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Forum Review

Redox Regulation of Lung Inflammation by Thioredoxin

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ABSTRACT

The lungs are the richest in oxygen among the various organs of the body and are always subject to harmful reactive oxygen species. Regulation of the reduction/oxidation (redox) state is critical for cell viability, activation, proliferation, and organ functions. Although the protective importance of various antioxidants has been reported, few antioxidants have established their clinical usefulness. Thioredoxin (TRX), a key redox molecule, plays crucial roles as an antioxidant and a catalyst in protein disulfide/dithiol exchange. TRX also modulates intracellular signal transduction and exerts antiinflammatory effects in tissues. In addition to its beneficial effects in other organs, the protective effect of TRX in the lungs has been shown against ischemia/reperfusion injury, influenza infection, bleomycin-induced injury, or lethal inflammation caused by interleukin-2 and interleukin-18. Monitoring of TRX in the plasma, airway, or lung tissue may be useful for the diagnosis and follow-up of pulmonary inflammation. Promotion/modulation of the TRX system by the administration of recombinant TRX protein, induction of endogenous TRX, or gene therapies can be a therapeutic modality for oxidative stress-associated lung disorders. *Antioxid. Redox Signal.* 7, 60–71.

OXIDATIVE STRESS AND THE LUNGS

Oxidative stress and lung injury

ALTHOUGH THE EUKARYOTIC CELLS of many creatures utilize oxygen as an energy source, they are at the same time exposed to reactive oxygen species (ROS) generated in the respiratory chain of mitochondria, enzyme activities, and hypoxia/reoxygenation (20). Cells in multicellular organisms are also subject to oxidative stress originating from neighboring cells and tissues. Furthermore, exogenous stress, including ultraviolet (UV), irradiation, or drugs, also accelerates the generation of ROS in the body.

The lungs are the richest in oxygen among the organs in the body and are exposed to air pollutants that often contain ROS. Therefore, the lungs are always subject to oxidative stress. For protection, cells are equipped with antioxidant systems, including catalase, superoxide dismutase (SOD), glutathione (GSH), and thioredoxin (TRX).

The imbalance of oxidants/antioxidants, *i.e.,* reduction/oxidation (redox) equilibrium, seems to play an important role in the development and manifestation of various pulmonary diseases, including acute respiratory distress syndrome (ARDS) (20, 41) and chronic obstructive pulmonary disease (COPD). A number of studies have shown increased oxidant burden and markers of oxidative stress in the airspaces, breath, blood, and urine in smokers and patients with COPD. The sources of increased oxidative stress are cigarette smoke, or leukocytes both in the airspaces and in the blood. Pathophysiological examination reveals the oxidative inactivation of antiproteinases, airspace epithelial injury, increased neutrophils in the pulmonary microvasculature, and the gene expression of proinflammatory mediators (77).

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Oxidative stress may play an important role in the pathogenesis of idiopathic pulmonary fibrosis (IPF) by affecting the apoptosis of structural and inflammatory cells and altering the balance of cytokines (84). Oxidant/antioxidant imbalance in the lungs of patients with IPF has been observed, and reflected as systemic oxidant stress (120).

O_2 inspiration, even at therapeutic concentrations, can cause lung injury (49) due to the excessive production of ROS by lung mitochondria (35). Ambient ozone, together with diesel exhaust particles, results in lung toxicity (79).

ROS derived from various chemicals, including paraquat (133) and bleomycin (BLM) (40, 56, 99, 116, 142), cause severe pulmonary dysfunction.

DNA damage in the lungs by ROS has been shown in ischemia/reperfusion (I/R) injury (65).

Iron, essential for the survival of most aerobic organisms, also catalyzes the formation of ROS. Environmental pollutants, such as silica, asbestos, coal dust, tobacco, or diesel particles, contain iron and promote ROS production through iron metabolism (117) or through the activation of leukocytes (alveolar macrophages, neutrophils, eosinophils, and basophils), which consequently release ROS (30). Therefore, air pollutants often cause various chronic lung diseases, such as silicosis, asbestosis, COPD, mesothelioma, and lung cancer (117). Iron-catalyzed ROS formation may also contribute to chronic rejection after lung transplantation (122).

Hydrogen peroxide (H_2O_2) and derived oxidants increased neutrophil elastase-mediated lung injury in an isolated perfused animal model (11).

Oxidative stress and cell signaling

Alveolar oxygen tension or oxidative stress modulates signaling in cells via oxygen- and redox-sensitive transcriptional factors such as hypoxia-inducible factor-1α (HIF-1α), nuclear factor-κB (NF-κB), and activator protein-1 (AP-1). HIF-1α is activated by hypoxia over physiologically relevant ranges (131), whereas NF-κB is activated against inflammatory and oxidative stresses (42). AP-1, a transcriptional complex formed by the dimerization of Fos-Jun or Jun-Jun proteins, is also regulated by redox mechanisms (144). These transcriptional factors regulate the expression/suppression of various proinflammatory mediators and protective antioxidants (41, 77, 118).

NF-κB activation was determined in patients with acute lung injury (87). Asbestos fibers cause both cell proliferation and apoptosis, partially through the activation of signal transduction pathways by ROS. Asbestos activates NF-κB, which leads to the up-regulation of antioxidant enzymes, most importantly manganese-SOD (68).

Oxidative stress plays a role in lung inflammation also through the activation of stress kinases [c-Jun N-terminal kinase (JNK), mitogen-activated protein kinase (MAPK), and p38] (119).

Antioxidant and lung injury

Various studies have shown the implication and protective effect of antioxidants in acute and chronic pulmonary disorders.

GSH, a ubiquitous tripeptide thiol, is an important intra- and extracellular antioxidant against oxidative stress in the lungs (118). GSH levels decrease in the epithelial lining fluid in pulmonary fibrosis (18, 78), ARDS (16), cystic fibrosis (124), or lung allograft patients (12). Similarly, exposure to hypoxia/reoxygenation decreases the lung GSH content and increases the oxidized form of glutathione (GSSG) (61).

GSH protects cultured human lung epithelial cells against oxidant-mediated injury (15, 121) including paraquat toxicity (43). GSH aerosols suppress lung epithelial surface inflammatory cell-derived oxidants in cystic fibrosis (125). Tolerance to hyperoxia is associated with increased GSH peroxidase and reductase (66). Gene transfer of mitochondrial GSH reductase (105, 106) or GSH peroxidase (10) protects cells against oxidative stress. *N*-acetyl-L-cysteine (NAC), a precursor of GSH, attenuates apoptotic lung injury in a sepsis model (115).

Heme oxygenase (HO) is another critical defender of cellular homeostasis against oxidative stress. HO is responsible for the degradation of heme to biliverdin, free iron, and carbon monoxide (CO). Biliverdin is subsequently converted to bilirubin through the action of biliverdin reductase, and free iron is sequestered by ferritin (83, 88). Heme oxygenase-1 (HO-1), an inducible form of HO, is induced by oxidative stress (75) or endotoxin (19, 137). The expression of HO-1 is up-regulated in the airway of smokers (81), and levels of exhaled CO are increased in patients with asthma (55) or cystic fibrosis (8). These observations suggest the involvement of HO and CO in pulmonary stress response.

There is also increasing evidence that the HO/CO system protects lung tissue against oxidative stress, because exogenous CO (114), gene transfer of HO-1 *in vivo* (113), and the overexpression of HO-1 in cells from the lungs (136) counteract hyperoxia-induced injury. The cytoprotective function of HO-1 may depend partly on the prevention of free heme from participating in prooxidant reactions. Additionally, the three products of heme breakdown—bilirubin, CO, and ferritin induced by free iron release—have a cytoprotective function (103, 112, 153).

The effectiveness of various antioxidants in lung transplantation has been shown experimentally (69). Allopurinol (xanthine oxidase inhibitor), SOD, catalase, deferoxamine (iron chelator), dimethylthiourea (28), or NAC (both thiols) prevented reperfusion injury of the lungs (2, 67, 73). Lazaroid, which inhibits iron-dependent lipid peroxidation, also inhibits lung I/R injury in a canine model (141). Antioxidants may also be beneficial to diminish graft rejection after lung transplantation (17).

Furthermore, SOD attenuates endotoxin- (138), cytokine- (5), ischemia- (53), or hemorrhage- (14) induced lung injuries in animal models. The protective effects of catalase against air embolism (34) or green tea polyphenol against H_2O_2-induced cellular injury (85) have been reported. Iron chelation can also be a therapeutic tool for various diseases, but the appropriate degree and duration of chelation therapy should be determined with caution (117).

Although GSH is used in an organ preservation solution, University of Wisconsin solution (63), very few antioxidants have established their clinical usefulness. Even NAC showed no significance in clinical trails for the treatment of ARDS (31).

TRX

TRX was originally identified as a hydrogen donor for ribonucleotide reductase in *Escherichia coli* in 1964 (74). We cloned human TRX as adult T-cell leukemia-derived factor

(108, 139, 155, 156). TRX plays a crucial role in controlling the redox environment of the cell (51, 52).

TRX has multiple functions in the cells and the body. Firstly, TRX is a powerful antioxidant quenching singlet oxygen and scavenging hydroxyl radicals (23, 123). Collective studies (94) have shown the induction of TRX by various stresses such as UV (127), viral infection (36, 91, 154), ischemia (107, 145), a chemotherapeutic agent against malignant diseases (40, 129), H_2O_2 (92, 127), or even oxygen (25).

TRX is released from cells (33, 126). We recently showed that the redox-active site of the protein is essential for its release. The release is induced rapidly by H_2O_2, but is suppressed by exogenous NAC or recombinant TRX (rTRX). Extracellular TRX enters the cells and suppresses intracellular oxidative stress and cellular apoptosis. These results suggest that the release of TRX is regulated by negative feedback loops using ROS-mediated signal transduction (71). TRX also has extracellular chemotactic activity (13, 96) and regulates the expression of some cytokines as a potent costimulator (130).

TRX plays a role in the regulation of intracellular signal transduction by several molecules such as NF-κB (39, 44, 48, 86), AP-1 (50), apoptosis signal-regulating kinase 1 (ASK1), and p38 MAPK (147). Exogenous TRX is taken up into mammalian cells (7, 24) and activates NF-κB. Similarly, TRX overexpression activates NF-κB (22). TRX induces the gene expression of manganese-SOD in cell lines and primary human lung microvascular endothelial cells (24) (Fig. 1).

ASK1 is a MAPK kinase kinase that activates JNK and p38 MAPK and induces a stress-mediated apoptosis signal (58). Reduced TRX binds to ASK1 and inhibits the activity of ASK1, whereas oxidized TRX is dissociated from ASK1 and results in the activation of ASK1 (128). In addition, TRX negatively regulates p38 MAPK activation (45).

TRX also binds to TRX-binding proteins (TBPs). We identified TBP-1 as a phagocyte oxidase component (p40phox) and TBP-2 as vitamin D3 up-regulated protein 1 (VDUP1) (101, 102). TBP-2/VDUP1 negatively regulates the reducing activity of TRX (101). We recently reported that TBP-2 plays a crucial role in the growth regulation of T-cells and TBP-2 induces cell cycle G1 arrest by increasing p16 expression (100).

TRX protects cells and tissues against various oxidative stresses, such as activated neutrophils, H_2O_2 (92), chemotherapeutic agents (129, 132), light exposure (143), or I/R (9, 38, 46, 54, 64, 107, 140). These tissue-protective effects of TRX may be partly dependent on its antioxidant effect. However, our recent studies have also shown that TRX exerts an antiinflammatory effect by direct suppression of the chemotaxis of neutrophils (97) (Fig. 2).

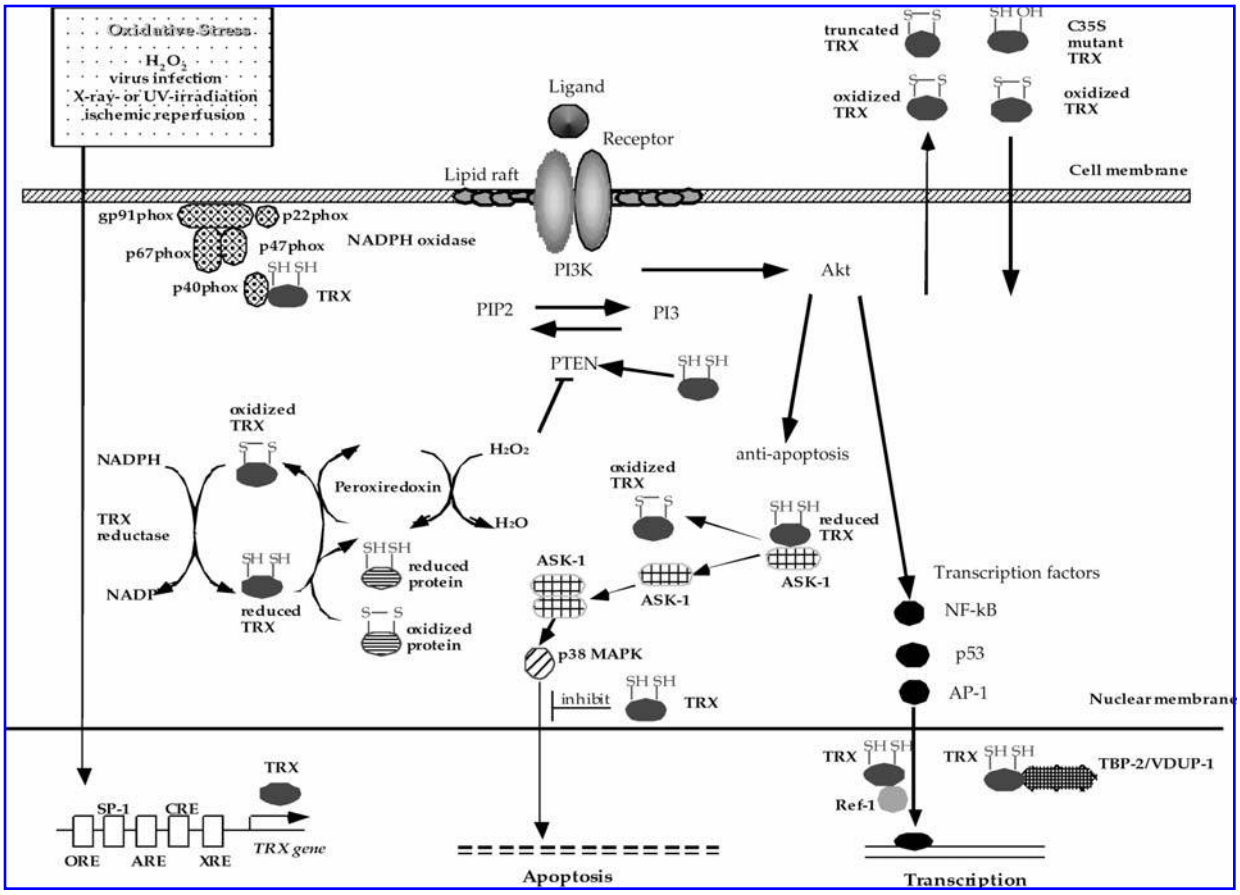

FIG. 1. Intracellular/extracellular regulation and functions of the TRX system.

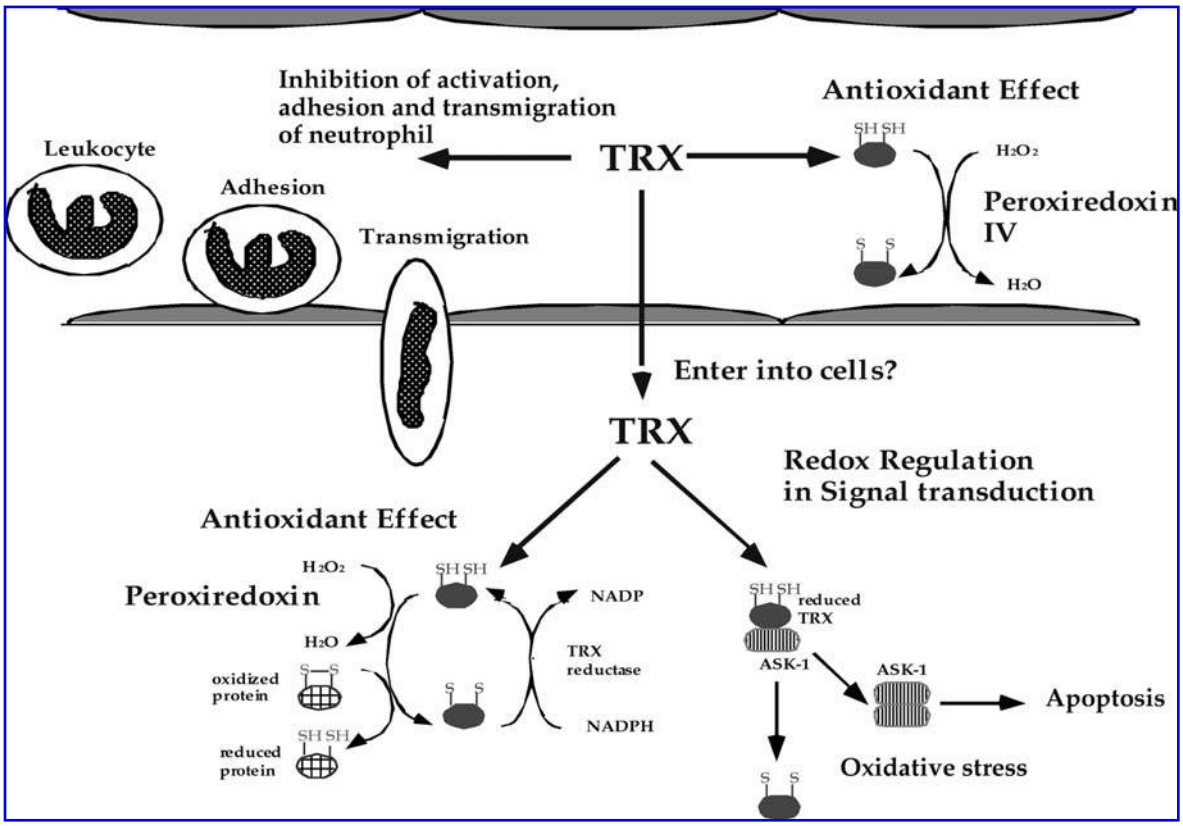

FIG. 2. Inhibition of neutrophil chemotaxis and inflammation by TRX.

TRX AND LUNG INFLAMMATION

TRX and I/R injury of the lungs

Lung transplantation has been established as a therapeutic modality for terminal organ dysfunction (27, 134, 146). More than 14,000 lung transplants have been performed around the world with an acceptable 5-year survival rate of ~40% (146). However, there are still complications and problems to overcome. Among them, I/R injury (reimplantation response) is responsible for morbidity and mortality, especially in the first weeks after surgery (27, 146). In addition, I/R injury to the lung is often encountered after cardiopulmonary bypass or pulmonary thromboendarterectomy.

Various antioxidants, including SOD (32, 57), NAC (110), allopurinol (2, 4), lodoxamine (76), vasoactive intestinal peptide (90), and lazeroid (47), have been experimentally effective against I/R injury to the lungs. However, few antioxidants have established regular use in clinics.

We have shown the protective effect of recombinant human TRX (rhTRX) against warm (normothermic) I/R injury to the lungs. Administration of rhTRX resulted in improved animal survival and gas exchange, as well as decreased tissue edema and lipid peroxidation in *in vivo* I/R injury to rat lungs (37, 157). In an isolated rat lung perfusion model, rhTRX protected against warm I/R injury in cooperation with L-cysteine (148). rhTRX administration also protected rabbit or canine lungs after warm ischemia (110, 150), where chemiluminescence examination showed decreased ROS generation by rhTRX (110). Furthermore, rhTRX attenuated hypoxia/reoxygenation injury of cultured murine vascular endothelial cells. Intracellular hydroperoxide and peroxide were decreased by rhTRX treatment (60).

Thus, rhTRX can be a therapeutic modality for I/R injury to the lungs. The application of rhTRX during reperfusion after cold (hypothermic) ischemia, or its supplementation in organ preservation solutions, may provide a more favorable outcome of lung transplants.

TRX and influenza infection

ROS may be involved in the deterioration of pneumonia by the influenza virus (3, 80, 104). TRX transgenic (TRX-Tg) mice were more resistant against sublethal virus infection than wild-type mice. Histopathological examination showed mild pneumonia in the TRX-Tg mice after influenza virus infection, whereas severe alveolar or bronchiolar destruction was seen in the wild-type mice. On the other hand, TRX overexpression did not affect the host's systemic immune responses to the infection.

These results indicate that TRX overexpression suppresses the inflammatory overshoot of viral pneumonia caused by influenza virus infection, resulting in reduced mortality. TRX seems to play important roles in regulating the inflammatory

process in the primary host defense against influenza viral infection by modulating ROS generation and redox-dependent signal transduction (98).

TRX and BLM-induced lung injury

BLM is a chemotherapeutic agent used for various human malignancies. However, BLM administration often results in lung injury accompanied by the infiltration of leukocytes in the pulmonary interstitium and progressive fibrosis in humans, as well as rodents. Previous studies showed that SOD (142) or NAC (62) partly inhibits BLM-induced lung injury, which is therefore thought be mediated, at least in part, by the generation of intracellular ROS.

Human TRX cDNA-transfected L929 murine fibrosarcoma cells were more resistant to BLM-induced cytotoxicity than the control transfected cells (40). In addition, the expression of TRX was strongly induced in bronchial epithelial cells (BEC) in the lungs of BLM-treated mice. TRX expression was also up-regulated at both the mRNA and protein levels in cultured BEC with BLM treatment. These observations suggest that the cellular redox state modified by TRX may be involved in the resistance against cytotoxicity by BLM. The induction of TRX expression in BEC may play a protective role in BLM-induced lung injury (40).

Recently, we have shown the protective effect of TRX in BLM-induced lung injury (56). Both wild-type mice treated with rhTRX (Fig. 3) and TRX-Tg mice demonstrated a decrease in BLM-induced cellular infiltration and fibrotic changes in the lung tissue. Therefore, TRX is thought to act as a powerful scavenger for BLM-induced ROS. In addition, TRX may suppress BLM-induced collagen synthesis in the lungs. Furthermore, TRX may modulate proinflammatory cytokine interleukin-18 (IL-18) signaling after BLM treatment (56).

TRX and lung injury by inflammatory cytokines

Acute and chronic lung disorders with pulmonary infiltration and fibrosis are referred to as interstitial lung diseases (ILD) (6). Recently, the possible involvement of multiple mediators, including ROS, cytokines, chemokines, or apoptosis-related genes, in the development of ILD has been reported (99, 116). The daily administration of proinflammatory cytokine IL-18 with interleukin-2 (IL-2) results in lethal interstitial pneumonia in mice (109). rhTRX administration strongly suppressed IL-18/IL-2-induced lethal interstitial pulmonary disorders in mice. Infiltration of leukocytes in the pulmonary interstitial space was attenuated by rhTRX treatment (56) (Fig. 4).

ILD, including IPF and ARDS, are often fatal. The current treatment for ILD is far from satisfactory although mechani-

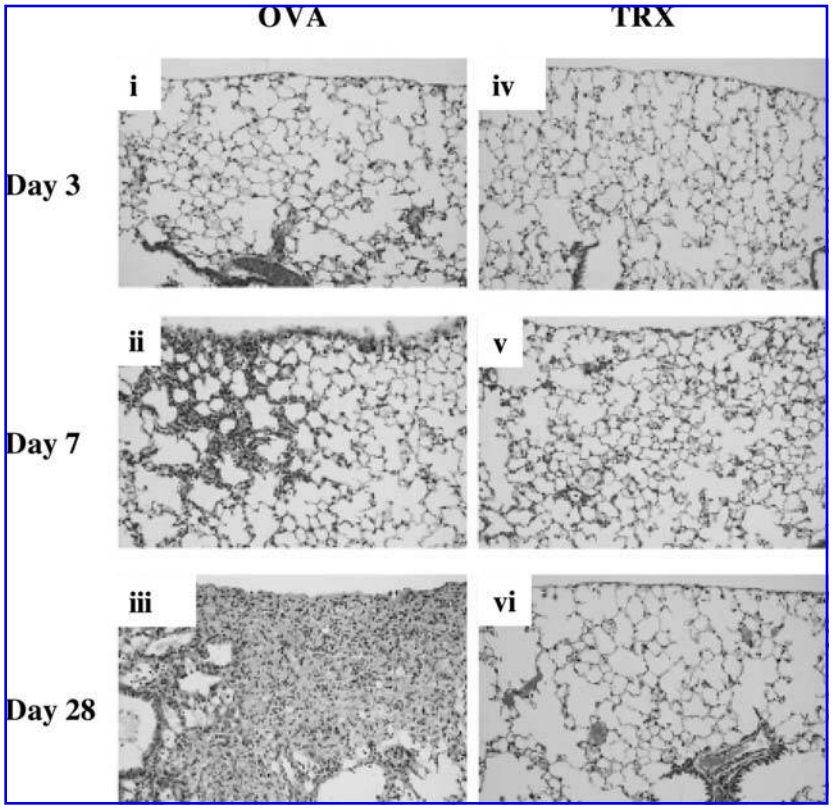

FIG. 3. Protective effect of rTRX against BLM-induced lung fibrosis. Juvenile female C57BL/6 (B6) mice were treated with an intraperitoneal injection of control ovalbumin (OVA) (i–iii) or 40 mg of rTRX (iv–vi) every second day from day −1. The mice were treated intraperitoneally with BLM (100 mg/kg) on days 0 and 7. Mice were killed on days 3, 7, or 28. The lung tissue was microscopically observed with hematoxylin and eosin staining. Original magnification at observation was 200×. (Modified from the original figure in reference 11.)

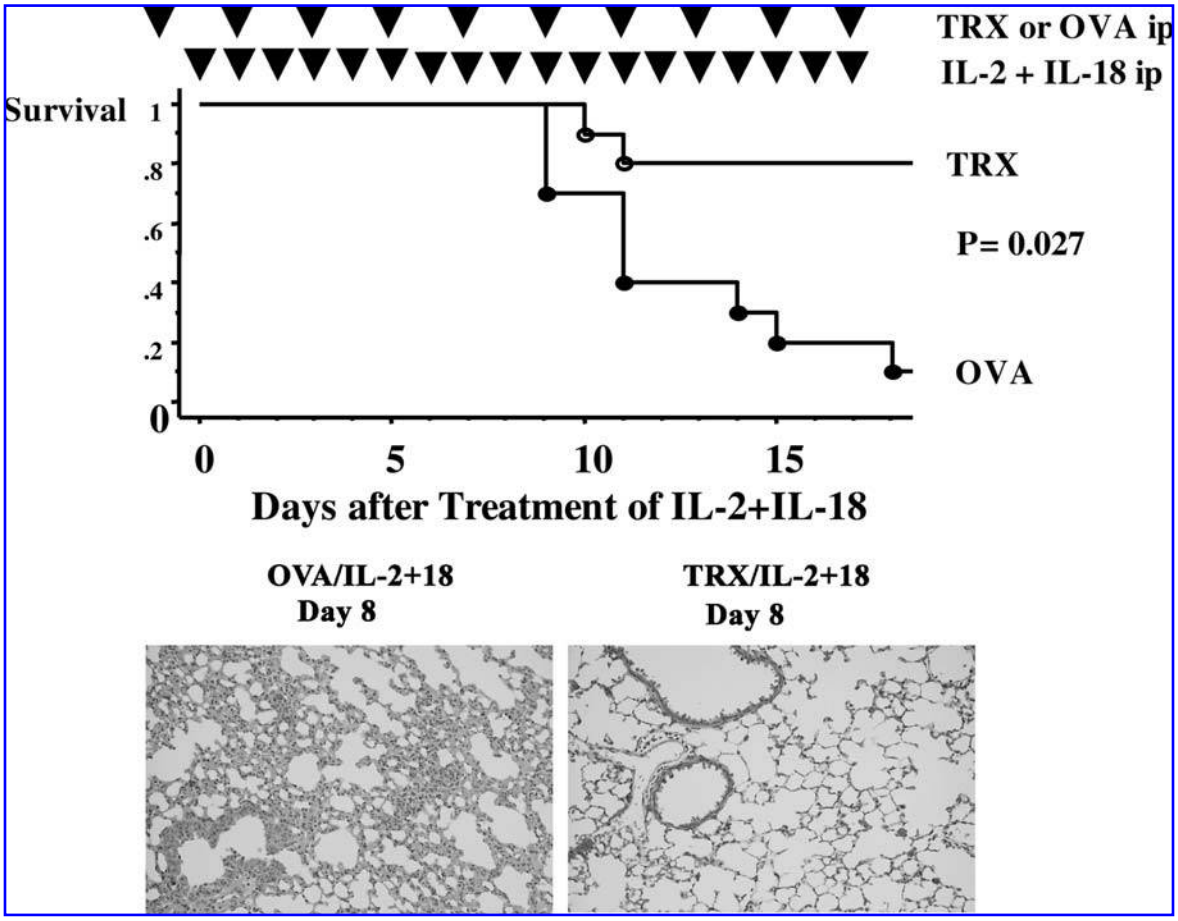

FIG. 4. Protective effect of rTRX against lethal lung injury caused by IL-18 plus IL-2. Juvenile female C57BL/6 (B6) mice were treated with an intraperitoneal injection of rTRX or ovalbumin (OVA) every second day from day −1. The mice were then treated daily with an intraperitoneal injection of IL-18 (0.2 mg) plus IL-2 (50,000 IU) from day 0. The lung tissue was stained with hematoxylin and eosin and was observed microscopically at 200×. (Modified from the original figure in reference 11.)

cal ventilation, steroids, antibiotics, and circulatory management are applied. Our results suggest that rhTRX may be a new modality for the treatment of ILD.

TRX and other pulmonary inflammations

TRX was highly expressed in the lungs and lymph node tissues, and was locally produced by granulomas in patients with sarcoidosis. TRX levels in bronchoalveolar lavage fluid (BALF) in patients with sarcoidosis were significantly higher than in the control (72). The activity of NF-κB in cells exposed to an aqueous extract of cigarette smoke was subject mainly to a redox-controlled mechanism dependent on the availability of reduced TRX (39). The transcription of TRX peroxidase-2 (peroxiredoxin-2) in the cDNA microarray was significantly elevated by exposure of the alveolar macrophage to an extract of diesel exhaust particles (70). We also have preliminary data showing that C57BL/6 TRX-Tg mice are more resistant to an intratracheal instillation of diesel-exhausted particles compared with wild-type C57BL/6 mice (unpublished observations).

These results suggest the involvement of the TRX system in the primary defense against oxidative air pollution.

FUTURE PROSPECTS

Monitoring of TRX

As ROS is involved in the pathogenesis of various inflammatory lung diseases, the equilibrium of ROS and antioxidants must play an important role in the prognosis of these diseases.

TRX is measurable with a sensitive sandwich enzyme-linked immunosorbent assay (93), and the plasma levels of TRX are indicative of inflammation induced by oxidative stress. For example, plasma levels of TRX are useful stress markers in patients with oxidative stress-related diseases, such as asthma (151), chronic hepatitis C (135), human immunodeficiency virus infection (93), burning (1), and I/R (95).

Similarly, TRX measurement in plasma, BALF, or lung tissues may be useful in the diagnosis and monitoring of many pulmonary diseases in which oxidative stress may play an important role. Previous studies have revealed that TRX levels were increased in BALF in patients with sarcoidosis and IPF (82) or the oxidant-induced fibrotic lungs of rats (59).

TRX expression has also been reported in lung tissues (89, 149) and in bronchoalveolar lavage cells (111) during rejec-

tion after canine lung transplantation. These results suggest that monitoring TRX levels can be useful for the early diagnosis of rejection after lung transplantation.

Clinical application of TRX

As described above, the endogenous expression and exogenous application of TRX have a protective effect in many oxidative stress-induced diseases. Therefore, the application of recombinant protein, gene therapy, and induction (21, 26, 29, 152) of TRX may be a therapeutic modality for various pulmonary inflammatory diseases.

Here at the Translational Research Center, Kyoto University Hospital, we have started a translational research program to continue for 5 years to treat patients with acute lung injury by TRX administration. The toxicity and safety of recombinant protein are to be confirmed in the first 2 years, and we will start a clinical trial after approval from the ethical committee. Further clinical applications of TRX are also planned for other oxidative stress-associated disorders.

ABBREVIATIONS

AP-1, activator protein-1; ARDS, acute respiratory distress syndrome; ASK1, apoptosis signal-regulating kinase 1; BALF, bronchoalveolar lavage fluid; BEC, bronchial epithelial cells; BLM, bleomycin; CO, carbon monoxide; COPD, chronic obstructive pulmonary disease; GSH, glutathione; HIF-1α, hypoxia-inducible factor-1α; H_2O_2, hydrogen peroxide; HO, heme oxygenase; HO-1, heme oxygenase-1; IL-2, interleukin-2; IL-18, interleukin-18; ILD, interstitial lung diseases; IPF, idiopathic pulmonary fibrosis; I/R, ischemia/reperfusion; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; NAC, *N*-acetyl-L-cysteine; NF-κB, nuclear factor-κB; rhTRX, recombinant human TRX; ROS, reactive oxygen species; rTRX, recombinant TRX; SOD, superoxide dismutase; TBP, TRX-binding protein; TRX, thioredoxin; TRX-Tg, TRX transgenic; UV, ultraviolet; VDUP1, vitamin D3 up-regulated protein 1.

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