Ann Ist Super Sanità 2003;39(4):573-582

New treatments for chronic obstructive pulmonary disease

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Summary. - No currently available treatments reduce the progression of chronic obstructive pulmonary disease (COPD) or suppress the inflammation in small airways and lung parenchyma. However, several new treatments now in development for COPD are targeted at the inflammation process. Antagonists of mediators, such as leukotriene B4, interleukin-8, and tumour necrosis factor-α and inhibitors of oxidative and nitrative stress are in clinical development. Phosphodiesterase-4 inhibitors are in clinical trials and drugs that inhibit p38 MAP kinase, nuclear factor-κB and phosphoinositide-3 kinase-γ are now in early development. There is also a search for elastase inhibitors to prevent the development of emphysema and drugs that may even reverse the lung destruction.

Key words: anti-inflammatory, phosphodiesterase-4 inhibitors, TNF-α, nuclear factor-κB, elastase.

Riassunto *(Nuove terapie per la broncopneumopatia cronica ostruttiva)*. - Nessuna terapia, attualmente disponibile, è in grado di diminuire la progressione della broncopneumopatia cronica ostruttiva o di inibire l'infiammazione nelle piccole vie aeree o nel parenchima polmonare. Comunque, esistono numerose nuove strategie terapeutiche, attualmente in fase di sperimentazione, che sono dirette contro il processo infiammatorio. Antagonisti di mediatori dell'infiammazione come leucotriene B4, interleuchina-8 e tumour necrosis factor-α, ed inibitori dello stress ossidativo e nitrosante sono in fase di sperimentazione clinica. Sono in corso studi clinici con inibitori della fosfodiesterasi-4 e farmaci che inibiscono la p38 MAP chinasi, il fattore nucleare κB e la fosfoinositide-3 chinasi-γ sono attualmente in fase iniziale di sperimentazione. Inoltre, sono in corso ricerche su inibitori della elastasi per prevenire la comparsa di enfisema e su farmaci che possano anche ripristinare la struttura polmonare.

Parole chiave: antiinfiammatori, inibitori della fosfodiesterasi-4, TNF-α, fattore nucleare kB, elastasi.

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most important causes of morbidity and mortality in the world and the only major cause of mortality whose incidence is rising [1]. The WHO and World Bank predict that COPD will become the 5th commonest global cause of disability and the 3rd commonest cause of death in the world by 2020 [2]. Despite its enormous global importance, there has been relatively little research into COPD and it is the most underfunded disease in relation to the global burden of disease [3].

There is a major need to develop new treatments for COPD, as no currently available drug therapy reduces the relentless progression of the disease. There is a particular need to develop drugs that control the underlying inflammatory and destructive processes that underlie this disease. There have been 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 underlying disease [4-6]. Although COPD is commonly treated with drugs developed for asthma, this is often inappropriate as the inflammatory process in COPD differs markedly from that in asthma [7, 8].

Recognition of the global importance and rising prevalence of COPD and the absence of effective therapies has now led to a concerted effort to develop new drugs for this disease [9, 10].

Rational therapy depends on understanding the underlying disease process and there have been recent advances in understanding the cellular and molecular mechanisms that may be involved. COPD involves a chronic inflammation in small airways and lung parenchyma, with the involvement of neutrophils, macrophages and cytotoxic ($CD8^+$) T-lymphocytes. This inflammation results in fibrosis with narrowing of small airways (chronic obstructive bronchitis) and lung parenchymal destruction due to the action of various proteases, such as neutrophil elastase and matrix metal-

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loproteinases (emphysema). This inflammation is quite different from that seen in asthma, indicating that different treatments are likely to be needed [7].

Discovering new drugs for COPD

There are several reasons why drug development in COPD may be difficult. Only recently there has been any research interest in the molecular and cell biology of COPD in order to identify new therapeutic targets [11]. There are no satisfactory animal models of COPD for early drug testing [12, 13]. There are uncertainties about how to test drugs for COPD, which may require long-term studies (over 3 years) in relatively large numbers of patients. There is little information about surrogate markers to monitor the short-term efficacy of new treatments. However, some progress is underway and there are several classes of drug that are now in pre-clinical and clinical development [9, 14].

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. The major approaches have involved behavioural approaches and nicotine replacement therapy, but the overall rates of quitting are small (5-15%) [15]. An important advance has been the discovery that the antidepressant bupropion given as a short course (6-9 weeks) is the most effective treatment so far described, with sustained quit rates of 18% at 12 months, compared with 9% with nicotine skin patches and 6% with placebo [16]. Results in patients with COPD are similar [17]. This does not appear to be a general effect of antidepressants, although nortryptiline has some effect [18]. Bupropion is well tolerated apart from sleeplessness, but epileptic fits occur in approximately 0.1% of patients, predominantly those with previous epilepsy [19]. In the future more effective drugs may arise from a better understanding of the neurotransmitter pathways involved in nicotine addition and advances are likely to come from research in neurosciences.

New bronchodilators

Since bronchodilators are the mainstay of current management, a logical approach is to improve existing bronchodilators. Once daily inhaled β_2-agonists are not in clinical development, but the long-acting inhaled anticholinergic tiotropium has recently become available in some countries.

Tiotropium bromide

Tiotropium bromide is a long-acting anticholinergic drug that has a unique kinetic selectivity, with very slow dissociation form M_1 and M_3 muscarinic receptors [20, 21]. Clinical studies in COPD now indicate that inhaled tiotropium once daily is an effective bronchodilator in patients with COPD and more effective than conventional ipratropium bromide four times a day [22-24]. 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 [25, 26]. Tiotropium is likely to become the bronchodilator of choice in COPD and may have additive effects with long-acting β_2-agonists.

Mediator antagonists

Several inflammatory mediators are likely to be involved in COPD as many inflammatory cells and structural cells are activated and there is an on-going

Table 1. - Mediator antagonists for chronic obstructive pulmonary disease (COPD)

LTB_4 antagonists (LY 29311, SC-53228, CP-105,696, SB 201146, BIIL284)
5'-lipoxygenase inhibitors (zileuton, Bay x 1005)
Chemokine inhibitors
Interleukin-8 antagonists (CXCR2 antagonists e.g. SB 225002)
MCP antagonists (CCR2 antagonists)
TNF-inhibitors (monoclonal antibodies, soluble receptors, TNF-α converting enzyme inhibitors)
Antioxidants (e.g. stable glutathione analogues)
iNOS inhibitors (e.g. L-NIL)

LTB_4: leukotriene B_4; MCP: monocyte chemotactic protein; TNF: tumor necrosis factor; COX: cyclo-oxigenase; iNIOS: inducible oxide synthase.

inflammatory process, even in patients who have given up smoking [27]. The profile of mediators in COPD is different from that in asthma, so that different drugs are likely to be effective. Since COPD is characterized by a neutrophilic inflammation, attention has largely focused on mediators involved in recruitment and activation of neutrophils or on reactive oxygen species in view of the increased oxidative stress in COPD (Table 1).

Leukotriene B_4 inhibitors

Leukotriene B_4 (LTB_4) is a potent chemoattractant of neutrophils and is increased in the sputum of patients with COPD [28]. It is probably derived from alveolar macrophages as well as neutrophils and may be synergistic with interleukin-8. Two subtypes of receptor for LTB_4 have been described, BLT_1 receptors are mainly expressed on granulocytes and monocytes, whereas BLT_2 receptors are expressed on T lymphocytes [29]. BLT_1 antagonists, such as LY29311, have now been developed for the treatment of neutrophilic inflammation [30]. LY29311 inhibits the neutrophil chemotactic activity of sputum from COPD patients, indicating the potential clinical value of such drugs [31]. Selective LTB_4 receptor antagonists are now in development, including SC-53228, CP-105,696, SB 201146 and BIIL284. LTB_4 is synthesised by 5'-lipoxygenase (5-LO), of which there are several inhibitors, although there have been problems in clinical development of drugs in this class because of side effects.

Chemokine inhibitors

Several chemokines are involved in neutrophil chemotaxis and mainly belong to the CXC family, of which the most prominent member is IL-8. IL-8 levels are markedly elevated in the sputum of patients with COPD and are correlated with disease severity [32]. Blocking antibodies to IL-8 and related chemokines inhibit certain types of neutrophilic inflammation in experimental animals and reduce the chemotactic response of neutrophils to sputum from COPD patients [28]. A human monoclonal antibody to IL-8 blocks the chemotactic response of neutrophils to IL-8 and is effective in animal models of neutrophilic inflammation [33]. This antibody is now in clinical trials, but it may be less effective than drugs that block the common receptor for other members of the CXC chemokine family. IL-8 activates neutrophils via a specific low affinity G-protein coupled receptor (CXCR1) coupled to activation and degranulation and a high affinity receptor (CXCR2), shared by other members of the CXC family, which is important in chemotaxis [34]. Other CXC chemokines, such as growth related oncoprotein-α (GRO-α), are also elevated in COPD [35] and therefore a CXCR2 antagonist is likely to be more useful than a CXCR1 antagonist, particularly as CXCR2 receptors are also expressed on monocytes. Small molecule inhibitors of CXCR2, such as SB225002, have now been developed and are entering clinical trials [36, 37].

CC-chemokines are also involved in COPD. There is increased expression of monocyte chemotactic protein-1 (MCP-1) and its receptor CCR2 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 [38]. This suggests that CCR2 antagonists may be of use and small molecule inhibitors are now in development.

Tumour necrosis factor-α inhibitors

Tumour necrosis factor-α (TNF-α) levels are also raised in the sputum of COPD patients and TNF-α induces IL-8 in airway cells via activation of the transcription factor nuclear factor-κB (NF-κB) [32]. 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 [39]. 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 [40, 41]. There may be problems with long-term administration because of the development of blocking antibodies and repeated injections are inconvenient. 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 [42, 43]. General anti-inflammatory drugs such as phosphodiesterase inhibitors and p38 MAP kinase inhibitors also potently inhibit TNF-α expression.

Antioxidants

Oxidative stress is increased in patients with COPD [44, 45], particularly during exacerbations, and reactive oxygen species contribute to its pathophysiology [46]. This suggests that antioxidants may be of use in the therapy of COPD. N-acetyl cysteine (NAC) provides cysteine for enhanced production of glutathione (GSH) and has antioxidant effects *in vitro* and *in vivo*. Recent systematic reviews of studies with oral NAC in COPD suggest small but significant reductions in exacerbations [47, 48]. More effective antioxidants, including stable glutathione compounds, analogues of superoxide dismutase and selenium-based drugs, are now in development for clinical use [46, 49].

iNOS inhibitors

Oxidative stress and increased nitric oxide release from expression of inducible nitric oxide synthase (iNOS) may result in the formation of peroxynitrite, which is a potent radical and may nitrate proteins, resulting in altered function. 3-Nitrotyrosine may indicate peroxynitrite formation and is markedly increased in sputum macrophages of patients with COPD [50]. Selective inhibitors of iNOS are now in development [51] and one of these L-N6-(1-imminoethyl)lysine (L-NIL) gives a profound and long-lasting reduction in exhaled nitric oxide [52].

New anti-inflammatory treatments

COPD is characterised by chronic inflammation of the respiratory tract, even in ex-smokers, with increased numbers of macrophages, neutrophils and cytotoxic ($CD8^+$) T lymphocytes in airways and lung parenchyma [4, 8]. This suggests that anti-inflammatory treatments may be of value and there are several possible approaches (Fig. 1).

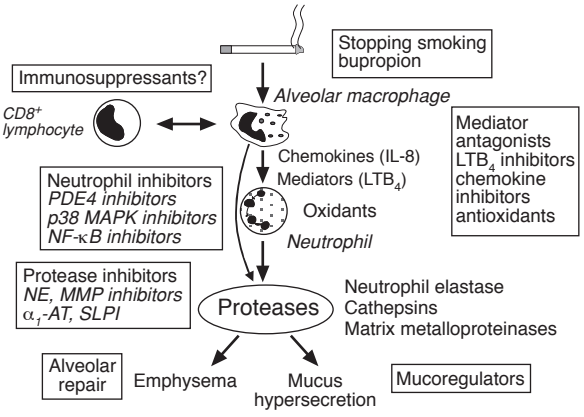

Fig. 1. - Targets for chronic obstructive pulmonary disease (COPD) therapy based on current understanding of the inflammatory mechanisms. Cigarette smoke (and other irritants) activate macrophages in the respiratory tract that release neutrophil chemotactic factors, including interleukin-8 (IL-8) and leukotriene B_4 (LTB_4). These cells then release proteases that break down connective tissue in the lung parenchyma, resulting in emphysema, and also stimulate mucus hypersecretion. These enzymes are normally counteracted by protease inhibitors, including α1-antitrypsin, secretory leukoprotease inhibitor (SLPI) and tissue inhibitor of matrix metalloproteinases (TIMP). Cytotoxic T cells ($CD8^+$) may also be involved in the inflammatory cascade.

Resistance to corticosteroids

Because there is chronic inflammation in COPD airways it was argued that inhaled corticosteroids might prevent the progression of the disease. However, four large 3 year controlled trials of inhaled corticosteroids have demonstrated no reduction in disease progression [53-56]. This might be predicted by the demonstration that neither inhaled nor oral corticosteroids have any significant effect on neutrophil counts, granule proteins, inflammatory or proteases in induced sputum [57-59]. Inhaled corticosteroids do not inhibit neutrophilic inflammation induced by ozone in humans [60] and this may reflect that corticosteroids prolong neutrophil survival [61]. There may also 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 [62]. The disappointing action of corticosteroids in COPD suggests that novel types of non-steroidal anti-inflammatory treatment may be needed. Alternatively, therapeutic strategies that unlock the molecular mechanism of resistance might be possible. For example drugs that increase histone deacetylase activity may resensitise cells to the effects of corticosteroids. There are several new approaches to anti-inflammatory treatment in COPD (Table 2).

Phosphodiesterase-4 inhibitors

Phosphodiesterase-4 (PDE4) is the predominant PDE expressed in neutrophils, $CD8^+$ cells and macrophages [63], suggesting that PDE4 inhibitors would be effective in controlling inflammation in COPD. Selective PDE4 inhibitors, such as cilomilast and roflumilast, are active in animal models of neutrophil inflammation [64, 65]. Cilomilast has some beneficial clinical effect in COPD patients [66] and larger studies are currently underway [67]. Roflumilast appears to be well tolerated at doses that significantly inhibit TNF-α release from peripheral blood monocytes [68]. PDE4 inhibitors are limited by side effects, particularly nausea and other gastrointestinal effects, but it might be possible to develop isoenzyme subtype selective inhibitors in the future which are less likely to be dose-limited by adverse effects.

NF-κB inhibitors

Nuclear factor κB regulates the expression of IL-8 and other chemokines, TNF-α, and some matrix metalloproteinases. There are several possible approaches to inhibition of NF-κB, including gene transfer of the inhibitor of NF-κB (IκB), a search for inhibitors of IκB kinases (IKK), NF-κB-inducing kinase (NIK) and IκB ubiquitin ligase, which regulate the activity of NF-κB,

and the development of drugs that inhibit the degradation of IκB [69]. The most promising approach may be the inhibition of IKK_{β} by small molecule inhibitors which are now in development. An apparently selective IKK inhibitor, hypoestoxide, is component of African folk remedy for inflammatory diseases. One concern about long-term inhibition of NF-κB is that effective inhibitors may result in immune suppression and impair host defences, since mice which lack NF-κB genes succumb to septicaemia. However, there are alternative pathways of NF-κB activation that might be more important in inflammatory disease [70].

Adhesion molecule blockers

Recruitment of neutrophils, monocytes and cytotoxic T cells into the lungs and respiratory tract is dependent on adhesion molecules expressed on 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-$Lewis^x$, TBC1269, blocks selectins and inhibits granulocyte adhesion, with preferential effects on neutrophils [71]. 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 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 [72].

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, but tips the balance in favour of antiproteases, by decreasing the expression of matrix metalloproteinases, while increasing the expression of endogenous tissue inhibitors of matrix metalloproteinases (TIMP). IL-10 concentrations are reduced in induced sputum from patients with COPD, so that this may be a mechanism for increasing lung inflammation [73]. 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 [74]. Treatment with daily injections of IL-10 over several weeks has been well tolerated. 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.

p38 MAP kinase inhibitors

Mitogen-activated protein (MAP) kinases play a key role in chronic inflammation and several complex enzyme cascades have now been defined. One of these, the p38 MAP kinase pathway, is involved in expression of inflammatory cytokines, including IL-8, TNF-α and MMPs [75, 76]. Non-peptide inhibitors of p38 MAP kinase, such as SB 203580, SB 239063 and RWJ 67657, have now been developed and these drugs have a broad range of anti-inflammatory effects [77]. SB 239063 reduces neutrophil infiltration after inhaled endotoxin and the concentrations of IL-6 and MMP-9 in bronchoalveolar lavage fluid of rats, indicating its potential as an anti-inflammatory agent in COPD [78]. 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

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-3Kγ, is involved in neutrophil recruitment and activation. Knock-out of the PI-3Kγ gene results in inhibition of neutrophil migration and activation, as well as impaired T-lymphocyte and macrophage function [79]. This suggests that selective PI-3Kγ inhibitors may have relevant anti-inflammatory activity in COPD.

Table 2. - New anti-inflammatory drugs for chronic obstructive pulmonary disease (COPD)

Phosphodiesterse-4 inhibitors (SB 207499, CP 80633, CDP-840)
NF-κB inhibitors (proteasome inhibitors, IκB kinase inhibitors, IκB-α gene transfer)
Adhesion molecule inhibitors (anti CD11/CD18, anti-ICAM-1, E-selectin inhibitors)
Interleukin-10 and analogues
p38 MAP kinase inhibitors (SB203580, SB 220025, RWJ 67657)
PI3 kinase-γ inhibitors
Immunomodulators: $CD8^+$ lymphocyte inhibitors

NF-κB: nuclear factor-kappa B; IκB: inhibitor of NF-κB; MAP: mitogen activated protein; PI: phosphoinositide.

Table 3. - Protease inhibitors

Endogenous antiproteases (α1-antitrypsin, secretory leukoprotease inhibitor, elafin, tissue inhibitors of MMP)
Serine protease inhibitors (ONO-5046, FR901277)
Cysteine-protease inhibitors
MPP inhibitors (marimastat, MMP-9 inhibitors)

MMP: matrix metalloproteinase.

Protease inhibitors

There is compelling evidence for an imbalance between proteases that digest elastin (and other structural proteins) and antiproteases that protect against this. 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 (Table 3). 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 [80, 81].

Endogenous antiproteases

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. 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.

Protease inhibitors

A more promising approach is to develop small molecule inhibitors of proteinases, particularly those that have elastolytic activity. Small molecule inhibitors, such as ONO-5046 and FR901277, have been developed which have high potency [82, 83]. These drugs inhibit neutrophil elastase-induced lung injury in experimental animals, whether given by inhalation or systemically and also inhibit the other serine proteases released from neutrophils cathepsin G and proteinase-3. Small molecule inhibitors of neutrophil elastase are now entering clinical trials, but there is concern that neutrophil elastase may not play a critical role in emphysema and that other proteases are more important in elastolysis. Inhibitors of elastolytic cysteine proteases, such as cathepsins K, S and L that are released from macrophages [84] are also in development [85]. Matrix metalloproteinases with elastolytic activity (such as MMP-9) may also be a target for drug development, although non-selective MMP inhibitors, such as marimastat, appear to have considerable side effects. 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 overexpressed by alveolar macrophages from patients with COPD [86], so a selective inhibitor might be useful in the treatment of emphysema.

Remodelling agents

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 [87, 88]. 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. A short-term trial of all-trans-retinoic acid in patients with emphysema that did not show any improvement in clinical parameters is currently underway [89].

Another approach to repairing damaged lung in emphysema is the use of stem cells to seed the lung [90]. Type 2 pneumocytes and Clara cells might be suitable for alveolar repair and this is an active area of research.

Mucus hypersecretion

Mucus hypersecretion is a feature of COPD and chronic simple bronchitis and usually responds to stopping smoking. There is increasing evidence that it might predispose to COPD and is a component of airflow limitation. Mucus secretion is very difficult to quantify in clinical trials and the effects of existing drugs, including mucolytics, on mucus secretion in COPD is uncertain. There are several new drugs, including protease inhibitors that may reduce mucus secretion [91]. Anti-inflammatory drugs that target neutrophils inflammation should also be effective.

Drug delivery

Bronchodilators are currently given as metered dose inhalers or dry powder inhalers that have been optimised to deliver drugs to the respiratory tract in

asthma. But in emphysema the inflammatory and destructive process takes place in the lung parenchyma and in chronic obstructive bronchitis the predominant irreversible changes are in small airways. This implies that if a drug is to be delivered by inhalation it should have a lower mass median diameter, so that there is preferential deposition in the lung periphery. It may be more appropriate to give therapy parenterally as it will reach the lung parenchyma via the pulmonary circulation, but parenteral administration may increase the risk of systemic side effects. Targeted delivery of drugs to particular cell types is another approach to limit toxicity. For example, alveolar macrophages may be targeted by molecules that are packaged to be phagocytosed by these cells. Another important concept is the idea of disease activation of drugs; for example, in COPD active drugs that are released from inactive prodrugs by elastases might be considered. This would concentrate the active drug at the site of disease activity and reduce systemic exposure.

Future directions

New drugs for the treatment of COPD are needed. While preventing and quitting smoking is the obvious preferred approach, this has proved to be very difficult in the majority of patients and even with bupropion only ~15% of patients are sustained quitters [16]. In addition, it is likely that the inflammatory process initiated by cigarette smoking may continue even when smoking has ceased [27]. Furthermore, COPD may be due to other environmental factors (cooking fumes, pollutants, passive smoking, other inhaled toxins) or due to developmental changes in the lungs [92].

Identification of novel therapeutic targets

It is important to identify the genetic factors that determine why only 10-20% of smokers develop COPD [93, 94]. Identification of genes that predispose to the development of COPD in smokers may identify novel therapeutic targets. Powerful techniques, including high density DNA arrays (gene chips) are able to identify multiple polymorphisms, differential display may identify the expression of novel genes and proteomics of novel proteins expressed.

Surrogate markers

It will be difficult to demonstrate the efficacy of novel treatments as determination of the effect of any drug on the rate of decline in lung function will require large studies over at least 2 years. There is a need to develop surrogate markers, such as analysis of sputum parameters (cells, mediators, enzymes) or exhaled condensates (lipid mediators, reactive oxygen species, cytokines) [95, 96], that may predict the clinical usefulness of such drugs. More research on the basic cellular and molecular mechanism of COPD and emphysema are urgently needed to aid the logical development of new therapies for this common and important disease for which no effective preventive treatments currently exist. It may also be important to more accurately define the presence of emphysema *versus* small airway obstruction using improved imaging techniques, as some drugs may be more useful for preventing emphysema, whereas others may be more effective against the small airway inflammatory-fibrosis process.

Submitted on invitation.
Accepted on 8 April 2003.

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