprotease inhibitor; TIMP: tissue inhibitor of matrix metalloproteinases.

antioxidants may be of use in the therapy of COPD. N-acetyl cysteine (NAC) provides cysteine for enhanced production of the antioxidant glutathione and has antioxidant effects *in vitro* and *in vivo*. A systematic review of studies with oral NAC in COPD suggested a small reduction in exacerbations [27]. More effective antioxidants, including stable glutathione compounds, analogues of superoxide dismutase and selenium-based drugs, are now in development for clinical use [28, 29].

Resveratrol

Resveratrol is a phenolic component of red wine that has anti-inflammatory and antioxidant properties. It has a marked inhibitory effect on cytokine release from alveolar macrophages from COPD patients that show little or no response to corticosteroids [30]. The molecular mechanism of this action is currently unknown [31], but identification of the cellular target for resveratrol may lead to the development of a novel class of anti-inflammatory compounds. Resveratrol itself has a very low oral bioavailability so related drugs or a suitable inhaled formulation will need to be developed.

Nitric oxide synthase inhibitors

Oxidative stress and increased nitric oxide release from activity of inducible nitric oxide synthase (iNOS) may result in the formation of peroxynitrite; this is a potent radical that nitrates proteins and alters their function. 3-Nitrotyrosine may indicate peroxynitrite formation and is markedly increased in sputum macrophages of patients with COPD [32]. Selective inhibitors of iNOS are now in development and one of these, a prodrug of L-N⁶-(1-iminoethyl)lysine gives a profound and long-lasting reduction in the concentrations of nitric oxide in exhaled breath [33].

Leukotriene inhibitors

LTB₄ is a potent chemoattractant of neutrophils and is increased in the sputum and exhaled breath of patients with COPD [34, 35]. It is probably derived from alveolar macrophages as well as neutrophils and may be synergistic with interleukin (IL)-8. Two subtypes of receptor for LTB₄ have been described; leukotriene B₄ receptor type 1 (BLT₁) receptors are expressed mainly on granulocytes and monocytes, whereas B₄ receptor type 2 (BLT₂) receptors are expressed on T-lymphocytes [36]. BLT₁ antagonists, such as LY29311, have now been developed for the treatment of neutrophilic inflammation [37]. LY29311 and another antagonist, SB225002, inhibit the neutrophil chemotactic activity of sputum from COPD patients, indicating the potential clinical value of such drugs [38, 39]. Several selective BLT₁ antagonists are now in development. LTB₄ is synthesised by 5'-lipoxygenase, of which there are several inhibitors, although there have been problems in clinical development of drugs in this class because of side effects. A recent pilot study in COPD patients with a 5'-lipoxygenase inhibitor BAYx1005 showed only a modest reduction in sputum LTB₄ concentrations but no effect on neutrophil activation markers [40].

Chemokine inhibitors

Several chemokines are involved in neutrophil chemotaxis, these being mainly chemokines of the cysteine-x-cysteine (CXC) family, and chemokine antagonists are of potential therapeutic benefit in COPD [41]. IL-8 levels are markedly elevated in the sputum of patients with COPD and are correlated with disease severity [42]. Blocking antibodies to IL-8 reduce the chemotactic response of neutrophils to sputum from COPD patients [39]. A human monoclonal antibody to IL-8 is now in clinical trials for COPD, but other CXC chemokines are also involved in COPD. IL-8 activates neutrophils *via* a specific low affinity G-protein coupled receptor (CXCR1) coupled to activation and degranulation and *via* a high affinity receptor (CXCR2), shared with other members of the CXC

family, which is important in chemotaxis. Other CXC chemokines, such as growth related oncoprotein- α , are also elevated in COPD [43] and therefore a CXCR2 antagonist is likely to be more useful than a CXCR1 antagonist, particularly as CXCR2 are also expressed on monocytes. Indeed, inhibition of monocyte chemotaxis may prevent the marked increase in macrophages found in the lungs of patients with COPD. Small molecule inhibitors of CXCR2, such as SB225002, have now been developed and are entering clinical trials [44].

CC-chemokines are also involved in COPD. There is increased expression of monocyte chemotactic protein-1 and its receptor cysteine-cysteine receptor (CCR)2 in macrophages and epithelial cells from COPD patients and this may play a role in recruitment of blood monocytes to the lungs of COPD patients [45]. This suggests that CCR2 antagonists may be of use and small molecule inhibitors are in clinical development.

Chemokine receptors are also important for the recruitment of CD8+ T-cells, which predominate in COPD airways and lungs and might contribute to the development of emphysema. CD8+ cells show increased expression of CXCR3 and there is up-regulation of CXCR3 ligands, such as CXCL10 (IP-10), in peripheral airways of COPD patients [46]. This suggests that CXCR3 antagonists might also be useful.

Tumour necrosis factor- α inhibitors

TNF- α and soluble TNF receptor concentrations are raised in the sputum of COPD patients [42, 47]. TNF- α augments inflammation and induces IL-8 and other chemokines in airway cells *via* activation of the transcription factor nuclear factor- κ B (NF- κ B). The severe wasting in some patients with advanced COPD might be due to skeletal muscle apoptosis, resulting from increased circulating TNF- α . COPD patients with cachexia have increased release of TNF- α from circulating leukocytes [48]. Humanised monoclonal TNF antibody (infliximab) and soluble TNF receptors (etanercept) that are effective in other chronic inflammatory diseases, such as rheumatoid arthritis and inflammatory bowel disease, should also be effective in COPD, particularly in patients who have systemic symptoms [49]. Trials of anti-TNF therapies in patients with systemic features of COPD are currently underway. TNF- α converting enzyme (TACE), which is required for the release of soluble TNF- α , may be a more attractive target as it is possible to discover small molecule TACE inhibitors, some of which are also matrix metalloproteinase inhibitors. General anti-inflammatory drugs, such as phosphodiesterase inhibitors and p38 mitogen-activated protein (MAP) kinase inhibitors, also potentially inhibit TNF- α expression.

ANTI-INFLAMMATORY APPROACHES

Adhesion molecule blockers

Recruitment of neutrophils, monocytes and cytotoxic T-cells into the lungs and respiratory tract is dependent on adhesion molecules expressed by these cells and on endothelial cells in the pulmonary and bronchial circulations. Several adhesion molecules can now be inhibited pharmacologically. For example, E-selectin on endothelial cells interacts with sialyl Lewis(x) on neutrophils. A mimic of sialyl Lewis(x), bimosiamose (Revotar Biopharmaceuticals, Henningsdorf, Germany), blocks selectins and inhibits granulocyte adhesion, with preferential effects on neutrophils [50]. However, there are

concerns about this therapeutic approach for a chronic disease, as an impaired neutrophilic response may increase the susceptibility to infection. The expression of macrophage associated antigen-1 (Mac-1) (CD11b/CD18) is increased on neutrophils of patients with COPD, suggesting that targeting this adhesion molecule, which is also expressed on monocytes and macrophages, might be beneficial [51].

Interleukin-10

IL-10 is a cytokine with a wide spectrum of anti-inflammatory actions. It inhibits the secretion of TNF- α and IL-8 from macrophages, and tips the balance in favour of antiproteases by decreasing the expression of matrix MMP, while increasing the expression of endogenous tissue inhibitors of MMPs. IL-10 concentrations are reduced in induced sputum from patients with COPD, so that this may be a mechanism for increasing lung inflammation [52]. IL-10 is currently in clinical trials for other chronic inflammatory diseases (inflammatory bowel disease, rheumatoid arthritis and psoriasis), including patients with steroid resistance, but IL-10 may cause haematological side effects. IL-10 may have therapeutic potential in COPD, especially if a selective activator of IL-10 receptors or unique signal transduction pathways can be developed in the future.

Phosphodiesterase-4 inhibitors

PDE4 is the predominant PDE expressed in neutrophils, CD8+ cells and macrophages, suggesting that PDE4 inhibitors would be effective in controlling inflammation in COPD [53]. Selective PDE4 inhibitors, such as cilomilast and roflumilast, are active in animal models of neutrophil inflammation. Cilomilast had promising beneficial clinical effects in a 6-week study in patients with moderate-to-severe COPD [54] and has some anti-inflammatory effects measurable in airway biopsies [55]. Roflumilast appears to be better tolerated at doses that significantly inhibit TNF- α release from peripheral blood monocytes. PDE4 inhibitors have been limited by side effects, particularly nausea and other gastrointestinal effects, but it might be possible to develop more selective inhibitors in the future that are less likely to be dose-limited by adverse effects.

Several steps may be possible to overcome the limitation of side effects. It now seems likely that vomiting is due to inhibition of a particular subtype of PDE4. At least four human PDE4 genes have been identified and each has several splice variants [56]. This raises the possibility that subtype-selective inhibitors may be developed that may preserve the anti-inflammatory effect, while having less propensity to side effects. PDE4D appears to be of particular importance in nausea and vomiting and is expressed in the chemosensitive trigger zone in the brain stem [57] and in mice deletion of the gene for PDE4D prevents a behavioural equivalent of emesis [58]. This isoenzyme appears to be less important in anti-inflammatory effects and targeted gene disruption studies in mice indicate that PDE4B is more important than PDE4D in inflammatory cells [59]. PDE4B selective inhibitors may therefore have a greater therapeutic ratio and theoretically might be effective anti-inflammatory drugs. Cilomilast is selective for PDE4D and therefore has a propensity to cause emesis, whereas roflumilast, which is nonselective for PDE4 isoenzymes, has a more favourable therapeutic ratio. Several other potent PDE4 inhibitors with a more favourable therapeutic

ratio are now in clinical development for COPD. Another approach is to give the PDE4 inhibitor by inhalation and some PDE4 inhibitors have a low oral bioavailability and are retained in the lung, so appear to be suitable for inhaled delivery [60].

NF- κ B inhibitors

NF- κ B regulates the expression of IL-8 and other chemokines, TNF- α and other inflammatory cytokines, and some MMPs. NF- κ B is activated in macrophages and epithelial cells of COPD patients, particularly during exacerbations [61, 62]. There are several possible approaches to inhibition of NF- κ B, including gene transfer of the inhibitor of NF- κ B, inhibitors of IKK, NF- κ B-inducing kinase and I κ B ubiquitin ligase, which regulate the activity of NF- κ B, and the development of drugs that inhibit the degradation of I κ B [63]. The most promising approach may be the inhibition of IKK-2 by small molecule inhibitors, several of which are now in development [64]. A small molecule IKK-2 inhibitor suppresses the release of inflammatory cytokines and chemokines from alveolar macrophages and might be effective in COPD as alveolar macrophages are resistant to the anti-inflammatory actions of corticosteroids [17]. One concern about long-term inhibition of NF- κ B is that effective inhibitors may result in immune suppression and impair host defences, since mice that lack NF- κ B genes succumb to septicemia. However, there are alternative pathways of NF- κ B activation *via* kinases other than IKK that might be more important in inflammatory disease [65].

p38 mitogen-activated protein kinase inhibitors

MAP kinases play a key role in chronic inflammation and several complex enzyme cascades have now been defined [66]. One of these, the p38 MAP kinase pathway is activated by cellular stress and regulates the expression of inflammatory cytokines, including IL-8, TNF- α and MMPs. Small molecule inhibitors of p38 MAP kinase, such as SB 203580, SB 239063 and RWJ 67657, have been developed and these drugs have a broad range of anti-inflammatory effects [67]. SB 239063 reduces neutrophil infiltration after inhaled endotoxin and the concentrations of IL-6 and MMP-9 in the bronchoalveolar lavage fluid of rats, indicating its potential as an anti-inflammatory agent in COPD [68]. It is likely that such a broad spectrum anti-inflammatory drug will have some toxicity, but inhalation may be a feasible therapeutic approach.

Phosphoinositide 3-kinase inhibitors

Phosphoinositide (PI)-3Ks are a family of enzymes that lead to the generation of lipid second messengers that regulate a number of cellular events. A particular isoform, PI-3K γ , is involved in neutrophil recruitment and activation. Knock-out of the PI-3K γ gene results in inhibition of neutrophil migration and activation, as well as impaired T-lymphocyte and macrophage function [69]. This suggests that selective PI-3K γ inhibitors may have relevant anti-inflammatory activity in COPD and small molecule inhibitors of PI-3K γ and PI-3K δ are in development [70].

Peroxisome proliferators-activated receptor activators

Peroxisome proliferator-activated receptors (PPARs) are a family of ligand-activated nuclear hormone receptors belonging to the steroid receptor superfamily, and the three

recognised subtypes PPAR- α , - γ and - δ are widely expressed. There is evidence that activation of PPAR- α and PPAR- δ may have anti-inflammatory and immunomodulatory effects. For example, PPAR- γ agonists, such as troglitazone, inhibit the release of inflammatory cytokines from monocytes and induce apoptosis of T-lymphocytes, suggesting that they may have anti-inflammatory effects in COPD [71, 72].

DRUGS ACTING ON STRUCTURAL CELLS

Mucoregulators

Mucus hypersecretion is commonly seen in cigarette smokers, but is not necessarily associated with airflow limitation. In individuals with COPD mucus hypersecretion is associated with more rapid decline in forced expiratory volume in one second and increased frequency of exacerbations [73]. Reducing mucus hypersecretion may therefore have therapeutic benefit, although suppression of the normal airway mucus secretion may be detrimental. Mucolytic drugs have been used for many years to reduce mucus viscosity but these drugs do not appear to have any clinical value. Several novel approaches to inhibiting mucus hypersecretion are currently being explored [74]. Mucus hypersecretion in COPD appears to be largely driven by the neutrophil inflammatory response, so that effective anti-inflammatory treatments would be expected to reduce mucus hypersecretion [74].

Epidermal growth factor (EGF) plays a critical role in airway mucus secretion from goblet cells and submucosal glands and appears to mediate the mucus secretory response to several secretagogues, including oxidative stress, cigarette smoke and inflammatory cytokines [75]. EGF may also be responsible for the mucus hyperplasia seen in chronic bronchitis. Small molecule inhibitors of EGF receptor kinase, such as gefitinib, have now been developed for clinical use.

Another novel approach involves inhibition of CACC, which are important in mucus secretion from goblet cells. Activation of human hCLCA1 induces mucus secretion and mucus gene expression and may therefore be a target for inhibition. Small molecule inhibitors of CACC, such as niflumic acid and MSI 1956, have been developed [76]. Other approaches include inhibition of the neural mechanisms driving mucus secretion, including tachykinin receptor antagonists and potassium channel openers [77].

Fibrosis inhibition

TGF- β_1 is highly expressed in airway epithelium and macrophages of small airways in patients with COPD [78, 79]. It is a potent inducer of fibrosis, partly *via* the release of the potent fibrogenic mediator connective tissue growth factor, and may be important in inducing the fibrosis and narrowing of peripheral airways (obstructive bronchiolitis) in COPD. TGF- β_1 also activates MMP-9, which then further activates TGF- β_1 , thus providing a link between small airway fibrosis and emphysema in COPD. MMP-9 may mediate proteolysis of TGF- β -binding protein, and this may be a mechanism for physiological release of TGF- β_1 [80]. TGF- β_1 also down regulates β_2 -adrenoceptors [81] and impairs bronchodilator responses to β_2 -agonists [82]. Inhibition of TGF- β_1 signalling may therefore be a useful therapeutic strategy in COPD. Small molecule antagonists that inhibit TGF- β receptor kinase or TGF- β activated pathways are now in development [83],

although the long-term safety of such drugs might be a problem, particularly as TGF- β affects tissue repair and is a potent anti-inflammatory mediator.

Proteinase-activated receptor-2 (PAR-2) expression is widespread in the airways, and expression is increased in the central airways of smokers and nonsmokers [84]. PAR-2 may be involved in MMP-9 release from airway epithelial cells and proliferation of fibroblasts [85, 86]. However, a potential drawback for strategies to antagonise PAR-2 is that activation of epithelial PAR-2 causes bronchoprotection in the airways.

Antiproteases

There is compelling evidence for an imbalance between proteases that digest elastin (and other structural proteins) and antiproteases that protect against this [87]. This suggests that either inhibiting these proteolytic enzymes or increasing endogenous antiproteases may be beneficial and theoretically should prevent the progression of airflow obstruction in COPD. Considerable progress has been made in identifying the enzymes involved in elastolytic activity in emphysema and in characterising the endogenous antiproteases that counteract this activity [87]. The fact that there are so many proteinases implicated in COPD might mean that blocking a single enzyme may not have a major effect.

One approach is to give endogenous antiproteases (α_1 -antitrypsin, secretory leukoprotease inhibitor, elafin, tissue inhibitors of MMP), either in recombinant form or by viral vector gene delivery [88, 89]. These approaches are unlikely to be cost effective as large amounts of protein have to be delivered and gene therapy is unlikely to provide sufficient protein.

A more promising approach is to develop small molecule inhibitors of proteases, particularly those that have elastolytic activity [90]. Small molecule inhibitors, such as ONO-5046 and FR901277, have been developed that have high potency. These drugs inhibit neutrophil elastase-induced lung injury in experimental animals, whether given by inhalation or systemically and also inhibit the other serine proteinases released from neutrophils, cathepsin G and proteinase-3. Small molecule inhibitors of neutrophil elastase are in clinical development, but there is concern that neutrophil elastase may not play a critical role in emphysema and that other proteinases are more important in elastolysis. Inhibitors of elastolytic cysteine proteinases, such as cathepsins K, S and L that are released from macrophages, are also in development [91]. MMPs with elastolytic activity (such as MMP-9) may also be a target for drug development, although nonselective MMP inhibitors, such as marimastat, appear to have considerable musculoskeletal side effects [92]. It is possible that side effects could be reduced by increasing selectivity for specific MMPs or by targeting delivery to the lung parenchyma. MMP-9 is markedly over-expressed by alveolar macrophages from patients with COPD and is the major elastolytic enzyme released by these cells [93], so a selective MMP-9 inhibitor might be useful in the treatment of emphysema.

Lung regeneration

Since a major mechanism of airway obstruction in COPD is due to loss of elastic recoil due to proteolytic destruction of

lung parenchyma, it seems unlikely that this could be reversible by drug therapy, although it might be possible to reduce the rate of progression by preventing the inflammatory and enzymatic disease process. Retinoic acid increases the number of alveoli in developing rats and, remarkably, reverses the histological and physiological changes induced by elastase treatment of adult rats [94, 95]. However, this is not observed in other species [96]. Retinoic acid activates retinoic acid receptors, which act as transcription factors to regulate the expression of many genes involved in growth and differentiation. The molecular mechanisms involved and whether this can be extrapolated to humans is not yet known. Several retinoic acid receptor subtype agonists have now been developed that may have a greater selectivity for this effect and therefore a lower risk of side effects. The receptor mediating the effect on alveoli appears to be the retinoic acid receptor- γ [95]. A short-term trial of all-trans-retinoic acid in patients with emphysema did not show any improvement in clinical parameters [97], but a longer study is currently underway. This approach is unlikely to be successful as adult human lung, unlike rat lung, has less potential for repair after surgical resection for example.

Another approach to repairing damaged lung in emphysema is the use of stem cells to seed the lung [98]. Type 2 pneumocytes and Clara cells might be suitable for alveolar repair and this is currently an active area of research.

FUTURE DIRECTIONS

New drugs for the treatment of COPD are greatly needed. While preventing and quitting smoking is the obvious preferred approach, this has proved to be very difficult in the majority of patients. It is important to identify the genetic factors that determine why only a minority of heavy smokers develop COPD [99], and identification of genes that predispose to the development of COPD may provide novel therapeutic targets. However, it will be difficult to demonstrate the efficacy of novel treatments on the rate of decline in lung function, since this requires large studies over 3 yrs. Hence, there is a need to develop novel outcome measures and surrogate biomarkers, such as analysis of sputum parameters (cells, mediators, enzymes) or exhaled condensates (lipid mediators, reactive oxygen species) [100]. The use of imaging techniques, such as high resolution computerised tomography (CT) to measure disease progression is another promising approach as scanning resolution increases [101]. It may also be important to more accurately define the presence of emphysema *versus* small airway obstruction using CT scans, as some drugs may be more useful for preventing emphysema, whereas others may be more effective against the small airway inflammatory-fibrotic process. More research on the basic cellular and molecular mechanisms of COPD is urgently needed to aid the logical development of new therapies for this common and important disease, for which no effective preventative treatments currently exist.

Of the drugs currently in development phosphodiesterase-4 inhibitors, p38 mitogen activated protein kinase inhibitors and low affinity G-protein coupled receptor antagonists show particular promise as anti-inflammatory therapies over the next 5–10 yrs. It is likely that effective anti-inflammatory therapies would not only reduce exacerbations, but would also

improve symptoms and health status. In the long-term these drugs should slow the decline in lung function and prevent the considerable morbidity imposed by this common disease.

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