ANTIOXIDANTS & REDOX SIGNALING
Volume 10, Number 4, 2008

DOI: 10.1089/ars.2007.1961

Forum Editorial

Redox-Based Therapeutics for Lung Diseases

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ABSTRACT

Because oxidative stress is such a common factor of lung diseases, we cannot help asking why so many diseases are caused by the same oxidative stress. It is likely to be a consequence of diversity in sources and location of oxidative stress, and concomitant factors. The aim of this forum is to characterize the disease-specific involvement of oxidative stress and to make use of it for therapeutics. It is also of note that oxidative-stress biomarkers are useful tools for disease management. Exhaled nitric oxide has been established as a marker of bronchial asthma in clinical practice. By using recent noninvasive techniques, such as exhaled breath condensate, other markers of lipid peroxidation or antioxidants are now under evaluation. Antioxidant therapy, as represented by *N*-acetylcysteine, has widely been tested as a treatment for lung disorders, but it has had limited success in clinical practice. The clinical outcome might be improved by combination therapy or better patient selection. Novel antioxidant drugs are also under investigation. Molecular targeted therapy against redox-sensitive signaling pathways could be an alternative therapeutic approach. Moreover, disease-specific pathways have been identified whose regulation could be more efficient and less toxic than regulating universal pathways. *Antioxid. Redox Signal.* 10, 701–704.

OXIDATIVE STRESS is undoubtedly involved in the pathogenesis of wide variety of lung disorders. In this forum issue, "Redox Regulation in Pulmonary Health and Disease," we are especially focused on diseases such as chronic obstructive pulmonary disease (COPD), bronchial asthma, acute respiratory distress syndrome (ARDS), idiopathic pulmonary fibrosis (IPF), and sleep disorders. It also must be noted that oxidative stress plays key roles in other lung disorders including cystic fibrosis, pulmonary sarcoidosis, and lung cancer (13, 14, 20). Because so many reports suggest relations between oxidative stress and pulmonary disease, we must put them in order and try to understand some common messages. These messages fall into the following categories: (a) oxidative stress in the pathogenesis of lung disease, (b) oxidative stress marker for lung disease, or (c) antioxidant therapy for lung disease. In this article, we discuss what is known and what remains to be clarified, focusing on these three points.

In terms of oxidative stress in disease pathogenesis, it must be clarified why so many diseases are induced by the same oxidative stress. For example, it is quite confusing that oxidative stress is reported to be a factor of both IPF, a fibrotic lung disease, and COPD, a destructive lung disease. To answer this question, we must characterize disease-specific involvement of oxidative stress.

First, it must be stressed that, in the lungs, two sources of oxidative stress exist, both of which are likely to be associated with the pathogenesis of lung disorder. One is an exogenous oxidant such as tobacco smoke or diesel particles. The other one is intrinsic and usually generated by inflammatory cells. It is therefore speculated that different sources of oxidative stress contribute to disease specificity. It also depends on where it acts (*e.g.*, interstitium, parenchyma) and what kind of other factors are involved in combination with the oxidative stress. Taking into consideration these factors, we characterize the disease specificity of oxidative stress.

Bronchial asthma is characterized as eosinophilic inflammation in airways, which causes bronchoconstriction and occasionally airway remodeling when prolonged. Leukotrienes and

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proteases are major mediators whose production is enhanced by the oxidative stress, mainly generated by the inflammatory cells. Interaction between leukotrienes and the glutathione system is well described in this issue (28). Therapeutics of bronchial asthma should therefore be directed to the airway (usually central airways) and eosinophils. In this context, anti-inflammatory drugs such as inhaled corticosteroids have been used and are effective in most cases (95%). The remaining 5% are refractory cases, and this subset of patients might be a good target for antioxidant therapy, because oxidative stress is suggested to be a factor in this glucocorticoid resistance.

COPD is a chronic lung disease caused mainly by chronic cigarette smoking. Smoking-induced inflammation in combination with oxidative stress and excessive proteases is the center of its pathogenesis. These components induce airway inflammation (chronic bronchitis) and alveolar destruction (emphysema). In COPD, small airways and alveoli are injured by oxidative stress, either contained in cigarette smoke itself or induced by the inflammatory cells such as neutrophils and alveolar macrophages. This smoke-induced inflammation is though to be resistant to glucocorticoids. The mechanism of this resistance is suggested by Rajendrasozhan *et al*. (22) in this issue; oxidative stress may inactivate histone deacetylases (HDACs) and enhance NF-κB signaling. Therefore, in COPD, redox regulation could restore HDAC activity and glucocorticoid sensitivity. An involvement of Duox, a novel oxidase, in COPD also is suggested in this issue (18).

Fibrotic lung diseases, including IPF, are also affected by oxidative stress. Although the precise mechanism of inflammation in IPF is not well understood, inflammatory cells such as lymphocytes and macrophages are somehow activated in lung interstitium and promote remodeling of alveolar structure *via* fibrogenic cytokines production, such as TGF-β. Some unique signaling molecules, PTEN and Gremlin, are inactivated in the fibrogenic process, as suggested by Kinnula *et al*. (10) in this issue. These signaling molecules are regulators of fibrosis that are inactivated by oxidative stress in IPF lungs. It is thus assumed that redox regulation or restoration of these oxidant-sensitive pathways could be good strategy in IPF therapeutics. Conversely, because the pathologic feature of acute exacerbation of IPF resembles that of ARDS, the same strategy as that for ARDS can be applied for this exacerbation.

In contrast these chronic disorders, ARDS is a severe acute lung disease caused by various stress conditions such as severe infection or open-heart surgery. Oxidative injury by inflamed neutrophils is targeted mainly to pulmonary endothelium and enhances vascular permeability, leading to pulmonary edema. Therefore, to protect pulmonary endothelium from neutrophil-induced oxidative stress should be a key strategy in ARDS therapeutics. Disease-specific signaling pathways have not been suggested. In the fibroproliferative phase of ARDS, the pathology is similar to that in pulmonary fibrosis, such as IPF. A therapeutic strategy similar to that used with IPF could be applied in this phase.

Sleep disorder is rather a systemic disease caused by apnea/hypopnea. Intermittent hypoxia in this disease is a similar condition to ischemia/reperfusion, which is a well-known cause of oxidative stress. The oxidative stress is directed mainly to systemic vessels, causing vascular inflammation, which leads to atherosclerosis and other cardiovascular disorders. Continuous positive airway pressure (CPAP) therapy is usually effective by improving hypoxia during sleep. Antioxidant therapy could be applied for those patients who cannot tolerate the CPAP therapy or when CPAP therapy is insufficient for removing oxidative stress.

As a biomarker for pulmonary disease, oxidative stress (in other words, disturbed redox balance) not only is detected in conventional clinical material such as peripheral blood, sputum, urine, and bronchoalveolar lavage fluid, but also is detected by some novel noninvasive techniques such as induced sputum and exhaled breath condensates. Biomarkers are helpful for differential diagnosis, reflect disease activity, or predict prognosis or therapeutic response. Some established or promising markers exist in this context.

Exhaled nitric oxide is an establish marker of bronchial asthma and useful for monitoring disease activity. The advantage of this marker is that it can be evaluated easily and repeatedly. It is not effort dependent and is more reliable than pulmonary function tests. However, we must be careful about smoking, because it significantly affects the measurement. It is also a good biomarker of other lung disease such as ARDS. Urine nitric oxide level reflects disease severity and predicts the therapeutic response of ARDS (16).

Isoprostane is one of the most investigated biomarkers of oxidative stress. It is a stable product of lipid peroxidation and can be detected even in noninvasive material such as exhaled breath condensates. Although it is a nonspecific disease marker, plasma isoprostane reflects the disease severity of mild bronchial asthma (29). In COPD, 8-isoprostane in induced sputum is a marker of disease severity (11). In obstructive sleep apnea, exhaled 8-isoprostane reflects disease severity and therapeutic response (2). Other markers, such as ethane and hydrogen peroxide in exhaled breath, are also suggested to be good markers of disease activity and severity in IPF (8, 21).

Antioxidant levels also are altered by oxidative stress; these are usually found to be decreased in lung diseases, reflecting an impaired antioxidant capacity. In contrast, it is suggested that levels of thioredoxin (TRX), a redox-acting molecule, are increased in patients with acute lung injury, particularly of pulmonary origin, and provide a useful indication of inflammation (1). The significance of TRX as a biomarker of sleep disorder also is suggested by Takahashi et al. (24) in this issue. They found that plasma TRX is a unique marker for evaluating oxidative stress and monitoring the effectiveness of CPAP therapy in obstructive sleep apnea (OSA) patients. The significance of the TRX system in COPD also is discussed in this issue (15).

Disease-specific markers are still needed for differential diagnosis or to discriminate the activity of coexisting disease (*e.g*., COPD with asthmatic component, COPD with focal fibrosis).

Finally, the current status of antioxidant therapy in pulmonary disease is discussed. *N*-Acetylcysteine (NAC) has been tested widely for treatment of cystic fibrosis, COPD, and IPF. Despite many outstanding results in *in vitro* and *in vivo* studies, NAC treatment has had limited success in clinical practice. It is reported to improve some biomarkers, such as neutrophil activity in cystic fibrosis, exhaled hydrogen peroxide in COPD, and lung glutathione levels in IPF (9, 17, 26). However, most reports failed to demonstrate improved clinical outcome in NAC treatment (3). A study demonstrated that NAC treatment slows disease progression of IPF (4).

It is speculated that clinical ineffectiveness of antioxidant therapy is partly because oxidative stress is not the only factor of the lung diseases. Combination therapy with antioxidants and some other drugs, such as antiinflammatory drugs, might be effective in this case. NAC has been proven to be effective for IPF only in combination with corticosteroids and immunosuppressants, as described earlier. This kind of strategy is well established as therapeutic for lung tuberculosis and malignancies in which multiple drugs with different functions are usually administered together. Alternatively, antioxidant therapy should be limited for patients with severe oxidative stress. This subset of patients could be selected by using the mentioned biomarkers.

Novel antioxidative drugs, among which is thioredoxin (TRX), are now under investigation for lung disorders. TRX is an endogenous redox-regulating protein and is known to have various effects such as antiapoptosis and antiinflammation. It is reported to be effective in wide variety of animal models for bronchial asthma, COPD, interstitial pneumonia, and ARDS (6, 7, 12, 19, 27). Protective mechanisms of TRX in bronchial asthma are well summarized in this issue (5). Based on these preclinical observations, we are now preparing a clinical trial of intravenous TRX injection against acute lung injury. This method could be applied for acute exacerbation of COPD or asthma attacks, once drug safety and kinetics have been established. For chronic lung diseases, however, it would not be practical to administer such an expensive protein compound for a prolonged period. Better drug delivery must be developed, such as inhalers, small mimic, or inducing agents.

Another issue of current antioxidant therapy is that it is based on either supplementation of an antioxidant itself or an enhancement of antioxidant defense by antioxidant inducers. However, to restore proper oxidant/antioxidant balance disturbed by lung disease, an enormous amount of antioxidant is required, and that is likely to cause drug toxicity. Regulation of redox-sensitive pathways could be an alternative therapeutic approach. As shown in Fig. 1, NF-κB and AP-1 are well-known pathways leading to pro-inflammation, whereas Keap1/Nrf2 signaling enhances antioxidant production. Because abnormal regulation of these pathways is detected in most lung diseases, including bronchial asthma, COPD, IPF, ARDS and sleep disorder, as intensively discussed in this issue (10, 22, 23, 25, 30), that might be a potential target for therapeutics. Several disease-specific redox-sensitive pathways are suggested in this issue, such as leukotriene/glutathione interaction in bronchial asthma (28), HDACs in COPD and refractory asthma (22, 23), and PTEN and Gremlin in IPF (10). Regulation of these pathways would be more efficient and less toxic than regulating universal pathways, such as NF-κB and AP-1. Further investigation is necessary to evaluate the molecular targeted therapy.

In conclusion, redox regulation is promising as therapeutic for lung diseases. Conventional antioxidants would still be effective with better patient selection and combination therapy. To identify disease-specific signaling mechanism could be helpful for development of novel molecular targeted therapy.

ABBREVIATIONS

ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive air-

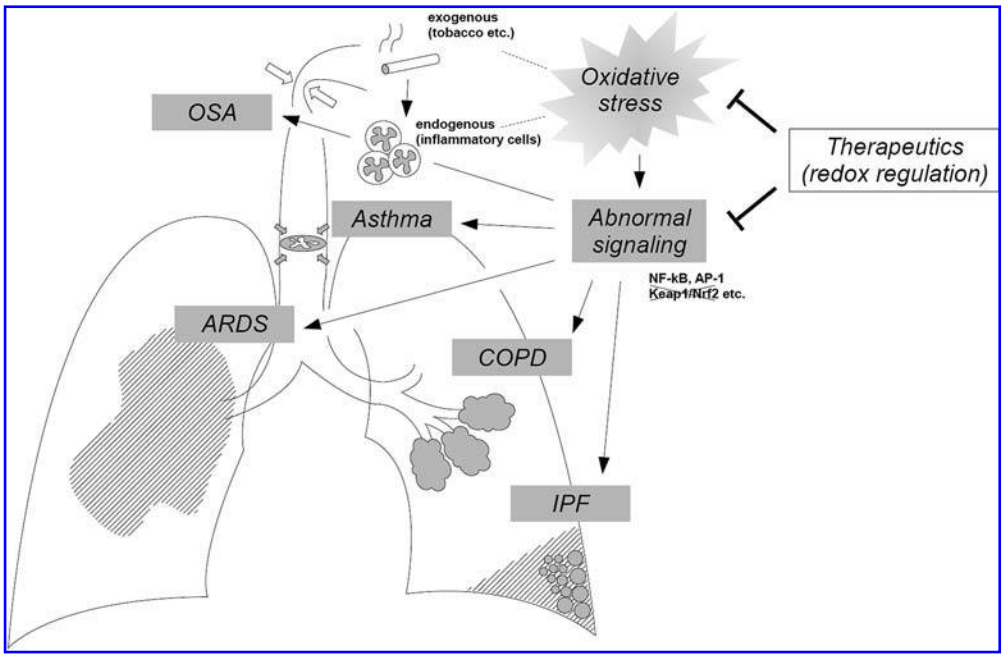

FIG. 1. A schematic review of oxidative stress in lung diseases and redox-based therapeutics. Involvement of oxidative stress in lung disease is diverse, depending on location and cell types affected. Redox-based therapeutics for lung diseases are based on either direct attenuation of oxidative stress or regulation of redox-sensitive abnormal signaling. Regulation of disease-specific pathways would be more efficient than that of common pathways such as NF-κB, AP-1, and Keap1/Nrf2.

way pressure; Duox, dual oxidase; HDAC, histone deacetylase; IPF, idiopathic pulmonary fibrosis; Keap1; Kelch-like ECH-associated protein 1; NAC, *N*-acetylcysteine; Nrf2; NF-E2–related factor 2; OSA, obstructive sleep apnea; PTEN, phosphatase and tensin homologue; TRX, thioredoxin.

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Date of first submission to ARS Central, October 21, 2007; date of acceptance, October 21, 2007.

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