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Targeting oxidant-dependent mechanisms for the treatment of respiratory diseases and their comorbidities

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Abstract

Oxidative stress is implicated in the pathogenesis of respiratory diseases, such as COPD and its comorbidities, asthma, idiopathic pulmonary fibrosis and radiation pneumonitis. Antioxidants drugs, such as small molecule thiols, nuclear erythroid-2 related factor 2 activators and catalytic enzyme mimetics have been developed to target oxidant-dependent mechanisms. The therapeutic effects of antioxidants have been generally disappointing. A small number of antioxidants are approved for clinical use, such as the small molecule thiol N-acetyl-L-cysteine for chronic obstructive pulmonary disease, and in the United States, the superoxide dismutase mimetic AEOL 10150 for severe radiation pneumonitis. The future use of antioxidants for the treatment of chronic respiratory diseases may require a precision medicine approach to identify responsive patients.

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Introduction

Oxidant-antioxidant (redox) balance in the respiratory system is an important component of host defense against pathogens. Oxidative stress occurs when oxidants overwhelm neutralizing antioxidants due to excess generation of free radicals, termed reactive oxygen species (ROS) and reactive nitrogen species (RNS) and/or due to reduced endogenous antioxidant defences (Figure 1). The generation of ROS occurs from exposure to exogenous factors, such as cigarette smoke, atmospheric pollutants and ionizing radiation and from endogenous sources including inflammatory cells, such as activated macrophages and neutrophils, epithelial cells and by the activation of intracellular oxidative enzymes, such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX2). ROS contains one or more unpaired electrons, a state that makes them highly reactive and unstable. Important ROS that contribute to oxidative stress are oxygen radicals, such as the superoxide anion ($O_2^{\bullet -}$) and hydroxyl radical ($HO^{\bullet}$) and nonradical species, such as hydrogen peroxide (H_2O_2). RNS include nitric oxide ($^{\bullet}NO$), peroxynitrite ($ONOO^-$) and nitrogen dioxide ($^{\bullet}NO_2$). Antioxidant defenses against ROS occurs by the activation of the endogenous enzymes superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) and by non-enzymatic antioxidants that include albumin, mucin and dietary sources, such as vitamins E (tocopherol), vitamin C (ascorbic acid), carotenoids and flavonoids.

Excess oxidative stress causes DNA damage, protein carbonylation and lipid peroxidation and these adverse effects are thought to contribute to lung injury in respiratory diseases. Increased oxidative stress is implicated in the pathogenesis of chronic obstructive pulmonary disease COPD [1,2••,3,4•] and its associated co-morbidities including cardiovascular diseases [2••], osteoporosis [5] and skeletal muscle wasting [2••,6] and in the pathogenesis of asthma [7,8•], cystic fibrosis [9,10], bronchiectasis [11], idiopathic pulmonary fibrosis (IPF) [12,13], pulmonary hypertension [14] and radiation pneumonitis [15]. Detailed reviews on the pathways involved in oxidant-antioxidant balance in chronic respiratory diseases are published elsewhere [1,3,4•,16,17]. Targeting oxidant-dependent mechanisms is a potentially attractive approach to the treatment of chronic respiratory diseases and their comorbidities. This review summaries the results of recent clinical trials of antioxidants in several chronic diseases, discusses their place in management and considers the reasons for the failure of many synthetic antioxidants to reach the clinic.

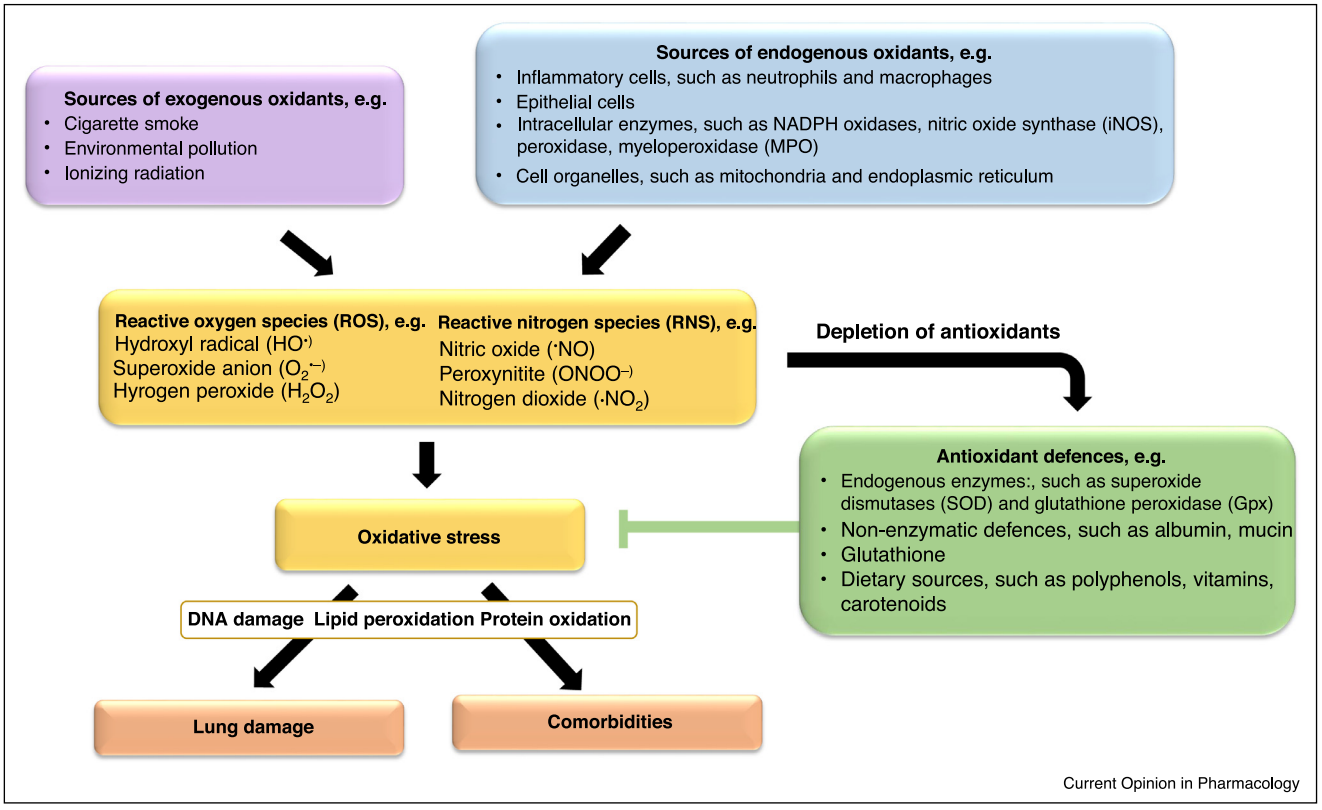
Interventions to target oxidative stress

Small molecule synthetic drugs and dietary supplements have potential antioxidant properties that suggest that they may be effective in the treatment of respiratory diseases (Table 1). However, only a few of these compounds have been evaluated in large clinical trials.

Small molecule thiol antioxidants

Small molecule thiol drugs decrease oxidant activity by increasing the synthesis of intracellular glutathione

Figure 1



Oxidative stress in the pathogenesis of lung damage and comorbidities. Oxidative stress occurs when oxidants overwhelm neutralizing antioxidants due to excess generation of free radicals, termed reactive oxygen species (ROS) and reactive nitrogen species (RNS) and/or due to reduced endogenous antioxidant defences. The generation of ROS occurs from exposure to exogenous factors, such as cigarette smoke, atmospheric pollutants and ionizing radiation and from endogenous sources including inflammatory cells, such as activated macrophages and neutrophils, epithelial cells and by the activation of intracellular oxidative enzymes, such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX2). Increasing generation of ROS and RNS causes depletion of antioxidants. Antioxidant defenses against ROS occurs by the activation of the endogenous enzymes superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) and by non-enzymatic antioxidants that include albumin, mucin and dietary sources, such as vitamins E (tocopherol), vitamin C (ascorbic acid), carotenoids and flavonoids. Excess oxidative stress causes DNA damage, protein carbonylation and lipid peroxidation and these adverse effects are thought to contribute to lung injury in respiratory diseases and the development of systemic comorbidities.

levels in depleted cells, although their antioxidant effect is considered to be weak when glutathione levels are normal [18]. Thiol drugs also reduce disulfide bonds in mucus glycoproteins to produce mucolytic effects. In the treatment of respiratory diseases that are associated with chronic mucus hypersecretion, it is uncertain whether the clinical benefits of small molecule thiol drugs are due to their antioxidant and/or mucolytic properties.

N-acetyl-L-cysteine (NAC) is the most frequently investigated small molecule thiol antioxidant for the treatment of chronic respiratory diseases, mainly COPD and IPF. Several large randomized controlled clinical trials have investigated the clinical benefits of treatment with NAC in patients with COPD [19,20••]. In the BRONCUS (Bronchitis Randomized on NAC) study, 523 patients with COPD received 600 mg daily NAC or placebo for 3 years. NAC had no effect on the primary outcomes of yearly decline in FEV_1 and number of exacerbations per year [19]. More recently, the PANTHEON (Placebo-controlled study on efficAcy and safety of N-acetylcys-Teine High dose in Exacerbations of chronic Obstructive pulmonary disease) study investigated the clinical effects of higher dose NAC (600 mg twice daily) in 1006 Chinese patients with moderate to severe COPD [20••]. Higher dose NAC reduced the rate of exacerbations, that were mainly mild in severity, by 22% compared with placebo over 1-year. A further small trial of high dose NAC treatment reported reductions in exacerbation rates in Chinese patients with COPD [21] who were at a high risk of an exacerbation [22]. A meta-analysis of 13 studies in 4155 patients with COPD that were treated with low dose (<600 mg daily) or high doses of NAC concluded that the lower dose was effective in reducing exacerbations of chronic bronchitis, whereas the higher dose was required