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Treating systemic effects of COPD

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The emerging recognition that chronic obstructive pulmonary disease (COPD) is a complex disorder, characterized not only by local pulmonary inflammation, but also by systemic inflammation that might have an adverse impact on various extrapulmonary organs, such as the blood vessels and the heart, among others, emphasizes the need for new and more effective forms of therapy for this debilitating disorder. Fortunately, many of the 'standard' therapeutic options used to treat COPD have the potential to influence systemic inflammation. Moreover, several new therapeutic strategies aimed at controlling the underlying inflammatory processes of COPD more specifically are under development. Unfortunately, we still do not know whether treatment of lung inflammation decreases, for example, the risk of acute cardiac events, progression of atherosclerosis or thrombotic events. It is also unclear whether, alternatively, treatment of heart disease can affect the progression of lung disease. Nonetheless, initial data seem to indicate that drugs, such as statins, ACE inhibitors, AT1 receptor blockers and PPAR agonists, used to treat a co-morbid condition have the potential to benefit COPD patients.

Introduction

Chronic inflammation has a central role in chronic obstructive pulmonary disease (COPD). It is characterized by an increase in neutrophils, macrophages and $CD8^+$ T lymphocytes in small and large airways as well as in lung parenchyma and pulmonary vasculature [1] (Figure 1). Alveolar macrophages are a crucial factor in orchestrating this inflammation through their release of proteases, such as matrix metalloproteinase (MMP)-9, inflammatory cytokines, such as tumor necrosis factor (TNF)-α, and other cytokines, such as interleukin (IL)-8, that attract neutrophils into the airways.

A solid body of evidence indicates that levels of inflammatory proteins, such as TNF-α and IL-6, and C-reactive protein (CRP), an acute phase protein induced by systemic spill of IL-6, are increased in the systemic circulation of patients with COPD [2] (Figure 2). Furthermore, cross-sectional studies show that CRP is associated inversely with forced expiratory volume in 1 s (FEV_1) and PaO_2 in those with a diagnosis of COPD [2]. These findings support the concept that there is a systemic inflammatory response in this progressively debilitating disease [3]. It is probable that systemic inflammation is associated with various complications in COPD, including weight loss, skeletal muscle dysfunction, cachexia, osteoporosis, depression, normocytic anemia, cancer and cardiovascular diseases [3] (Box 1). If systemic inflammation contributes to the pathophysiology of COPD, this would provide a rationale to consider using novel therapeutic interventions that target this response. Although the extrapulmonary, systemic component of COPD has yet to be addressed properly in terms of possible pharmacological intervention, the fact that we have now begun to uncover the origin and consequences of, and seek potential therapy for, this systemic inflammation in this disease might be of great relevance and lead to better management of patients with COPD [3].

In this article, we review the current literature regarding the treatment of systemic inflammation and its complications in COPD and then suggest strategies for further improving this treatment.

Traditional treatment and its potential to modify systemic effects of COPD

Smoking cessation and bronchodilator therapy form the cornerstone of treatment in COPD [4]. In severe cases, this is complemented with inhaled corticosteroids, oxygen therapy and rehabilitation [4]. Interestingly, many (if not all) of these 'standard' therapeutic options have the potential to modify systemic inflammation [3].

Smoking cessation

Chronic smoking causes systemic inflammation in humans [5]. Quitting smoking is therefore thought to reduce this inflammation [3]. However, smokers with COPD and asymptomatic smokers with normal lung function respond differently to long-term smoking cessation with respect to the smoke-induced airway inflammation. Differences in inflammatory response to smoking cessation have suggested perpetuation in COPD but a reduction in some aspects of inflammation in asymptomatic smokers, 1-year after quitting smoking [6]. The observed persistent inflammation in COPD might be, at least partly, related to repair of the smoke-induced tissue damage in the airways [6]. It remains to be elucidated whether smoking cessation might reduce systemic inflammation; however, this seems to be improbable because elevated CRP levels have been found in ex-smokers with COPD [2].

Bronchodilators

Loaded breathing initiates an inflammatory response consisting of elevation of plasma cytokines that are produced within the diaphragm as a result of increased muscle

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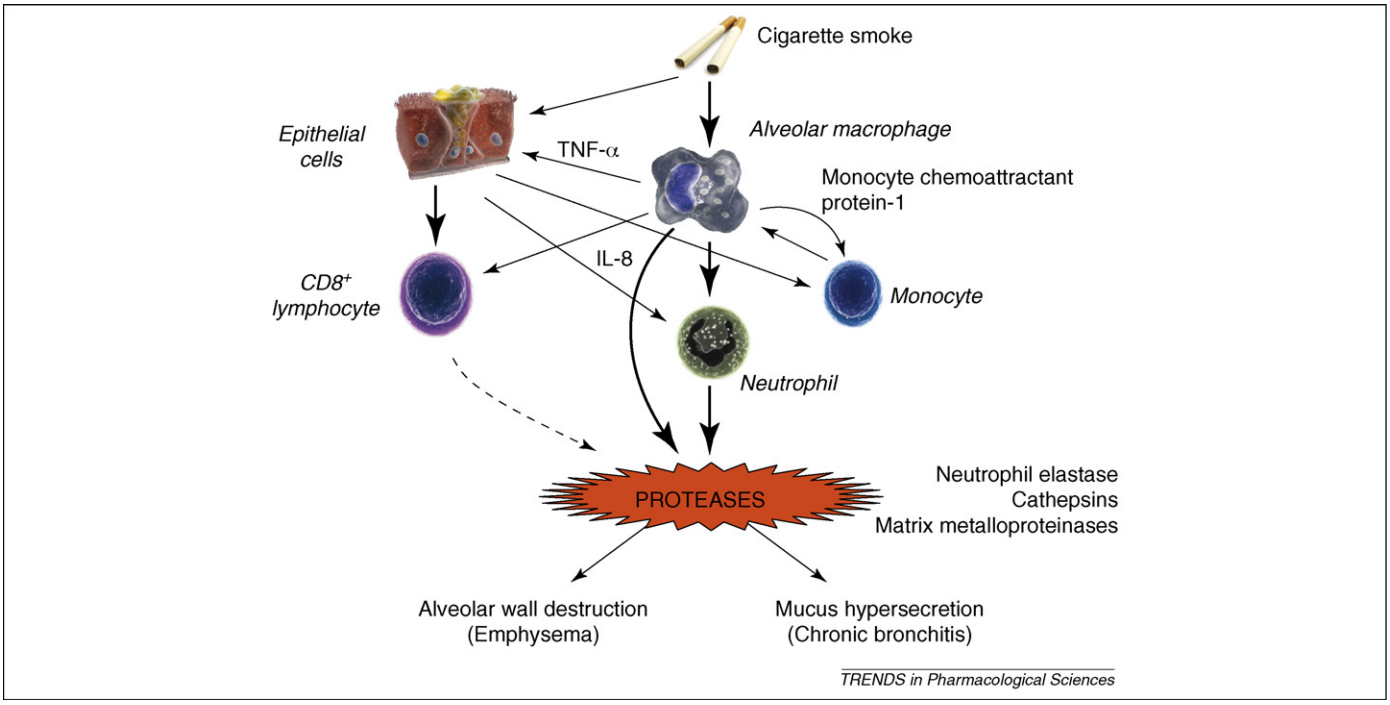

Figure 1. Chronic inflammation in COPD is driven initially by cigarette smoking and other inhaled irritants, which induce a specific pattern of inflammation that predominantly involves the peripheral airways and lung parenchyma. This pattern of inflammation is characterized by an increase in neutrophils, macrophages and $CD8^+$ T lymphocytes in small and large airways and in lung parenchyma and pulmonary vasculature. Alveolar macrophages have a crucial part in orchestrating this inflammation through the release of proteases, such as MMP-9, inflammatory cytokines, such as TNF-α, and other cytokines, such as IL-8, that attract neutrophils into the airways.

activation and recruitment and activation of lymphocyte subpopulations [7]. These cytokines might mediate the diaphragm muscle injury and also compromise diaphragmatic contractility and contribute to the development of muscle cachexia. In addition, they might have systemic effects, mobilizing glucose from the liver and free fatty acids from the adipose tissue to the strenuously working respiratory muscles [7]. By decreasing dynamic hyperinflation

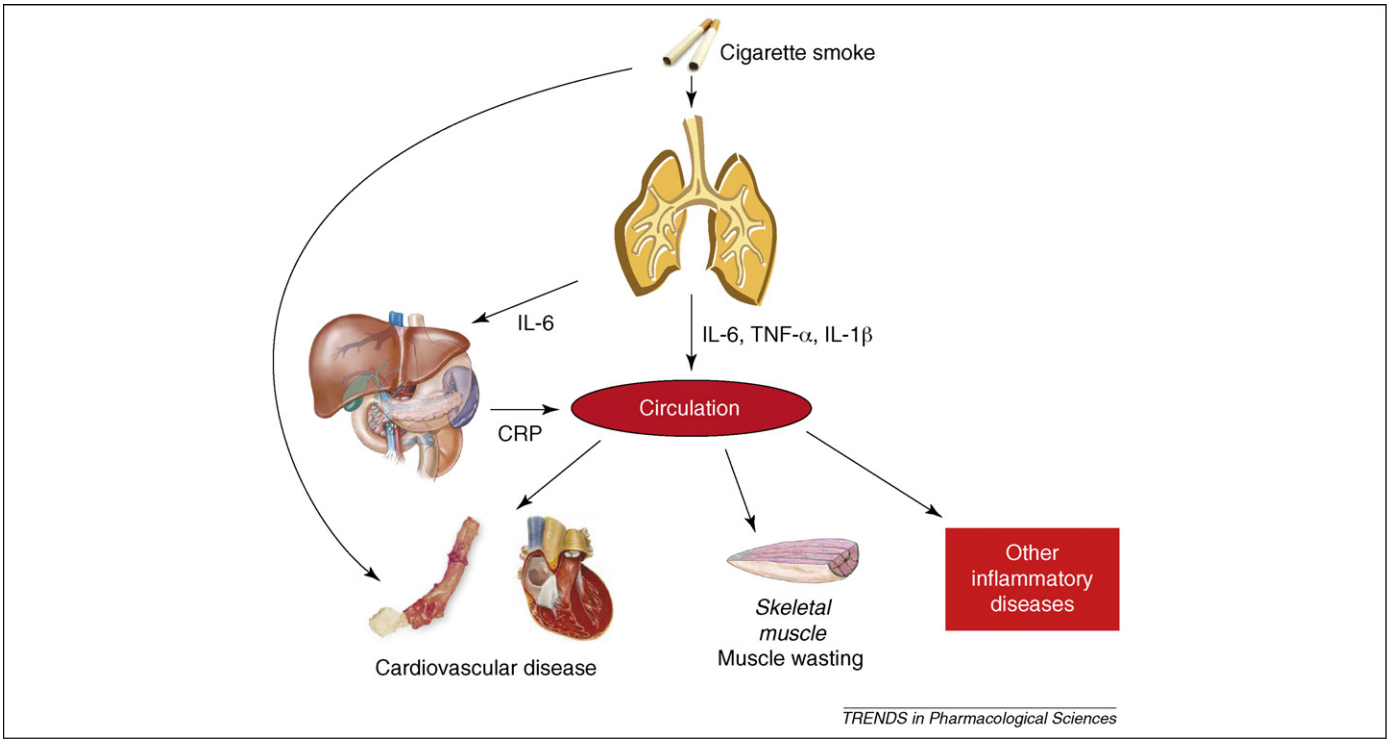

Figure 2. The inflammation in the lung 'spills over' into the systemic circulation to produce systemic effects, such as muscle weakness or cardiovascular complications. The levels of inflammatory proteins, such as TNF-α and IL-6, and CRP, an acute phase protein induced by the systemic spill of IL-6, are in fact increased in the systemic circulation of patients with COPD. It is also possible that co-morbid diseases have a common causal mechanism, such as cigarette smoking, that self-induces systemic inflammation (i.e. induces it in the absence of COPD). This systemic inflammation in smokers is believed to contribute significantly to atherosclerosis. CRP is synthesized predominantly by hepatocytes in response to tissue damage or inflammation. It is elevated in patients who smoked actively, had reduced lung function or stable COPD. CRP levels predicted cardiovascular mortality. IL-6 and IL-1β are implicated directly because CRP is induced principally by IL-6 and this is amplified by IL-1 β.

Box 1. Systemic effects of COPD related to systemic inflammation

- Involuntary weight loss
- Muscle wasting
- Reduced functional capacity and health status
- Increased cardiovascular morbidity and mortality
- Impaired bone metabolism
- Normocytic anemia
- Cancer
- Depression
- Diabetes
- Peptic ulceration

and influencing resistive breathing in this way, bronchodilators have the potential to reduce systemic inflammation [7].

β_2-Adrenoceptor agonists. Studies on the effect of β_2-adrenoceptor (β_2-AR) agonists (β_2-agonists) on contractility of the diaphragm have produced controversial results [8–10]. These findings question the importance of β_2-agonists in reducing systemic inflammation caused by loaded breathing. Nevertheless, one could argue that β_2-ARs are also expressed by cells (in particular neutrophils, monocytes and macrophages) involved in the regulation of inflammation and the stimulation of these receptors might result in anti-inflammatory effects, although it is likely that these effects become tolerant rapidly [11].

Even so, β_2-agonists could be considered helpful in influencing the systemic effects of COPD because of non-anti-inflammatory, non-bronchodilator effects [12]. Their chronic administration causes skeletal muscle hypertrophy in humans, probably because they induce changes in protein turnover [12]. This action suggests the potential use of β_2-agonists for treating muscle wasting and weakness and it is well known that skeletal-muscle dysfunction and wasting is an important systemic manifestation of COPD [3]. In any case, the use of these agents in clinical practice also needs an understanding of the possible effects of the activation of cardiac β_2-ARs [13]. Adverse consequences could include an increased probability of arrhythmias in susceptible patients [14].

Muscarinic receptor antagonists. Muscarinic receptor antagonists act on inflammatory cells, including neutrophils, macrophages and T lymphocytes, and this raises the possibility that they might act as mild anti-inflammatory agents [15], also considering that bronchial epithelial cells release eosinophil, monocyte and neutrophil chemotactic factors in response to acetylcholine [16].

However, recent research has questioned the importance of muscarinic receptor antagonists as anti-inflammatory drugs [17]. Nevertheless, because the expression of non-neuronal acetylcholine is relatively high in bronchial epithelial cells [16], this finding could suggest a role for epithelial acetylcholine in initiating inflammatory responses. Interestingly, the latest work indicates that the expression and function of muscarinic receptors on neutrophils is increased in COPD [18].

Unfortunately, the documentation that muscarinic receptor antagonists affect the systemic inflammation of COPD is still lacking, although tiotropium can sustain significant reductions in lung hyperinflation and, consequently, reduce loaded breathing [19].

Theophylline. *In vitro*, theophylline stabilizes or inactivates several inflammatory cells, including mast cells, basophils, neutrophils, T-lymphocytes, macrophages and platelets [20]. The anti-inflammatory properties of theophylline are seen at concentrations less than 10 mg/l, which is below the dose at which significant clinically useful bronchodilation is evident [20].

It is unknown whether these anti-inflammatory effects can influence the systemic inflammation in COPD, although there is evidence that long-term treatment with theophylline reduces myeloperoxidase and neutrophil elastase [21] as well as IL-8 and TNF-α and the number of neutrophils in the sputum of patients with COPD [22]. Theophylline is also an activator of histone deacetylases (HDACs), an effect that might be important because smokers with COPD present a cigarette-smoke-induced reduction in HDAC activity in peripheral lung, airways and alveolar macrophages. This reduction in HDAC worsens as the disease becomes more severe and might account for the increased pulmonary inflammation and resistance to corticosteroids as COPD progresses [23].

Inhaled corticosteroids (ICSs)

Therapy with ICSs might suppress systemic inflammation in stable COPD patients [24,25]. In particular, ICSs could reduce systemic CRP, which is believed to contribute to the pathogenesis of atherosclerosis [26] (Figure 2), and this reduction might be linked with decreased cardiovascular events, which are frequent in COPD patients [27]. It has been postulated that the reduction in serum CRP is probably owing to a reduction in IL-6 production, which is the result of the action of ICSs in the airway [24]. Alternatively, it is possible that any ICS that might be absorbed systemically could affect hepatocyte function directly [24].

It must be highlighted that the anti-inflammatory actions of corticosteroids involve the modification of the expression of a number of genes, which inhibit the synthesis of cytokines or encode adhesion molecules, enzymes and other proteins implicated in the pathogenesis of acute coronary syndromes [28]. Their anti-atherogenic properties have been demonstrated in several animal studies [29].

It is not surprising, therefore, that a retrospective study demonstrated that very low doses of ICSs (50–200 mg day^{-1}) might be associated with a reduction in the risk of acute myocardial infarction [30]. However, with higher doses of ICSs, the risk returned to baseline [30]. The lack of benefit at higher doses might plausibly reflect counterbalancing adverse effects of other risk factors or the fact that patients with more severe disease, itself linked to cardiovascular morbidity, are dispensed higher doses [30]. This finding fits well with the results of the TORCH study, which have documented that the regular use of a high dose of ICS increases the risk of dying [31].

Combination therapy

There is evidence that combination therapy with an ICS and a long-acting β_2-agonist reduces local inflammation in the lung, at least at high ICS dosage, with decreased tissue

expression of TNF-α and interferon (IFN)-γ in the larger airways and decreased sputum eosinophil and subepithelial mast-cell counts in the bronchial tissues [32]. However, whether combination therapy reduces systemic inflammation is still unknown. Using the UK General Practice Research Database, COPD patients who received a prescription for an ICS plus a long-acting β_2-agonist within 90 days of hospital discharge were observed to be 41% less likely to experience a combined end point of a repeat hospitalization for COPD or all-cause mortality, an effect size that was larger than that observed with each individual drug alone [33]. Moreover, the specifically designed TORCH study [31] has documented a trend towards a reduction of mortality in those patients treated with the combination-therapy, although the risk of death in the combination-therapy group did not differ significantly from that in the long-acting β_2-agonist group.

If we accept that airway inflammation in COPD is a risk factor for cardiovascular events, it is probable that, at least in part, the observed reduction in mortality is related to a therapeutic effect on systemic effects or inflammation, although it remains unclear why the TORCH study has also documented an increased risk of death in the ICS group [31]. We also do not know the exact mechanism by which this combined therapy works better than the separate therapies. It has been speculated that synergistic action on cell receptors might lead to less muscle contraction or inflammation [34], but this has yet to be proved.

Potential more specific anti-inflammatory therapies

The role of more specific anti-inflammatory therapies to treat systemic inflammation in COPD is a matter of future research. However, anticytokine therapy, chemokine-receptor antagonists, nuclear factor (NF)-κB blockers and inducible nitric oxide-synthase inhibitors, among others, offer some potential, as reviewed recently [35]. It remains to be determined whether any of these targets represents redundant pathways, the inhibition of one of which would have little effect, or whether any are crucially located, such that inhibition would have widespread effects [35]. The documentation that an IL-8-neutralizing strategy might be effective only for the short-term use in patients with COPD is a good example of this perplexing and challenging problem [36]. In any case, the therapeutic rationale behind many of these treatments is mainly speculative and, moreover, they are fraught with important safety issues. One concern about the long-term inhibition of NF-κB, for example, is that effective inhibitors might cause immune suppression and impair host defenses [35].

Taking into account the systemic implications of TNF-α in COPD [4], a blocking humanized monoclonal antibody to TNF-α (infliximab) or soluble TNF receptors (etanercept) might be a logical therapeutic approach to systemic effects in COPD. However, subjects with moderate-to-severe COPD did not benefit from treatment with infliximab [37].

Nonetheless, it is now known that mitogen-activated protein kinases (MAPKs) have a key role in chronic inflammation. One of these, the p38 MAPK, is activated by cellular stress and, in turn, phosphorylates and activates downstream substrates, such as other protein kinases and transcriptional factors. This results ultimately in significant transcriptional up-regulation of the proinflammatory cytokines TNF-α, IL-1β IL-6 and IL-8, as well as of the proinflammatory prostaglandin pathway by cyclooxygenase-2 (COX-2) [35]. Small-molecule inhibitors of p38 MAPK, such as SB 203580, SB 239063 and RWJ 67657 or doramapimod (BIRB796BS), have been developed, potentially offering a broad range of anti-inflammatory effects that might be beneficial in COPD [32]. Such broad-spectrum anti-inflammatory drugs will probably infer some toxicity when administered systemically, although inhalation might be a feasible therapeutic approach [38].

Selective phosphodiesterase inhibitors

Phosphodiesterases (PDEs) can influence a large number of pharmacological processes, including inflammatory mediator production, cellular differentiation and apoptosis, smooth muscle contraction, ion-channel function and glycogenesis [20].

In particular, PDE type 4 inhibitors are under investigation as potential therapies for inflammatory airway diseases because PDE4 is expressed in inflammatory cells involved in the pathophysiology of COPD [19]. One of the major anti-inflammatory effects of PDE4 inhibitors is their ability to reduce TNF-α release [20]. This effect illustrates the potential of these agents for treating the systemic inflammation of COPD. Unfortunately, PDE4 inhibitors possess significant limiting gastrointestinal side effects and, very recently, proinflammatory activities in the lung have been described [39]. Therefore, targeting other PDE isoenzymes that are expressed specifically in proinflammatory and immune cells is an attractive approach to controlling inflammatory conditions. Of the possibilities available currently, dual-specificity inhibitors that target PDE4 and PDE1, PDE3, PDE5 or PDE7 are worthy of empirical investigation [40].

Glycosaminoglycans

Because numerous studies have reported many anti-inflammatory and immunomodulatory properties of heparin in both experimental and clinical settings, it has been proposed that this agent, which belongs to the glycosaminoglycan family, serves as an endogenous anti-inflammatory molecule, involved in the control and resolution of inflammatory responses [41]. Of particular relevance to COPD, heparin potently inhibits the activity of neutrophil-derived proteases, such as elastase [42] and cathepsin G [43]. In addition, it inhibits other neutrophil activities, including degranulation, the respiratory burst and processes involved in neutrophil trafficking into tissues [42].

The addition of enoxaparin to conventional therapy of COPD might provide more clinical benefit [44] and this finding seems to encourage the further investigation of the effects of heparin in the treatment of COPD. As commercially available heparin preparations are standardized for their anticoagulant activity, an alternative would be to remove the anticoagulant fractions and to isolate the remaining heparin fractions and optimize these for anti-inflammatory activity. Several other approaches to developing anti-inflammatory molecules related to heparin are

under development, including the identification of novel polysaccharides that exhibit anti-inflammatory activity but lack anticoagulant activity [45].

Antioxidant therapy

Oxidative stress is thought to be one of the prime factors contributing to the systemic components of COPD. Because there is evidence for impaired antioxidant levels in COPD patients, any antioxidant therapy might have a significant role in targeting both the inflammatory and systemic components of the vicious cycle of COPD in the future [46].

Various approaches have been proposed [47]. The glutathione (GSH) system scavenges oxidants efficiently, thereby protecting cells and tissues from damage by oxidants released by inflammatory cells or delivered from other exogenous sources [47]. N-acetylcysteine (NAC) is thought to affect both oxidative stress and inflammation in COPD because it is metabolized rapidly to cysteine, which is a direct precursor in the synthesis of intracellular GSH, and, in this way, NAC acts as an antioxidant by restoring the pool of intracellular reduced GSH, which is often depleted as a consequence of the increased status of oxidative stress and inflammation [48]. NAC can also exert reducing and antioxidant properties by acting as a direct scavenger of free radicals, such as $OH^{\bullet}$, H_2O_2 and $O_2^{-\bullet}$ [48]. As a direct consequence of these properties, NAC restores cellular redox status. In this way, it can modulate the activity of redox-sensitive cell-signaling and transcription pathways, such as the NF-κB pathway, which regulates a variety of proinflammatory genes. Although NAC is successful in inhibiting oxidative stress and inflammation in *in vitro* studies, its role in controlling systemic inflammation is doubtful [48]. Interestingly, 3-year treatment with low dose (600 mg day^{-1}) NAC was ineffective at preventing the deterioration in lung function and also at preventing exacerbations in patients with COPD [49].

More effective antioxidants, including stable GSH compounds, analogues of superoxide dismutase and selenium-based drugs, are now in development for clinical use [38]. In any case, intuitively, a combination of antioxidants is expected to be more effective than any single agent. In fact, such an approach has been proven capable of attenuating the plasma cytokine response to inspiratory resistive breathing [50]. This is probably because multiple sources of reactive oxygen species (ROS) exist in cells (such as the mitochondrial electron transport chain, the cytosolic NADH oxidase, the xanthine oxidase and, probably, membrane-bound oxidases).

Statins

Statins (cholesterol-lowering drugs that decrease mortality from cardiovascular disease) lower CRP levels [51], probably because they also reduce the production of IL-6 [51]. Therefore, the therapeutic effect of statins on cardiovascular disease seems to be broadly anti-inflammatory, which is also likely to apply to lung diseases in which there is an inflammatory component [51].

Experimentally, simvastatin inhibited cigarette smoking-induced emphysema and reduced peribronchial and perivascular inflammatory-cell infiltration and induction of MMP-9, a major inflammatory mediator [51]. Moreover, it reduced mRNA expression of IFN-γ, TNF-α and MMP-12 in the whole lung and the numbers of neutrophils and lymphocytes and the concentration of TNF-α in bronchoalveolar lavage [51]. These effects might justify why statins slow the decline in pulmonary function in smokers and former smokers and reduce the risk of required emergency department visits or subsequent hospitalization in COPD patients [52].

Interestingly, lovastatin increases efferocytosis (phagocytosis of apoptotic cells) [53]. An impaired phagocytic removal of apoptosed cells in bronchoalveolar lavage fluid samples from COPD patients has been documented [50] and decreased clearance of apoptotic cells by itself is likely to contribute to COPD through the effects of post-apoptotic necrosis, including promotion of inflammation, liberation of intracellular proteases and possible enhancement of autoimmune responses [54].

It must be highlighted that hospitalizations owing to exacerbations and mortality among COPD patients seem to be lower among those who are taking a statin [55], although combined use of statins and ICSs is associated with a more favorable prognosis than the use of a statin alone [56].

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II (Ang II) type 1 (AT1) receptor blockers

In chronic heart failure, ACE inhibitors reduce the risk of weight loss [57]. Moreover, renin–angiotensin-system blockade exerts an anti-inflammatory action in many systems [58]. Ang II induces proinflammatory genes and other proinflammatory substances and increases oxidative stress that could damage endothelium, myocardium and renal tissue [58]. Activations of NF-κB and NAD(P)H oxidase are fundamental steps in these proinflammatory mechanisms in which intramitochondrial oxidative stress could have a crucial role [58]. This sequence of events might explain why a reduction in Ang II synthesis by ACE inhibitors and AT1-receptor antagonists has a protective effect against cardiovascular disease [58]. These findings could be translated into COPD patients, also considering that lower ACE activity is associated with improved pulmonary hemodynamic variables and improved tissue oxygenation during exercise [59].

Unfortunately, no study has yet investigated the impact of ACE inhibitors or AT1-receptor antagonists on the systemic effects of COPD. Nonetheless, ACE inhibitors combined with statins reduce hospitalization and total mortality even in COPD patients without previous myocardial infarction and newly treated with nonsteroidal anti-inflammatory drugs [55]. Moreover, an AT1-receptor antagonist irbesarten reduces hyperinflation significantly in patients with COPD by an unknown mechanism [60].

Peroxisome proliferator-activated receptor (PPAR) agonists

PPAR-γ activators, such as the thiazolidinediones rosiglitazone and pioglitazone, are used in the treatment of diabetes. These agents have the potential to influence the systemic effects of COPD because they might have anti-inflammatory effects in the lungs [61] and the cardiovascular system [62]. However, *in vitro* research has

documented that only large doses of thiazolidinediones produce anti-inflammatory effects, leading touestions about the relevance of PPAR-γ stimulation in COPD [58]. In any case, these large doses might enable thiazolidinediones to act by non-PPAR-γ-related mechanisms [61].

Concluding remarks

The emerging recognition that COPD is a complex disorder, characterized by systemic inflammation in addition to local pulmonary inflammation, which might adversely impact on various extrapulmonary organs, such as the blood vessels and the heart, among others, emphasizes the need for more research on the underlying cellular and molecular mechanisms to discover new and more effective forms of therapy for this debilitating disorder. However, such an approach does not seem to be sufficient. In fact, unfortunately, a large number of crucially important questions remain unanswered [63]. For example, we still do not know whether treatment of lung inflammation decreases the risk of acute cardiac events, progression of atherosclerosis and/or thrombotic events. It is also unclear whether, alternatively, the treatment of heart disease can affect the progression of lung disease.

Several new therapeutic strategies aimed at controlling the underlying inflammatory processes of COPD more specifically are under development [35]. We do not know if all these new therapies will reach the market, however, although we think that there is still much to be learned about the mechanisms involved in the inflammatory component of COPD, findings from preclinical studies reveal promising avenues for the design of better therapeutics [35]. Nonetheless, we are not entirely optimist because, although considerable experimental evidence suggests that a specific target might have a role in the pathogenesis of COPD, dealing with the same target in subjects with COPD is often without benefit [36,37]. In any case, ideally, the new therapies that will reach the market will, potentially, enable combination with existing therapies that target airway inflammation and/or mucociliary dysfunction, thus addressing the systemic effects of COPD [46].

Addressing new compounds, it will be important to consider that inhaled anti-inflammatory drugs have the potential to reduce pulmonary inflammation while having low systemic exposure. Therefore, orally administered drugs and injectable therapies might have the advantage of better targeting both systemic and pulmonary inflammation in COPD. Nonetheless, systemic side effects might limit the therapeutic dose and, consequently, reduce the efficacy of the drug significantly.

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