Future Treatments for Chronic Obstructive Pulmonary Disease and Its Comorbidities

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The recognition that patients with chronic obstructive pulmonary disease (COPD) may have systemic manifestations and often suffer from comorbid conditions has important implications for therapy that require further research. The most likely link between COPD and extrapulmonary effects is that inflammation in the lung periphery "spills over" into the systemic circulation and effects on other organs that may also be affected by the systemic effects of cigarette smoking. The peripheral lung inflammation of COPD and systemic inflammatory effects could be treated by systemic antiinflammatory treatments, but this may have a high risk of systemic side effects, or by inhaled administration of antiinflammatory treatments that suppress inflammation in the lung and prevent the spillover of inflammatory mediators into the systemic circulation. Current therapies for COPD, including inhaled corticosteroids, long-acting β_2-agonists, and theophylline, have the potential to reduce systemic features of COPD and comorbid diseases. Treatments for comorbid diseases, such as statins, angiotensin-converting enzyme inhibitors, and peroxisome proliferator–activated agonist agonists, may also have beneficial effects on COPD inflammation. Novel antiinflammatory treatments, such as phosphodiesterase-4, nuclear factor-κB, and p38 mitogen-activated protein kinase inhibitors, may provide benefits in both COPD and comorbidities, but have a high risk of adverse effects when given systemically, and may need to be given by inhalation. Increased oxidative stress may be an important mechanism linking COPD inflammation, systemic effects, and comorbid disease, so the development of antioxidants, including nuclear factor erythroid-2–related factor 2 activators, is a priority. Accelerated aging may be associates in common to COPD and several comorbidities, prompting the development of antiaging molecules, such as sirtuin 1 agonists, which may also be effective in reducing the risk of lung cancer.

Keywords: statins; peroxisome proliferator-activated receptor agonists; phosphodiesterase-4 inhibitors; nuclear factor-κB inhibitors; antioxidants

There are two broad approaches to the treatment of chronic obstructive pulmonary disease (COPD) and its comorbidities. The first involves suppression of pulmonary inflammation to prevent associated systemic diseases if they are due to or exacerbated by "spillover" of inflammatory mediators from the lung into the systemic circulation (Figure 1). The second is to treat the systemic disease and see whether this reduces features of COPD pulmonary disease. It has proven extremely difficult to discover novel treatments for COPD, other than bronchodilators (1–3). Novel antiinflammatory treatments, such as phosphodiesterase (PDE)-4, p38 mitogen-activated protein kinase (MAPK), and nuclear factor (NF)-κB inhibitors, are likely to be toxic or have dose-limiting side effects when given systemically, because of widespread target distribution, non-selectivity, and interference with innate immunity. This is well illustrated for PDE4 inhibitors, which have major mechanism-related side effects when given systemically (nausea, vomiting, diarrhea) that limit the doses to those that are largely ineffective on clinical outcome measures (4). The obvious solution is to give these drugs by inhalation, but this may not reach peripheral lung (small airways and alveoli), which is the main site of inflammation in patients with COPD, and may not treat associated systemic inflammation and comorbid diseases if the drugs are retained in the lung. Two inhaled PDE4 inhibitors have so far been found to be without side effects, but are also without clinical effect, indicating that it is not easy to develop inhaled therapies.

TREATMENTS OF COMORBIDITIES THAT MAY BE BENEFICIAL IN COPD

Chance observation and epidemiological studies have shown that some treatments used for comorbid diseases, such as statins and angiotensin-converting enzyme (ACE) inhibitors, may apparently be beneficial in COPD, with reduction in exacerbations and mortality (5–7). This may reflect beneficial effects of these drugs on the comorbidities associated with COPD, such as cardiovascular disease, but there may also be a therapeutic effect on the inflammatory disease process of COPD.

Statins

Although 3-hydroxy-3-methyl-3-glutaryl coenzyme A reductase inhibitors (statins) reduce cholesterol, they have several other pharmacological actions that might be beneficial in COPD, including antioxidant, antiinflammatory, and immunomodulatory effects. Many of these pleiotropic effects of statins are mediated by inhibition of isoprenylation of small GTP-binding signaling molecules, such as Rho, Ras, and Rac (8). Through these mechanisms, statins reduce the expression of adhesion molecules, such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin, that are involved in recruitment of inflammatory cells (neutrophils, monocytes, and lymphocytes) from the circulation into the lungs. Statins also reduce the expression of chemokines, such as CCL2 and CXCL8, and matrix metalloproteinases (MMPs), such as MMP-9, all of which are increased in COPD (9). Some of these effects may be mediated via activation of peroxisome proliferator–activated receptors (PPAR)-α and -γ, and some via inhibition of NF-κB. Statins prevent the development of emphysema in mice exposed to cigarette smoke, and this is associated with a reduction in expression of tumor necrosis factor (TNF)-α, IFN-γ, and MMP-2, -9, and -12, and a reduction in neutrophils in bronchoalveolar lavage fluid (10). Statins also prevent elastase-mediated emphysema in mice, and are associated with evidence for proliferation and regeneration of alveolar epithelial cells (11). At a cellular level, statins inhibit the effects of IL-17 and transforming growth factor (TGF)-β in stimulating mediator release from primary airway epithelial cells, indicating their potential to modulate the inflammatory response and small airway fibrosis in COPD (12). Statins also stimulate the

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uptake of apoptotic neutrophils by alveolar macrophages (efferocytosis), an effect that is mediated via inhibition of the prenylation and activation of RhoA, which is involved in the phagocytosis of apoptotic cells (13). Because phagocytosis of apoptotic cells is impaired in COPD (14), this suggests that statins may accelerate the resolution of neutrophilic inflammation in COPD. Recently, statins have been shown to inhibit Th17 cells through an inhibitory effect on their regulatory transcription factor, retinoic acid orphan receptor-γt (15). Th17 cells may play an important role in orchestrating neutrophilic inflammation in COPD through the effect of IL-17 on epithelial cells to release CXCL1 and CXCL8 (16). All of these studies on the pleiotropic effects of statins suggest that they may have a beneficial effect in COPD, and this may contribute to the reduction in exacerbations in patients with COPD treated with statins in observational studies (5–7, 17). Through their pleiotropic effects, statins may have beneficial effects not only on cardiovascular disease, but also on other comorbidities associated with COPD, including diabetes, osteoporosis, and lung cancer (18). However, prospective, controlled trials are needed to establish whether statins have a beneficial effect in patients with COPD, especially those with systemic complications and comorbidities. The dose–response for the pleiotropic effects of statins has not yet been established and may differ from their cholesterol-lowering effects. High doses of statins may have adverse effects, particularly on skeletal muscles, so it is possible that statins could be delivered by the inhaled route.

ACE Inhibitors

ACE inhibitors are widely used to treat hypertension and heart failure and, in observational studies, these drugs have been associated with reduced exacerbation and mortality in patients with COPD (5). ACE inhibitors reduce pulmonary hypertension, but may have other beneficial effects in COPD, as angiotensin II may have proinflammatory effects (19). Indeed, an angiotensin II receptor (AT_1) antagonist, irbesartan, has been shown to reduce hyperinflation in patients with COPD, although its mechanism of action is uncertain (20). Polymorphisms of the ACE gene have been linked to increased susceptibility to COPD (21) and quadriceps strength in patients with COPD (22). Because ACE inhibitors are routinely used in the management of hypertension, cardiac failure, and diabetes, all of which are common comorbidities of COPD, prospective trials of ACE inhibitors in patients with COPD are now warranted.

PPAR Agonists

PPARs play an important role in the regulation of cellular metabolism and energy homeostasis, and have been implicated in several systemic manifestations of COPD, including cachexia, skeletal muscle weakness, and systemic inflammation (23). Several antiinflammatory mechanisms of PPAR agonists have now been documented, including suppression of adhesion molecule expression, chemokines secretion, and certain Toll-like receptors (24) (Figure 2). Of particular interest to COPD inflammation is the immunomodulatory effects of PPAR agonists on IL-17 and IFN-γ secretion, which may account for the effects of statins described above. There is reduced expression of PPAR-α and PPAR-δ in skeletal muscle of patients with COPD who have cachexia, as well as reduced expression of the transcription factor, PPAR-γ coactivator 1α (25). Reduced PPAR-α expression is correlated with cachexia and systemic inflammation, suggesting that PPAR-α agonists, such as clofibrate and fenofibrate, may have therapeutic potential in treating the systemic features of COPD. PPAR-α and -γ agonists inhibit the expression of several inflammatory genes in inflammatory cells, such as macrophages, suggesting that they have potential for treating pulmonary inflammation in COPD as well as systemic effects. PPAR-γ agonists, such as rosiglitazone, which are used to treat diabetes, reduce neutrophilic inflammation in lungs of mice exposed to intratracheal endotoxin, and this is associated with a reduction in CXC chemokines and granulocyte-macrophage colony–stimulating factor (26). Recently, it has been shown that PPAR-γ agonists inhibit the profibrotic effect of TGF-β on fibroblasts, and have been shown to reduce pulmonary fibrosis in animal models (27). Thus, rosiglitazone inhibits the effects of TGF-β on differentiation and collagen secretion by human lung fibroblasts and myofibroblasts (28, 29) and in animal models of bleomycin-induced pulmonary fibrosis (29). This suggests that PPAR-γ agonists might reduce small airway fibrosis in COPD, which is currently untreatable. So far, no trials of PPAR-α agonists (fibrates) or PPAR-γ agonists (thiazolidinediones) in COPD have been reported. Concern about the cardiovascular side effects of thiazolidinediones has recently limited their use in the treatment of diabetes, but it is possible that these drugs may work by inhalation to avoid any cardiovascular risk in a high-risk population, such as patients with COPD.

TREATMENT OF SYSTEMIC EFFECTS OF COPD WITH CURRENT THERAPY

Inhaled therapy may reduce inflammation in the lung and thereby reduce systemic inflammation that results from spillover from the lungs into the systemic circulation. Alternatively, inhaled drugs may reach the systemic circulation after absorption from the lungs or from the gastrointestinal tract after swallowing.

Inhaled Corticosteroids

Although high-dose inhaled corticosteroids (ICS) are widely used in the management of COPD, either alone or combined with a long-acting β_2-agonist (LABA). ICS, even in high doses, fails to suppress inflammation in COPD lungs and airways, and this may be due to an active resistance mechanism linked to a reduction in histone deacetylase-2 (HDAC2) expression (30). Observational studies suggested that ICS reduce all-cause mortality in patients with COPD, including cardiovascular mortality (31), and were shown prospectively to reduce markers of systemic inflammation, such as C-reactive protein (CRP) (32). However, a prospective study of high-dose ICS in patients with COPD (the TORCH [Towards a Revolution in COPD Health] study) showed no reduction in all-cause mortality, indicating that there is unlikely to be a significant clinical benefit of ICS on COPD comorbidities, such as cardiovascular disease or lung cancer, which are the commonest causes of death in patients with COPD (33). A controlled trial of high-dose ICS with or without a LABA showed no reduction in systemic inflammation in patients with COPD, as measured by circulating IL-6 and CRP concentrations, indicating likely corticosteroid resistance of systemic, as well as local inflammation in patients with COPD (34).

LABAs

LABAs are useful bronchodilators in patients with COPD, but it is uncertain whether they have antiinflammatory effects. Formoterol reduces neutrophilic inflammation in patients with asthma, but this has not been studied in COPD (35). The combination inhaler, salmeterol/fluticasone, reduces inflammation in COPD airways (36, 37), whereas a corticosteroid is ineffective (37). This suggests that there is a synergistic interaction

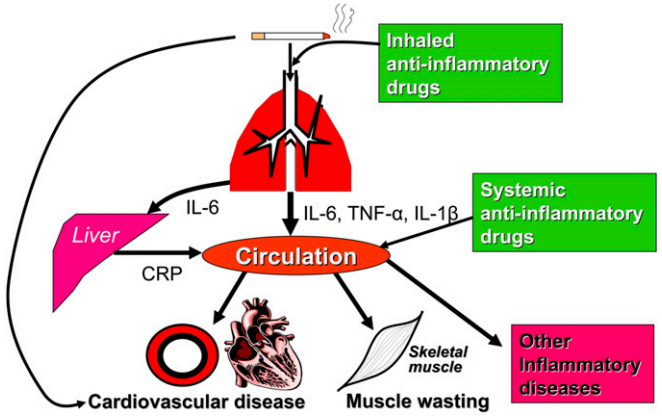

Figure 1. Inflammatory mediators from the peripheral lung of patient with chronic obstructive pulmonary disease (COPD), such as IL-6 and tumor necrosis factor (TNF)-α, may spill over into the systemic circulation where they may promote systemic abnormalities such as skeletal muscle weakness and exacerbate cardiovascular disease directly or through the increased production of C-reactive protein (CRP) from the liver.

between the LABA and the corticosteroid, or that the LABA is responsible for the antiinflammatory effects. Indeed, the benefits of combination inhaler in the TORCH study appear to be due to salmeterol rather than to fluticasone (38). Whether inhaled LABA or oral β_2-agonists have any beneficial effects on systemic features of COPD has not yet been systematically investigated. There is a large body of literature documenting the effects of various β_2-agonists increasing skeletal muscle mass and strength, and preventing fatigue (39), suggesting that there is potential for improving skeletal (and respiratory) muscle weakness in patients with COPD. However, cardiovascular complications of systemic β_2-agonists may be a problem, although the sustained effects over 24 hours of the prodrug, bambuterol, are relatively well tolerated in patients with COPD, in whom it is an effective bronchodilator (40).

Anticholinergics

There is considerable evidence that acetylcholine can be released from nonneuronal cells, such as epithelial cells and macrophages, and that it may activate muscarinic receptors on inflammatory and structural cells, including neutrophils, macrophages, T lymphocytes, and epithelial cells (41). This suggests that anticholinergics have the potential for antiinflammatory effects in COPD, particularly because tiotropium bromide reduces exacerbations. However, tiotropium has no effect on inflammatory markers in sputum (IL-6, CXCL8, myeloperoxidase) or in the circulation (IL-6, CRP) of patients with COPD, despite a reduction in exacerbations (42). Anticholinergics (and other bronchodilators) may reduce the mechanical forces in the lung due to airway closure, and this might reduce the expression of TGF-β and other mediators released in response to mechanical strain of epithelial cells (43, 44).

Theophylline

Theophylline has more potential as a treatment for lung inflammation in COPD, as low-dose oral theophylline reduces neutrophilic inflammation and sputum CXCL8 in patients with COPD (45). However, it is not known whether theophylline has any beneficial effects on systemic features or comorbidities of COPD. High doses of theophylline were shown to increase

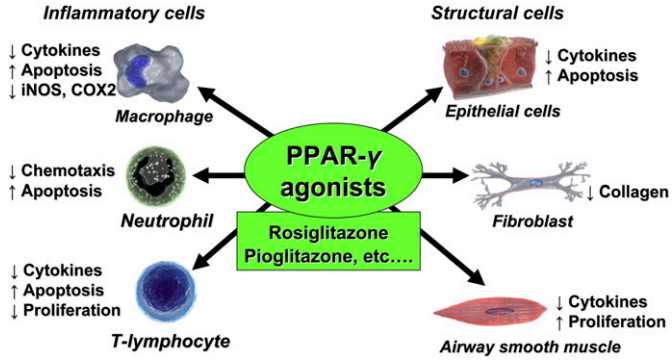

Figure 2. Peroxisome proliferator–activated agonist (PPAR)-γ may have many effects on inflammatory and structural cells. iNOS = inducible nitric oxide synthase; COX2 = cyclooxygenase 2.

diaphragm strength in patients with COPD, but this was not confirmed in other studies (46). As discussed subsequently here, theophylline has the potential to reverse corticosteroid resistance in COPD.

NEW ANTIINFLAMMATORY TREATMENTS

As corticosteroids fail to suppress inflammation in COPD, in marked contrast to asthma, several alternative antiinflammatory approaches are currently being investigated (2, 3). These drugs have largely been developed as systemic treatments, and would therefore be expected to reduce systemic inflammation and perhaps treat systemic manifestations of COPD, such as skeletal muscle weakness. However, a major limitation of the broad-spectrum antiinflammatory treatments currently in development has been side effects, which have limited the doses that can be given. This has lead to a search for inhaled antiinflammatory drugs that are retained in the lung or inactivated in the systemic circulation.

Anti-TNF Therapy

TNF-α is increased in sputum of patients with COPD, particularly during exacerbations, and is also released from circulat-

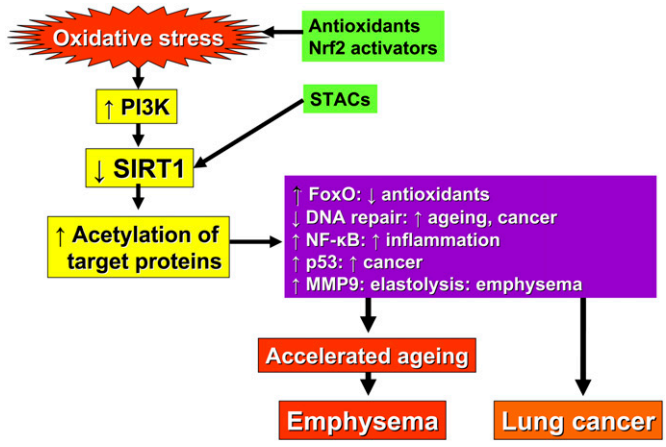

Figure 3. Aging pathways in COPD. Oxidative stress may reduce the activity and expression of sirtuin (SIRT) 1 in lungs via activation of phosphoinositide-3-kinase (PI3K) pathways, resulting in acetylation of several key target proteins linked to aging and cancer, including the transcription factors forkhead box (FOX) O and nuclear factor (NF)-κB, the tumor suppressor p53, and matrix metalloproteinase (MMP)-9.

ing cells in patients with COPD with cachexia. Increased systemic TNF-α has been implicated as a mechanism of cachexia, skeletal muscle atrophy, and weakness in patients with COPD. Blocking TNF-α with monoclonal antibodies (such as infliximab or adalimumab) and soluble receptors (etanercept) has been very effective in treating other chronic inflammatory diseases, such as rheumatoid arthritis and inflammatory bowel disease. However, using the same doses of infliximab that are effective in these inflammatory diseases, there is no clinical benefit in patients with COPD (47), although a *post hoc* analysis suggested that there might be some improvement in exercise tolerance in patients with cachexia (48). However, a subsequent, small study with infliximab in patients with severe COPD showed no benefit on markers of systemic inflammation (49). A major problem with anti-TNF therapy is the high incidence of cancers and pulmonary infections, indicating that it is unlikely to be safe in patients with COPD (50).

Anti–IL-6

IL-6 is increased in sputum and in the systemic circulation of patients with COPD, particularly during exacerbations, and may account for the increase in circulating CRP found in patients with COPD (51). The functional role for IL-6, apart from increasing acute-phase proteins, has not yet been determined, but there is evidence that it may be related to skeletal muscle weakness. In rats, infusion of IL-6 induces both cardiac failure and skeletal muscle weakness (52). A potent inhibitor of IL-6, the receptor antibody, tocilizumab, is effective in rheumatoid arthritis (53), but has not yet been tested in patients with COPD.

Anti-CRP

CRP is an acute-phase protein, which is increased in plasma of patients with COPD, particularly during acute infective exacerbations. In stable COPD, plasma concentrations are related to all-cause mortality in patients with mild to moderate COPD (54), but not in patients with severe and very severe disease (55). The link between increased CRP and prediction of cardiovascular risk has suggested that it might be a link between COPD and the increased incidence of cardiovascular disease, but this relationship may be confounded by established risk factors, such as smoking (56). The functional role of CRP is uncertain and disputed. CRP binds to damaged tissue and leads to activation of complement, resulting in endothelial injury and tissue inflammation. A small molecule inhibitor of CRP, 1,6-bis(phosphocholine)-hexane, counteracts the effects of CRP in animal models, and therefore may be cardioprotective (57). However, the role of CRP has been questioned by the recent demonstration that transgenic overexpression of human CRP in mice is neither proinflammatory nor proatherogenic (58). Furthermore, there is evidence to suggest that CRP may play an important role in innate defense against *Streptococcus pneumoniae*, so that inhibiting CRP could have detrimental effects in COPD, as this organism commonly colonizes the lower airways of these patients (59).

PDE4 Inhibitors

PDE4 inhibitors are the most advanced of the new antiinflammatory treatments for COPD, and have usually been administered orally. A selective PDE4 inhibitor, roflumilast, inhibits lung inflammation and emphysema in a smoking model of COPD in mice (60). In patients with COPD, oral roflumilast given over 4 weeks significantly reduces the numbers of neutrophils (by 36%) and CXCL8 concentrations in sputum (61). In clinical trials, roflumilast given over 6 or 12 months improves lung function in patients with COPD to a small extent, but has no significant effect on reducing exacerbations or improving health status (4, 62). These disappointing results likely reflect the fact that side effects, particularly nausea, diarrhea, and headaches, limit the dose that can be tolerated. This indicates that it may not be possible to reach an oral dose that is effective and acceptable to patients. This could be overcome by inhaled delivery, but, to date, two inhaled PDE4 inhibitors have been found to be ineffective, although well tolerated. Systemic inflammation or effects on skeletal muscles or comorbidities in patients with COPD have not yet been assessed. However, in rats, a PDE4 inhibitor prevented bone loss and increased skeletal muscle mass in ovariectomized animals, suggesting that PDE4 has the potential to prevent osteoporosis and skeletal muscle wasting in patients with COPD (63).

NF-κB Inhibitors

NF-κB regulates the expression of chemokines, TNF-α, and other inflammatory cytokines, as well as MMP-9. NF-κB is activated in macrophages and epithelial cells of patients with COPD, particularly during exacerbations (64). Although there are several possible approaches to inhibition of NF-κB, small molecule inhibitors of inhibitor of NF-κB kinase (IKK) 2 are the most promising. An IKK2 inhibitor is effective in some animal models of COPD (LPS exposure), but not in others (neutrophil elastase instillation), indicating that the effects may be complex (65). Although several IKK2 inhibitors are now in development, so far none have been tested in patients with COPD. NF-κB activation is also implicated in mediating systemic inflammation, and may be involved in skeletal muscle weakness in patients with COPD (66). NF-κB activation is important in skeletal muscle atrophy and inhibition of NF-κB may prevent this in animals (67). This suggests that IKK2 inhibitors may also treat some of the systemic complications of COPD. However, there is concern that long-term inhibition of NF-κB may result in immune suppression and impair host defenses, because mice that lack NF-κB–associated genes succumb to septicemia.

p38 MAPK Inhibitors

p38 MAPK is activated by cellular stress and regulates the expression of inflammatory cytokines, including CXCL8, TNF-α, and MMPs. p38 MAPK (measured by phosphorylated p38 MAPK) is activated in alveolar macrophages of COPD lungs, indicating the activation of this pathway in COPD (68). Several small molecule inhibitors of p38 MAPK have now been developed. A potent inhibitor of p38-α isoform, SD-282, is effective in inhibiting TNF-α release from human lung macrophages *in vitro* (69), and the same inhibitor is also effective in suppressing inflammation in a smoking model of COPD in mice in which corticosteroids are ineffective (70). The role of p38 MAPK in mediating systemic effects of COPD has not yet been determined. Several p38 MAPK inhibitors have now entered clinical trials, but there have been major problems of side effects and toxicity, indicating that it is probably necessary to deliver these drugs by inhalation to reduce systemic exposure.

OXIDATIVE STRESS

Oxidative stress, an imbalance between oxidants and antioxidants, is increased in patients with COPD, particularly during exacerbations (71), and reactive oxygen species contribute to its pathophysiology (72). Oxidative stress also reduces steroid

responsiveness via a reduction in HDAC2 activity and expression (30). Oxidative stress may also be critical to accelerated, nonprogrammed aging of the lung through inhibitory effects on antiaging molecules, such as sirtuin (SIRT) 1, thus resulting in accelerated decline in lung function (73). Systemic oxidative stress is also increased in patients with COPD, particularly during exacerbations, and this is linked to reduced antioxidant capacity (74). Systemic oxidative stress has been linked to skeletal muscle weakness, as evidenced by increased protein carbonylation in the quadriceps of patients with COPD, which is correlated with muscle weakness (75).

Increased oxidative stress in COPD may be due to reduced concentrations of endogenous antioxidants, and many of the genes encoding these endogenous antioxidants are regulated by the transcription factor, NF erythroid-2–related factor 2 (Nrf2), the master controller of antioxidant genes (76). Nrf2 in the cytoplasm is associated with the cysteine-rich protein, Keap1, an adapter protein for the enzyme, Cul3 ubiquitin ligase, which ubiquitinates Nrf2 and thus targets it for destruction by the proteasome, so that, under normal conditions, Nrf2 is undetectable. Oxidants oxidize cysteine residues on Keap1, so that it dissociates from Nrf2, thereby preventing its degradation so that it is able to translocate to the nucleus. Within the nucleus, Nrf2 combines with other transcription factors (small Maf proteins) and binds to antioxidant response elements, which are found on more than 200 antioxidant enzyme and detoxifying enzyme genes, including heme oxygenase-1, glutathione peroxidase, glutathione-S-transferase, glutathione reductase, γ-glutamylcysteine synthetase, thioredoxin, and catalase (77). The protein, DJ-1 (or PARK7), which has previously been implicated in early-onset Parkinson's disease, acts as a stabilizer of Nrf2 to facilitate its effects (78). In this way, oxidant exposure upregulates endogenous antioxidants to counteract the increased oxidative stress and restore normal oxidant–antioxidant balance. Nrf2 plays an important role in defense of the lung against oxidative stress, and defective Nrf2 function has been implicated in COPD (76). Disruption of the Nrf2 gene in mice results in increased susceptibility to emphysema after cigarette exposure (79, 80), indicating that Nrf2 plays an important role in defending against oxidative stress in the lungs. Nrf2 activity and expression are reduced in peripheral lungs of patients with COPD and are associated with decreased expression of Nrf2-regulated antioxidant genes (81). This defect in patients with COPD appears to be related to a reduction in the stabilizing protein DJ-1, resulting in degradation of Nrf2, reduced antioxidant responses, and, therefore, persistent oxidative stress.

Reduction in oxidative stress in patients with COPD should provide clinical benefit through reducing inflammation and reversing corticosteroid resistance, but currently available antioxidants, such as *N*-acetyl cysteine, have proven disappointing in reducing progression and exacerbations of COPD (82). However, these glutathione-based antioxidants are consumed by oxidative stress, and so may not be efficient in the face of continued high oxidant exposure. It has been difficult to find new, more effective antioxidants that are not toxic. A more attractive approach may be to restore Nrf2 levels to normal through inhibiting the action of Keap1. This has been achieved *in vitro* and *in vivo* by isothiocyanate compounds, such as sulforaphane, which occurs naturally in broccoli (83). Sulforaphane restores antioxidant gene expression in a human bronchial epithelial cell line in which DJ-1 had been reduced by small interfering RNA (13). This interaction of isothiocyanates and Keap1 prevents the degradation of Nrf2, and might form the basis for the development of novel Nrf2 activators in the future. By implication, these drugs may also treat some aspects of systemic inflammation, such as skeletal muscle wasting.

REVERSING CORTICOSTEROID RESISTANCE

Resistance to the antiinflammatory actions of corticosteroids is a critical feature of COPD inflammation, and may also be relevant to systemic inflammation. The molecular pathways involved in corticosteroid resistance are now better understood and provide novel targets for COPD therapy, which may be less toxic than the drugs currently in development. A major mechanism for corticosteroid resistance in COPD is a reduction in the critical nuclear enzyme, HDAC2, which switches off multiple inflammatory genes in response to corticosteroid therapy. HDAC2 is markedly defective in COPD lungs and alveolar macrophages, but is also reduced in circulating leukocytes. This abnormity may be secondary to oxidative stress activity, through phosphoinositide-3-kinase (PI3K) pathways to phosphorylate and inactivate HDAC2 and with nitrative stress through tyrosine nitration leading to ubiquitination and degradation of HDAC2 (84, 85). Oral theophylline reverses corticosteroid resistance in COPD cells, smoking mice, and patients with COPD at doses that have no side effects (86). This molecular mechanism of theophylline is mediated via a direct inhibitory effect on PI3K-δ, which is activated by oxidative stress (85), and the effects of theophylline are mimicked by selective PI3K-δ inhibitors (which are currently being developed for the treatment of diabetes). Reversing corticosteroid resistance may also be useful in reducing systemic inflammation in patients with COPD, which also appears to be corticosteroid resistant. As theophylline markedly enhances the antiinflammatory effects of corticosteroids that are due to suppression of activated inflammatory genes rather than activation of the genes believed to cause side effects (87), it is possible that a combined tablet of low-dose theophylline and prednisolone might be a valuable treatment for COPD, systemic manifestations, and comorbidities (including lung cancer) worsened by chronic inflammation.

ACCELERATED AGING

Emphysema can be regarded as an acceleration of the normal aging process in the lung (73), and many of the comorbid diseases associated with COPD are also degenerative diseases of accelerated senescence, including heart failure, atherosclerosis, osteoporosis, and diabetes. There is relationship between COPD, systemic inflammation, arterial stiffness, and osteoporosis (88). Patients with COPD show increased wrinkling of the skin (89), and there may be a mechanistic link between skin wrinkling, emphysema, and other degenerative diseases through the increased expression of MMP-9. Many novel molecular targets are now being revealed by better understanding of aging pathways, and there is an association of aging with inflammation arising from activation of NF-κB and PI3K pathways (90). The concept of inflamm-aging is now gaining strength, with a reduction in adaptive immunity and an increase in innate immunity driven by NF-κB activation (91). Aging may be programmed as a result of telomere shortening from repeated cell division or nonprogrammed, mediated largely via oxidative stress. There is evidence of telomere shortening in alveolar macrophages from patients with COPD (92) and in circulating lymphocytes in smokers, irrespective of whether they have airflow limitation (93). Oxidative stress may be a more important mechanism of aging in COPD, and may result in NF-κB activation, as well as DNA damage and inability to repair this damage, thus linking oxidative stress, aging, and cancer (94). Animal models of accelerated aging, including the Klotho mouse and the SMP30 mouse, both develop early emphysema, which is associated with increased oxidative stress (95, 96).

This suggests that antiaging molecules may be beneficial in COPD and its associated degenerative diseases. There has been

particular interest in the protein deacetylase, SIRT1, which plays an important role in determining lifespan of all organisms, including mammals (97). SIRT1 has multiple cellular effects that counteract cellular stress and DNA damage by deacetylating multiple protein targets, including inhibiting NF-κB, forkhead box O transcription factors, PGC-1α, tumor suppressor p53, and DNA repair proteins, such as Ku70 (Figure 3). SIRT1 is markedly reduced in COPD lungs as a result of oxidative stress (98, 99). SIRT1 may be activated by resveratrol and more active drugs, known as SIRT1-activating compounds (STACs) (97, 100). STACs may provide a novel therapeutic approach to COPD and its associated aging diseases, and several novel drugs are now in clinical development for other aging diseases, such as diabetes. As the molecular pathways involved in aging are elucidated, it is likely that several new therapeutic targets will emerge.

LUNG CANCER

Patients with COPD are three to four times more likely to develop lung cancer than smokers without lung cancer (101), and this is probably linked to the increased inflammation and oxidative stress in COPD (102, 103). There are common factors involved in the aging lung and lung cancer, suggesting that antiaging therapies may also be beneficial in preventing the high risk of lung cancer in patients with COPD. As discussed above, these treatments may include STACs and Nrf2 activators. Defective function of Nrf2 may also contribute to the increased susceptibility of patients with COPD to lung cancer with smoking, as Nrf2 plays an important role in defense against certain carcinogens in tobacco smoke by regulating the expression of several detoxifying enzymes (76). However increased Nrf2 activation due to genetic mutations of Keap1 has been reported in lung cancer cells, so the role of Nrf2 in carcinogenesis is currently uncertain (104). NF-κB activation may be a link between inflammation and cancer, so IKK2 inhibitors may inhibit inflammation in COPD and prevent the development of cancers (105).

Patients with COPD show increased expression of epidermal growth factor receptors in airway epithelium (106), and this may be a mechanism of mucus hypersecretion and also of cell proliferation, leading to cancer. The epidermal growth factor receptor tyrosine kinase inhibitor, erlotinib, which is used to treat non–small cell lung carcinoma (107), might also be effective in reducing mucus hypersecretion (108).

Conflict of Interest Statement: P.J.B. has previously served as a consultant to GlaxoSmithKline (GSK). He is a member of scientific advisory boards for GSK, Boehringer Ingelheim, Altana, and Pfizer. He has received lecture fees from GSK, AstraZeneca, Boehringer Ingelheim, and unrestricted grants from GSK, AstraZeneca, Boehringer Ingelheim, and Novartis.

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