Oxidative Stress in Obstructive and Restrictive Lung Diseases

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Elena Bargagli and Alfonso Carleo

Abstract

The lung has ample and vascularized surface area constantly exposed to endogenous and environmental oxidants (in particular cigarette smoke). Thus, the imbalance between oxidants and antioxidant defenses has a pathologically important role in several lung disorders. This chapter describes the sources of free radical generation, ROS-induced signaling pathways, and mechanisms of oxidative stress damages in the pathogenesis of obstructive pulmonary diseases, idiopathic pulmonary fibrosis, and asthma. ROS are regulatory factors in different molecular pathways involved in miscellaneous lung diseases and might represent potential suggestions for therapeutic approaches. Given the limited effectiveness of current strategies, novel experimental approaches to develop improved antioxidant therapies are discussed.

Keywords

Oxidative stress · Damage mechanisms · Lung diseases · COPD · IPF · Asthma · Antioxidant therapies

9.1 Introduction

Oxidative stress is an insalubrious condition occurring when a variety of free oxygen radicals, collectively termed reactive oxygen species (ROS), prevail on antioxidant systems and lead to cellular damages [1, 2]. The lung is particularly susceptible to

E. Bargagli (✉)
Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy
e-mail: bargagli2@unisi.it

A. Carleo
Hannover Medical School, Hannover University, Hannover, Germany

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this imbalance being the organ designed for gas exchange, continuously exposed with a large surface area and blood supply to high oxygen tensions and exogenous oxidants such as ozone (O_3) and sulfur dioxide (SO_2) [3, 4]. Although some environmental pollutants (e.g., particulate matter, silica, or asbestos) are not oxidants, they may promote oxidative stress in the lung through recruitment and activation of ROS-producing cells and by triggering oxidative chemistry, as Haber-Weiss or Fenton's reactions [5–8]. The endogenous defense against oxidative stress induced by free radicals stress involves several preventive, repair, enzymatic, and non-enzymatic mechanisms [9]. Molecular antioxidant systems in the lung comprise scavengers (glutathione, ascorbic acid, tocopherol, uric acid, β-carotene, or thiol-containing proteins), detoxifying enzymes (superoxide dismutases, catalase, GSH-peroxidase, GSH S-transferase, peroxiredoxin-thioredoxin, glutaredoxions, or hemeoxygenase), and metal-binding proteins (transferrin or metallothioneins), and mucins [9, 10]. Except in some unusual exposures such as those to UV light and ionizing radiations, reactive oxygen and nitrogen species (RONS) are naturally generated by the cellular metabolism through enzymatic or non-enzymatic electron transfer reactions. These reactions are involved in a plethora of cellular processes, including cell signaling, microbial activity, cell fate, differentiation, proliferation, vasodilation, inflammation, neurotransmission, cell migration/adhesion, and hormone synthesis [11–13]. Mitochondrial electron transport chain, NADP oxidases, peroxidases, nitric oxide synthase, and xanthine oxidase are only some of the main RONS-generating pathways occurring in alveolar macrophage (AMs), fibroblasts, neutrophils, eosinophils, bronchiolar epithelial cells, alveolar epithelial cells (AECs), and endothelial cells [4, 14]. The expression of antioxidant enzymes is finely regulated and often induced in response to RONS exposure through transcription factors such as Nrf2 and FoxO3 in the bronchial and alveolar epithelium [15, 16].

As the oxidant/antioxidant imbalance is embroiled in the pathogenesis of miscellaneous diseases affecting the lung and pulmonary vasculature [3, 15, 17], this review will highlight its involvement especially in the chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) and will provide an overview of new therapeutic strategies.

9.2 Mechanisms of Oxidative Stress Damage

Reactive radical species can cause protein, DNA, and lipid oxidation and, through the generation of secondary metabolic RONS, can induce a variety of cellular responses [7, 10, 18]. The higher reactivity of RONS with different macromolecules (due to presence of unpaired electrons) leads to tissue damage, cellular dysfunction, and activation of different signaling pathways [11]. Proteins are the main target, and the oxidative/nitrosative stress through their oxidation, glycation, carbonylation, sulfonation, sulfenylation, or nitration affects their catalytic activity, conformation, and interactions and induces crosslinking [19]. Protein modifications, together with lipid peroxidation, impact on the cellular homeostasis; promote catabolite accumulation, cytotoxicity, and

apoptosis; and activate immune and inflammatory cytokines and chemokines (through TLR, NF-kB, p38-MAPK, or inflammasome pathway), such as IL-1, IL-6, IL-18, and TNF-α [e.g., 1, 14, 18]. Moreover the oxidative stress enhances the production of advanced glycation end products (AGE, heterogeneous compounds formed by glycated proteins or lipids), which contribute to pro-inflammatory and apoptotic response [1]. Positive feedback among the abovementioned inflammatory mediators and RONS is well-known, and it might sustain chronic inflammation and lung injury [1]. The RONS-induced protein modifications cause Endoplasmic Reticulum (ER) stress and the subsequent activation of Unfolded Protein Response (UPR), a protein folding restoration pathway [20]. Unresolved accumulation of misfolded proteins overcoming the UPR induces apoptosis (or senescence) and inflammation and strengthens the oxidative stress [21, 22]. There is substantial evidence that many respiratory diseases such as cystic fibrosis, COPD, IPF, and asthma are associated with excessive ER stress [21, 22]. RONS (or hypoxia) and ER stress can also regulate autophagy, an homeostatic catabolic process involving lysosomal degradation of damaged intracellular structures, that seems to influence cell differentiation [23, 24].

Interestingly, oxidative modifications of proteins and lipids are a potential source of autoantigens, and a role of oxidative stress in autoimmunity was postulated [2]. RONS damage DNA, and through chromatin remodeling and methylation inhibition they affect epigenetics, leading to instability, mutagenesis, and telomere shortening. Being close to endogenous ROS sources and unprotected by histones, the mitochondrial DNA (mtDNA) is more sensitive to oxidative stress damages than nuclear DNA. Thus, together with the well-know induction of intrinsic apoptosis or aging acceleration, oxidative damage altered the normal mitochondrial function, influencing the electron transport chain and promoting aerobic glycolysis (the Warburg effect) [25]. The structure and integrity of mitochondria are also compromised with swollen and elongated shape, fusion, and reduced cristae definition [26]. The leaks of cardiolipin or mtDNA are additional inflammatory and apoptotic signals [27]. The physiological response to mitochondrial dysfunction involves sensor proteins such as AMPK and sirtuin that further activate antioxidant gene regulators, such as Nrf2 and FoxO3 [28]. As a rule, alterations of mitochondrial function are observed in several pulmonary diseases and cancers [29].

Oxidative stress triggers the premature aging, through the abovementioned DNA instability and by inhibiting sirtuin-1, a regulatory protein of DNA repair system [15, 18]. Changes in cell morphology and physiology and their permanent proliferative arrest (senescence) further increase DNA damage, ER stress, insufficient autophagy, mitochondrial dysfunction, and ROS production [19, 28, 30, 31]. Furthermore, senescent cells express a peculiar secretory pattern, defined as Senescence-Associated Secretory Phenotype (SASP), consisting of cytokines, chemokines, and growth factors such as TNF-α, IL-β, IL-1, -6, CCL2, CXCL1, CXCL8, and TGF-β [32–34]. The SASP molecular microenvironment is linked with a persistent low level of inflammation and with immunosenescence (i.e., the immune cells, although chronically activate, show reduced functioning) [9, 15]. Premature aging markers and telomere shortening are often associated with IPF and COPD [31, 35].

9.3 Oxidative Stress in Chronic Obstructive Pulmonary Disease (COPD)

Exogenous oxidative stress and cigarette smoking are recognized as the principal pivotal factors in COPD etiology, prompting tissue injury, chronic inflammation, and mitochondrial dysfunction, accelerating aging, and altering the protease-antiprotease balance [36]. Increased levels of different markers of oxidative stress (such as 8-oxo-2′-deoxyguanosine, nitrotyrosine, isoprostanes, and AGEs) and pro-inflammatory molecules (TNF-α, IL-6, -8, CCL2, CCL3, ICAM-1, and leukotriene B4), as well as low levels of antioxidants, characterize biofluids and lung tissue of COPD patients [36–38]. The cellular mechanisms promoting the oxidative stress induced by smoking are complex and poorly understood; however, the gas and tar phases of cigarette smoke contain short-lived oxidants and long-lived radicals, respectively, and these compounds can react to form highly reactive molecules such as peroxynitrite or hydrogen peroxide [39]. Inhaled particles in ambient air have also the ability to generate free radicals and to activate cellular oxidative stress-response signaling pathways [40]. Thus, the inhalation of cigarette smoke and airborne particles depletes antioxidants (as glutathione), recruits macrophages, encourages AECs and inflammatory cells (especially AMs and neutrophils) to produce ROS and to release pro-inflammatory cytokines (through inflammasome, NF-kB, IRAK1, JNK, ERK, or TLR signaling), and, in parallel, induces apoptosis/cytotoxicity through ER stress [38, 41]. In fact, higher amounts of ROS and inflammatory proteins (as TNF-α, IL-1β, IL-6, IL-8, and CXCL1) as well as an increased number and altered functions of AMs and neutrophils are reported in COPD [15, 36, 38]. In particular, AMs from COPD patients show reduced phagocytic and antigen-presenting activity contributing to inflammation, apoptosis induction, reduced T-cell activation, and susceptibility to infections [36, 38]. The up-regulation of TNF-α signaling may have a pathogenic role in COPD by supporting further recruitment of inflammatory cells and tissue remodeling through induction of extracellular matrix (ECM)-degrading enzymes by neutrophils and AMs [42]. Indeed, BAL and sputum samples from COPD patients with exacerbations have higher TNFRII levels than those from healthy controls, and TNFRII concentrations are suggested as a prognostic biomarker of COPD [42]. Furthermore, ROS foster the breakdown of several ECM components (collagen, elastin, hyaluronic acid, fibronectin, and proteoglycans) and the inactivation of anti-proteases (α1-antitrypsin and other serine protease inhibitors) and, in parallel, induce the transcription and the proteolytic activation of proteases (as MMPs, cathepsins, or neutrophil elastase), triggering lung tissue destruction [26, 38, 43]. Independently of the smoking history of COPD patients, the increase of senescence markers and SASP proteins in their fibroblasts, endothelial cells, and AECs compared to controls shows that ROS influence the premature aging of the lung [15, 19].

ROS-induced mitochondrial abnormalities are reported in airway smooth muscle, bronchial epithelial cells, and AECs of COPD patients, and through accelerated cell senescence, apoptosis, and inflammation, they contribute to COPD pathogenesis and progression [7, 28]. Several protective mechanisms against DNA damage and mitochondrial stress are dysregulated by ROS in COPD lung, including reduced levels of parkin (a regulator of mitochondrial autophagy), sirtuin1, and FoxO3 [28, 38].

Nitrogen metabolism, in particular nitric oxide (NO), is hypothesized to impact on COPD pathogenesis [41]. It is well-known that oxidative stress can reduce the activity of nitric oxide synthase (NOS) positively regulating the metabolism of asymmetric dimethylarginine (ADMA), a potent inhibitor of this enzyme, and negatively influencing the production of arginine, a substrate of NOS [44]. Serum from COPD patients shows low NO concentration, high ADMA levels, and high ADMA/arginine ratio as compared to that in controls and correlates with disease severity. Interestingly, ADMA is hypothesized to be a comorbidity risk factor, as well as a prognosis and mortality biomarker, being increased in serum from non-survivors COPD and in patients with pulmonary hypertension or with acute exacerbation as compared to COPD stable patients [44]. Another possible mechanism of NOS down-regulation in COPD might involve PAR-1 (a ROS-induced protein involved in DNA repair and modulating NOS transcription) which is observed to be up-regulated in PBMCs from COPD patients [37].

9.4 Oxidative Stress and Idiopathic Pulmonary Fibrosis (IPF)

Several pieces of evidence show that oxidative and nitrosative stresses give a substantial contribution to IPF pathogenesis and progression, although they are not the main causative factor [26, 45]. Hence, insufficient concentration of antioxidants and high levels of oxidative/nitrosative markers (such as isoprostane, hydroperoxides, nitrogen oxides, nitrosotyrosine, uric acid, and etane), oxidized lipids, oxidized, nitrated, and carbonyl proteins have been found in biofluids or lung of IPF patients as compared to healthy subjects [45, 46]. Correlating with progressive worsening of dyspnea, acute exacerbation incidence, and BAL neutrophil content, some of these molecules may constitute potential prognostic biomarkers in serum or BAL samples from IPF patients [3, 4]. Positive and intricate interactions between the transforming growth factor β (TGF-β; the most well-known fibrogenic cytokine) and RONS signaling represent another important aspect in IPF pathogenesis [26]. TGF-β induces mitochondrial oxidant radical formation in lung fibroblasts by enhancing NADP oxidase, inhibiting sirtuin 3 expression and inactivating Nrf2; on the other hand, ROS support the profibrotic TGF-β downstream signaling at different levels [28, 47]. In general, ROS amplify the TGF-β-mediated pathway through oxidation of redox-sensitive proteins such as thioredoxin, which has inhibitory effects in physiological conditions [13]. In particular, the induction of NADPH oxidase-4 (NOX4) expression by TGF-β is postulated to have a central role in driving fibrotic response in IPF through ROS generation [13, 48]. NOX4 is highly expressed in fibroblast foci of IPF by myofibroblasts and AECs with opposite effects: it promotes differentiation (increasing expression of α-smooth muscle actin, fibronectin and procollagen I) and apoptotic resistance in fibroblasts/myofibroblast as well as apoptosis, mitochondrial stress, and epithelial-to-mesenchymal transition (EMT) in alveolar epithelial cells [25, 29]. The presence of myofibroblasts additionally boosts the ROS-TGF-β positive loop because these cells generate high levels of ROS which support myofibroblasts survival, differentiation, and contractility through ROCK pathway [49, 50].

Among the products released by damaged AECs in active sites of fibrosis, tenascin-C and sonic hedgehog (SHH) represent an interesting integration between ROS and TGF-β signaling in IPF patients [51, 52]. In AECs, TGF-β promotes tenascin-C secretion and inhibits SHH release; vice versa, oxidative stress stimulates the release of SHH and the transcription of tenascin-C. Tenascin-C is a profibrotic factor associated with EMT and tissue remodeling, while SHH is an AEC proliferative factor possibly related to re-epithelialization [51].

Furthermore, increased activity of NOS is observed in IPF lung and NO seems also to promote TGF-β and ECM-degrading enzymes in fibroblasts, at least in murine models [26, 43].

As abovementioned, the ECM degradation may occur through not only enzymatic but also oxidative mechanisms leading to remodeling and fibrosis. In IPF lung, there are increased levels of several ECM-degrading enzymes (in particular MMPs), whereas antioxidant enzymes (as extracellular superoxide dismutase) and pathways (as Nrf2) are barely present in fibroblast foci region [3, 4]. Thus, ROS critically contribute to the shedding and activation of latent form of TGF-β that is physiologically stored in intact ECM. In addition, low-molecular fragments of ECM components (as syndecan and hyaluronic acid) are observed in IPF and have been suggested to promote fibrosis and inflammation by facilitating the neutrophil recruitment [43, 48].

9.5 Oxidative Stress in Asthma

Oxidative stress may also affect asthma pathology, influencing several aspects associated with the disease, including alterations in airway smooth muscle contraction, mucus secretion/clearance, vascular permeability, and airway hyper-responsiveness [26].

In asthma, the observed high levels of oxidative stress markers in biofluids, as well as the low levels of NO and decreased activity of pulmonary antioxidant enzymes, are associated with disease severity [9, 15, 44]. The boost of oxidative stress seems to be related to the altered response to inhaled allergens or inflammation and is suggested to play a driving role in exacerbations [29]. Alterations in ROS production are observed in asthma in different cells. In particular, histamine and Th2 cytokines induce secretion of ROS by alveolar and bronchial epithelial cells [9, 29]. The latter exhibit elevated levels of NADPH oxidases (such as DUOX1 and DUOX2), and the activities of inflammasome, NOX4, and TNF-α signaling are increased in neutrophils and macrophages as compared to healthy controls [29, 42].

The enhanced inflammation and hyper-responsiveness in asthma airways through ROS-mediated mechanisms involve β-adrenergic receptor, DNA damage-response (especially PARP signaling), incorrect T cells maturation, and alteration of cytokines secretion by dendritic cells and epithelial cells [53, 54]. Hence, IL-8 (induced by NOX), IL-5 (induced by PARP1), and IL-33 and IL-25 (induced by DUOX1) foster inflammation, Th2 response, and leukocytes recruitment [29]. Cumulative evidence suggested the additional importance of oxidative stress in pathogenesis of neutrophilic, severe, and elderly asthma [9].

9.6 Conclusion and Future Perspectives

The oxidant/antioxidant imbalance and the accumulation of highly reactive molecules cause damage to DNA, lipids, proteins, and carbohydrates and are implicated in the pathogenesis of diseases affecting the lung and pulmonary vasculature. Redox-regulated signaling pathways are important mechanisms to regulate cellular functions, and ROS and RNS have specific targets conferring them signaling properties and determining their biologic effects [55]. For instance, GSH and NADP homeostasis is regulated by GSH peroxidases, S-transferases, and reductases, and when the mechanism is altered, the induced signaling pathway promotes airway inflammation in COPD and asthma [55]. There are several methods to measure the oxidative stress in lung pathologies such as increased lipid peroxidation products, DNA oxidation, or protein carbonyl formation in lung tissue, and several antioxidant scavengers have been tested in clinical trials to restore oxidant/antioxidant imbalance in pulmonary and cardiovascular diseases [4, 19, 36, 55]. Unfortunately, the results of these studies were conflicting or unsuccessful in IPF, COPD, and asthma treatments. Although dietary supplementation with antioxidants (vitamin A, C, E, β-carotene, glutamine, polyphenols, melatonin, and coenzyme Q10) may produce some beneficial effects, such as lower risk for COPD, asthma incidence, attenuation of inflammation, and lung deterioration, it cannot be considered a valid therapeutic strategy [55, 56].

Recently, a double-blinded, placebo-controlled crossover study on asthma patients reported that γ-tocopherol may have potential therapeutic effects reducing inflammation and eosinophils in the induced sputum [57]. N-acetyl-cysteine (NAC) is an antioxidant (acting as scavenger and restoring glutathione), mucolytic, and anti-inflammatory drug widely tested in lung diseases yielding contrasting results [52, 55]. In the context of COPD (and cystic fibrosis), NAC seems to ameliorate the pulmonary function and to reduce the risk of exacerbation, whereas it has not been shown to prevent mortality in asthma [52, 55]. Although there is evidence of an improvement of 6-min walking test distance, NAC therapy is not recommended (even when combined with antifibrotic drugs) for IPF therapy due to the lack of beneficial effects in pulmonary functional tests parameters such as DLCO and VC and in the mortality rate [52, 55].

Interestingly, pharmacogenomics seems to affect the NAC therapy in IPF, as reported by the differential response of patient with different *TOLLIP* genotypes [58]. For this reason, recent insights in personalized medicine are oriented toward implementing the efficiency of antioxidant therapy in selected stratified patients. In fact, genetic polymorphisms in antioxidant enzymes such as glutathione-S-transferase or superoxide dismutase are associated with susceptibility and symptom development in asthma and COPD patients [59–61]. Thus, for appropriate therapies it seems necessary to consider individual genetic and epigenetic factors that may influence the oxidant/antioxidant system. Moreover, the monitoring of oxidative stress markers as indicators of treatment response could be helpful in the optimization of individual dosage. The asthma management with inhaled corticosteroids based on the monitoring of fractional exhaled nitric oxide appears to reduce

exacerbations in adult patients [59]. However, the establishment of targeted and patient-specific therapies will be a difficult task without appropriate systems to directly provide a proper antioxidant, in the right concentration and in a specific tissue or cell of the lung environment, especially in the initial disease phase, before oxidative stress compromises the tissue integrity.

Conflict of Interest The authors declare no conflict of interest.

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