ANTIOXIDANTS & REDOX SIGNALING
Volume 8, Numbers 3 & 4, 2006


# Mini Review

# Current Concepts of Redox Signaling in the Lungs

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## ABSTRACT

**In the intracellular redox state (GSH/GSSG) the cell plays a key role in the regulation and potentiation of the inflammatory response in lung cells. Glutathione and thioredoxin are the important protective antioxidants in the lungs. Regulation of intracellular redox glutathione and thioredoxin levels in response to reactive oxygen/nitrogen species and in inflammation should have critical effects on different lung cells on the activation of redox sensor/signal transduction pathways and various transcription factors. Possibly via the modification of cysteine residues, oxidative stress activates multiple stress kinase pathways and transcription factors nuclear factor-κB and activator protein-1, which differentially regulate the genes for proinflammatory cytokines as well as the protective antioxidant genes. Emerging data suggest that protein-*S*-thiolation, protein-*S*-nitrosation, and oxidation of protein-SH (formation of sulfenic, sulfinic, and sulfonic acids) are critical in redox signaling during normal physiology and under oxidative stress in controlling the cellular processes. In this review, we discuss the recent findings in the context of redox signaling during inflammation, pathology, and the role of redox modulating agents/dietary interventions either to inhibit abnormal signaling or induce/boost the endogenous antioxidant systems. Furthermore, this also provides information as to how antioxidants are involved in redox signaling to control inflammatory and oxidative stress in the lung.** *Antioxid. Redox Signal.* 8, 681–689.

## INTRODUCTION

Due to the highest exposure to oxygen, the lungs are susceptible to attack by reactive oxygen metabolites popularly known as free radicals. The free radicals may be in the form of reactive oxygen species (ROS), reactive nitrogen species (RNS), and xenobiotic species. Proper homeostasis of the oxidation/reduction (redox) state is therefore an imperative for cell activation, proliferation, viability, survival, and other organ functions (61, 62, 64, 73).

To defend against such oxidant species, the lungs are endowed with efficient antioxidant defense systems such as antioxidant enzymes and nonenzymic antioxidants such as glutathione (GSH), albumin, uric acid, vitamins C and E, and other low molecular weight organic molecules (66). GSH, in association with the new class of recently discovered thioredoxins (TRxs), peroxiredoxins (PRxs), and glutaredoxins (GRxs), not only function as antioxidants in their redox systems, but also modify other proteins during redox signaling. GSH along with TRxs, PRxs, and GRxs have now been implicated in modulation of redox-regulated signal transduction, regulation of cell proliferation, remodeling of extracellular matrix, maintenance of surfactant and antiprotease screen, and apoptosis (66). Of the different types of cells present in the lungs, alveolar epithelial type II cells particularly are more prone to the injurious effects of oxidants and respond to such agents by releasing inflammatory mediators and cytokines/chemokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-8 (IL-8). Such a response in turn induces neutrophil recruitment and leads to activation of the key redox-sensitive transcription factors, nuclear factor-kappa B (NF-κB) and activator protein-1 (AP-1), which results in inflammation and tissue damage (1, 11, 62). Hence, oxidative stress affects intracellular redox regulators such as glutathione and thioredoxin, direct cell signaling, transcription of proinflammatory genes, cell survival, and

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cell proliferation. In addition, there has been a recent surge in information that protein thiolation may be a critical cellular defense and signaling mechanism during oxidative stress (73). This mini review on redox signaling comprehensively brings together the recent findings in the context of redox signaling during inflammation, pathology, and treatments with redox modulating agents/dietary interventions either to inhibit abnormal signaling or to induce/boost the endogenous antioxidant systems. This mini review also provides information of how antioxidants are involved in redox signaling to control inflammatory (73) and oxidative stress (82) in lung cells. Discussion on various key redox molecules and their regulation aims at dissecting not only the redox-regulated signal transduction mechanisms but also provides directions for future research on therapeutic strategies during lung inflammation and cell/tissue injury.

## REDOX PROTEIN MODIFICATIONS DURING LUNG INFLAMMATION

Several enzymatic and nonenzymatic proteins contain cysteine residues at key sites that may modulate the functions of the proteins in a redox-dependent manner (12). Cysteine has a free sulfhydryl group (-SH) and a distinct pKa at cellular pH. Therefore, cysteine serves as a reaction center for biochemical reactions such as formation of coordinate bonds with metals, reversible oxidation/reduction reactions, and electrophilic interactions. In addition it also provides sites for covalent attachment of chemical species that may reversibly or irreversibly modify the properties of proteins having physiological significance. Covalent modifications of protein-cysteines may be critical to a particular function of a given protein. For example, when the cysteine-SH is linked by a thioester bond, it may be transitory and have transitory regulatory effects on the protein function. Palmitolyation of proteins results from thioester protein links with reactive cysteines, and it is well known that this modification is dynamic (24). ADP-ribose is attached to a protein cysteine by an *S*-glycoside bond and this addition is also known to be reversible (17). Thioether linkages (i.e., prenyl anchored protoporphyrin rings), however, are not known to be reversible. On the other hand, if farnesyl or geranyl isoprenoid are attached to the C-terminal cysteine, they are thought to bring about membrane association of a protein (24). It is interesting to note that reactive cysteine found on protein surfaces may have no known metabolic role other than a postulated antioxidant or protective function (80). More functions of such reactive modifications of cysteine may be further elucidated by new experimental approaches for the study of protein function.

Reversible posttranslational modification of specific amino acid residues on proteins have now been identified as one of the important regulatory mechanism of protein function. Proteins bearing cysteine-SH (Cys-SH) residues in the thiolate form ($S^-$) are considered prone to oxidative modification. Oxidation of protein-Cys-SH (PrSH) may interfere with biological functions either as 'damage' or in context to oxidant-dependent signal transduction. Although PrSH behave as nonprotein thiols, their biochemistry is much complicated by their accessibility, steric interference, and charge distribution characteristics (16). The response of PrSH and their reaction mechanisms vary depending upon the source of the PrSH and are influenced by the existing p*K*a, disulfide susceptibility/accessibility to oxidants, and the conformation of the protein at a given time. GSH and most protein cysteines are nonreactive towards $H_2O_2$ unless they are in close proximity to a metal (12) or exist as the ionic thiolate anion ($-S^-$) (66). The oxidant load and oxidation potential largely determine whether a cysteine residue may be oxidized to form a disulfide bond (R-SS-R), sulfenic acid (-SOH), sulfinic acid ($-SO_2H$), or sulfonic acid ($-SO_3H$) (66). Whereas sulfinate and sulfonate derivatives are considered as irreversible damage generally associated with oxidative injury, protein sulfenic acid moieties are generally reversible states and are often considered as the mediators of redox signaling (12, 78).

An ingeniously designed study by Woo et al. however, indicates that sulfinic acid formation may not be actually irreversible at all, suggesting that oxidatively damaged proteins can be repaired (86). This observation was further confirmed by observation that formation of sulfinic acid derivatives is reversible by an enzyme peroxiredoxin capable of reducing sulfinic acid derivatives (15). This enzyme was termed sulfiredoxin and is found to be highly conserved in eukaryotes. The evolutionary conservation of the enzyme indicates its importance in the recovery of oxidatively modified proteins vital to cell signaling and/or functioning. Sulfiredoxin may catalyze a multistep reduction process in view of its intrinsic phosphotransferase and thioltransferase activities, a possible mechanism by which it may overcome the energy barrier that normally prevents the reduction of protein-Cys-$SO_2H$ by a transient introduction of a phosphate group in the peroxiredoxin–sulfinate moiety. Very recently, Poole *et al.* have considered the idea that Cys-sulfenic may play an important role in the catalytic centers of enzymes (58). They have suggested that Cys-sulfenates might be useful as sensors of both oxidative and nitrosative stress which affect enzymes and transcriptional regulators. Since the formation of sulfenic, sulfinic, or sulfonic species depend upon the degree of oxidative stress, the presence and stoichiometry of these species may yield useful information regarding the exact status of the prevailing oxidative stress. It is to be noted that oxidative stress can be generated as a result of both excessive ROS and or RNS production. Nitric oxide ($NO^{\bullet}$), a free radical of physiological significance may be scavenged with a variety of ROS species to form a range of RNS, which may lead to enhanced nitration of protein-tyrosine in the lungs and hence may play a pivotal role in airway inflammation (71). Such findings warrant immediate investigation of the transient and short-lived forms of oxidatively modified cysteines and their role in redox signaling during lung inflammation.

Regulation and potentiation of inflammatory responses in lung cells is often influenced by the redox status (GSH/GSSG ratio) of a cell (21). Increased gene expression of several proinflammatory mediators (21), regulation of heat-shock factor and induction of heme oxygenase-1 (HO-1) (44) are some of the myriad cellular processes affected by altered redox state of a cell. Exposure of epithelial and endothelial cells *in vitro* to TNF-α, was found to activate NF-κB and release of proinflammatory mediators; effects that were con-

comitant to depletion of intracellular GSH in the cells. Depletion of GSH levels, which is regulated by redox sensitive mechanism in lung cells may also be brought about by transforming growth factor ($TGF\beta_1$), an inflammatory cytokine released during inflammation. Redox status also modulates the activity of a single conserved cysteine in the DNA-binding domain of Fos-Jun heterodimer and thus its binding to the DNA (1). The cysteine-dependent AP-1 binding to DNA in presence of GSSG and enhancement by thioredoxin and a nuclear redox protein, Ref-1, further suggests the role of cellular redox status in such interactions (27). Recent identification of a novel thiol peroxidase, which acts as an $H_2O_2$ receptor and redox-transducer in gene transcription in yeast by Delaunay *et al.* have established the presence of redox sensors in eukaryotes, which will lead to further understanding of redox signal mechanisms (15).

Expression of stress proteins such as heat shock factor and heme oxygenase-1 (HO-1) have been associated with the GSH/GSSG ratio, and Bundy and co-workers have added further insight by showing that HO-1 and ICAM expression is redox modulated via p38 MAP kinase in human alveolar epithelial (A549) cells (7, 10, 77, 81). Carbon monoxide (CO) a product of HO-1 has also been shown by Ryter and Choi (72) to modulate redox signaling during oxidative stress and lung inflammation. Hence, it is evident that maintenance of intracellular GSH/GSSG ratio is important in the control of inflammatory responses in lungs involving stress response and heat-shock proteins.

GSH and other thiols such as *N*-acetyl-L-cysteine (NAC) inhibit TNF-α-induced generation of proapoptotic factors and regulate the expression of proinflammatory genes (23, 46, 76). Goldkorn *et al.* (23) have demonstrated that generation of ceramide, an apoptotic mediator, and epidermal growth factor (EGF) receptor trafficking may be modulated by oxidative EGF-receptor in lung epithelial cells by oxidative stress, thought to influence inflammatory processes (e.g., hyperplasia and proliferation in lungs) (23). Certain aldehydes and quinones may also regulate EGFR phosphorylation in lung cells. It is likely that ROS aberrantly phosphorylate the EGF receptor, thereby unable to recruit the ubiquitin ligase *c*-Cbl in the receptor complex. This would lead to prolonged downstream signaling of the receptor. Thus, oxidative stress and redox GSH/GSSG levels are intimately associated with cell proliferation and apoptosis in lung cells.

## LUNG REDOX SYSTEMS AND SIGNALING

Lung extracellular epithelial lining fluid (ELF) has abundant antioxidant GSH and associated redox components, which detoxify oxidants, free radicals, and a host of other xenobiotics (3, 85). Airway/airspace inflammation and/or oxidant/antioxidant imbalance leading to alteration in glutathione levels in the ELF is increasingly being implicated in many inflammatory lung diseases (65, 68). The imbalance of the redox system may lead to abnormal signaling associated with lung tissue damage and fibrosis. The importance of reactive oxygen species (ROS), modulation of GSH and extracellular antioxidants, in particular extracellular glutathione peroxidase (eGPx), for redox signaling in the lungs have been aptly highlighted by Comhair and Erzurum (13). eGPx also participates in airway inflammation and is an important defense against oxidative injury to the airway surface. The importance of redox modulation has been further elaborated by the observations of Land and Wilson, wherein they have reported that perinatal lung development and epithelial function is influenced by redox modulation in response to hypoxia and hyperoxia (43). Oxygen tensions in fetal and perinatal lungs can differentially influence lung morphogenesis through oxygen- and redox-responsive signaling pathways by hypoxia-regulated transcription factors (HIF-α), GSH/GSSG ratio, activation of NF-κB-dependent increase in transepithelial $Na^+$ transport and lung luminal fluid clearance (43, 49).

## THIOREDOXIN

Thioredoxin (TRx), a small ubiquitous protein with conserved -Cys-Gly-Pro-Cys- sequences in the active site (two redox-active cysteine residues), is an important class of redox modulator molecules (8). By virtue of the ability of these cysteines to undergo oxidation-reduction reactions, the importance of TRx has recently been highlighted in signal transduction, inflammatory response, and other biological functions such as cell growth, apoptosis, and proliferation (reviewed in 31, 51, 52). Equally important for redox-signaling reactions are glutaredoxins (GRx), thiol disulfide oxido-reductases responsible for glutathione dependent thiol-disulfide oxidoreduction reactions (25).

## REDOX REGULATION OF APOPTOSIS, SIGNAL-REGULATING KINASE 1 AND ANTIOXIDANT RESPONSE ELEMENT

Apoptosis signal-regulating kinase 1 (ASK1), which is activated in response to proinflammatory and stress signals, is regulated by thioredoxin (48, 74). ASK1 activation of JNK and p38 MAP kinase pathways has been implicated in various cell functions including cell survival, differentiation, and inflammation (29, 40). Furthermore, TRx and glutaredoxin associate with ASK1 at the N-terminus and inhibit ASK1 activity and subsequent ASK1-dependent apoptosis by reduction/oxidation regulation (74). One of the best examples for redox sensor mediated reactions are Nrf2, a member of the NF-E2 family of nuclear basic leucine zipper (bZIP) transcription factors, and Keap1, a cytoplasmic protein homologous to the *Drosophila* actin-binding protein Kelch. Keap1 is regulated by redox modification of thiol groups (thioredoxin). Under basal conditions Nrf2 is largely bound in the cytoplasm to Keap1, a process that is attributed to the critical thiol status of Keap1 (18). Oxidative modification of Keap1 thiol triggers Nrf2 dissociation from the Nrf2-Keap1 complex (39, 70). Nrf2 then translocates to the nucleus and binds with the 5′-upstream regulatory antioxidant response element (ARE) regions of phase 2 genes and accelerate their transcription (4). It has been recently shown that Nrf2 is also regulated by protein kinase C and other members of the MAP kinase family. Furthermore, disruption of the Nrf2 gene leads to severe al-

lergen-driven airway inflammation and hyperresponsiveness in mice. Enhanced response in asthmatics due to ovalbumin sensitization in Nrf2-disrupted mice was found to be associated with increased mucus cell hyperplasia emphysema and infiltration of eosinophils into the lungs as compared to wild-type littermates (70). The enhanced severity to such an allergen response was attributed to a lowered antioxidant status of the lungs caused by lower basal expression, as well as marked attenuation of the transcriptional induction of multiple antioxidant genes. Thus, it is possible that many of the redox-sensitive transcription factors which are regulated by GSH can also be regulated by TRx both in the cytoplasm and nucleus.

## REDOX REGULATION OF p21$^{CIP1/WAF1/SDI1}$

The cell cycle inhibitor p21$^{Cip1/WAF1/Sdi1}$ is regulated by redox signaling and is involved in DNA replication, repair, and apoptosis (53, 75) and may be directly involved in chronic inflammatory response seen in various lung diseases. ROS, which are produced during hyperoxia, not only cause cellular damage (DNA synthesis and cell proliferation), but also play a role in the repair process by promoting alveolar epithelial type II cell proliferation presumably by redox regulation of p21$^{Cip1/WAF1/Sdi1}$. Interestingly hydrogen peroxide at low concentration has been shown to regulate cell proliferation of primary epithelial cells that is mediated by MAP kinases (77). This suggests that alterations in intracellular oxidant levels can modulate downstream signaling pathways controlling alveolar type II cells proliferation.

## REDOX REGULATION OF NF-κB AND HISTONE DEACETYLASE

Lipid peroxidation products, such as 4-hydroxy-2-nonenal (4-HNE) can induce various cellular events such as proliferation and activation of MAP kinase signaling pathways (30, 56). 4-HNE is increased in lungs of patients with COPD and probably involved in many pathological reactions during lung inflammation (22, 69). $F_2$-isoprostanes and other cyclopentenone prostaglandins (15dPGJ2) can react with the sulfhydryl group of GSH and with various GSH transferases (40). These aldehydes decrease GSH levels and alter the GSH/GSSG ratio in the cells. Similarly acrolein, a small aldehyde, can lead to activation of MAP kinase pathways. Valacchi *et al.* (83) have shown that inhibition of basal and cytokine-induced NF-κB activation and IL-8 expression by acrolein in human bronchial epithelial cells was associated with reduced IκBα degradation (83). Since IκB kinase (IKK) is a redox-sensitive regulator of NF-κB activation, they postulated that acrolein may act directly with IKK, and immunochemical analysis of IKK suggested direct modification of the β-subunit of IKK by acrolein. This suggests that oxidative and inflammatory conditions may alter intracellular signaling via the modulation of sulfhydryl groups present in various redox-sensitive proteins.

A number of diseases of the respiratory tract are associated with increased amounts of nitric oxide (NO) in the exhaled breath. This increased oxidative metabolism leaves less bioavailable NO and coincides with lower amounts of *S*-nitrosothiols. Reynaert and co-workers have discussed the mechanisms responsible for *S*-nitrosothiols and NO-mediated events and how they transduce signals into cellular responses (71). This may be an important mechanism for redox sensing of NF-κB under some pathological conditions.

Recently it has been shown that redox regulation of signaling events can also occur in the nucleus (34). Changes in nuclear histone acetylation and deacetylation status, at least in part, regulate inflammatory gene expression by activation of the proinflammatory redox sensitive transcription factors. Oxidative stress can enhance inflammatory gene expression by stimulating AP-1 and NF-κB-mediated gene expression (59) and elevating histone acetylation. Adcock and colleagues (2) have shown the redox regulation of histone deacetylases and glucocorticoid-mediated inhibition of the inflammatory response in lung cells. One of the major mechanisms of glucocorticoid function is to recruit histone deacetylases to the site of active gene expression thus reducing inflammation (32). Oxidants can reduce glucocorticoid function by inhibiting histone deacetylase (HDAC) activity by post-translational modification of HDACs with aldehydes and nitric oxide metabolites (62, 63). Thus oxidant stress, acting through changes in chromatin structure, can enhance inflammation and induce a state of relative glucocorticoid-insensitivity (2, 62). This may account for the lack of glucocorticoid sensitivity in patients with COPD where oxidative stress and altered redox status occur (62, 67). Thiol antioxidants may reduce the inflammation and restore glucocorticoid sensitivity in these subjects (63, 67).

## ROLE OF POLYPHENOLS AND THIOL ANTIOXIDANTS IN REDOX SIGNALING

Recent studies have demonstrated that low amounts of phenolic (antioxidants) compounds can regulate redox signaling in lung cells (Fig. 1). Curcumin (diferuloylmethane), a dietary phenolic compound (9), has been shown to possess both antioxidant and anti-inflammatory properties in cultured alveolar epithelial cells (5). Similarly, red wine polyphenol, resveratrol, and pomegranate wine can act as antioxidant and anti-inflammatory agents by some novel mechanisms (37, 41, 45, 87) and even prolong aging (6, 28, 35). Small redox molecules such as strand mimetic template MOL 294 and PNRI-299 and thiol antioxidants such as *N*-acetyl-L-cysteine, Na-cystelyn and ergothioneine, which have potential as therapies in inflammatory diseases and have been shown in *in vitro* and *in vivo* experiments to block the release of these inflammatory mediators from epithelial cells and macrophages, by a mechanism involving increasing intracellular GSH and decreasing NF-κB activation and IL-8 release (26, 61, 63, 67). In a recent study, Cooke and Drury showed that intratracheal liposomal glutathione instillation in preterm infants was effective in raising pulmonary GSH levels and had biochemical antioxidant effects (14). However, studies are needed to validate the bioavailability of these compounds to regulate redox signaling in lung inflammation/chronic lung diseases. A re-

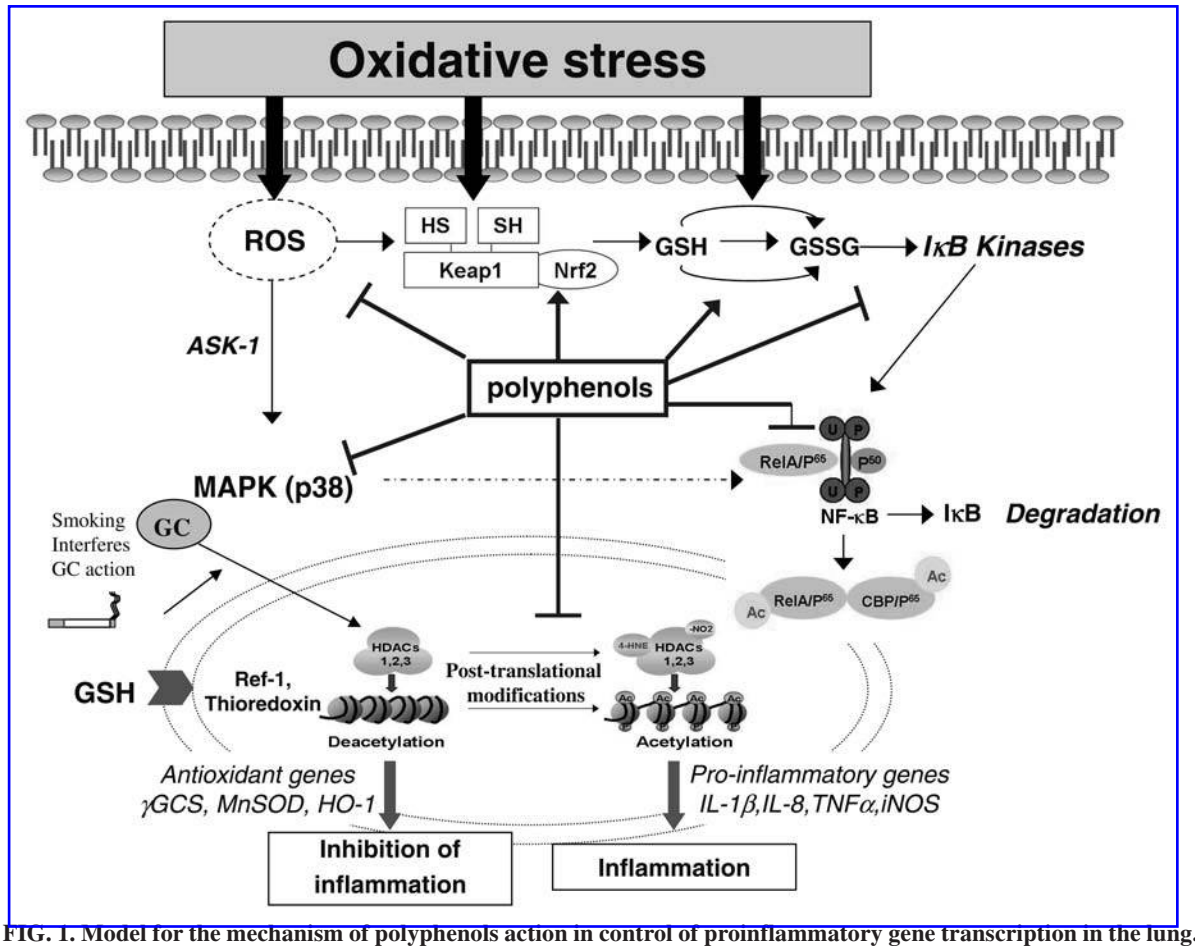


**FIG. 1. Model for the mechanism of polyphenols action in control of proinflammatory gene transcription in the lung.** Inflammatory response is mediated either directly by ROS or by reduced levels of glutathione, which in turn activates NF-κB and p38 MAP kinase. The activation of NF-κB leads to the expression of proinflammatory genes by acetylation of master transcriptional regulator (CBP-HAT) and p65 subunit/RelA of NF-κB resulting in inflammation. Polyphenols inhibit oxidative stress mediated inflammation by suppressing the activity of NF-κB either through Nrf2 induced phase-2 antioxidant enzymes (GSH), IκB pathway, or decreasing activity of ROS and p38 MAPK. Polyphenols may also upregulate HDAC activity and/or repair the modified HDAC proteins.

cent multicenter European study examining the effect of the antioxidant *N*-acetylcysteine on the progression of idiopathic pulmonary fibrosis suggest that the cellular redox state is involved in the progression of this disease (38). Patients with idiopathic pulmonary fibrosis have been found to have higher levels of oxidant stress, which include complex mechanisms such as activation of growth factors as well as regulation of matrix metalloproteinases and protease inhibitors.

## CONTROL OF INFLAMMATION VIA MODULATION OF NF-κB

NF-κB has been widely and increasingly implicated as a major mechanism underlying the inflammatory process. Therefore, a spate of approaches has been considered as a possibility of modulating this transcription factor in order to control inflammation (19, 55, 89). Recently, a large number of agents have been identified which can modulate NF-κB by diverse mechanisms. Roflumilast, a potent and selective phosphodiesterase-4 (PDE4) inhibitor, has been demonstrated to be an effective anti-inflammatory agent in airway inflammatory diseases (42). Roflumilast was further shown to inhibit NO, TNF-α, and IL-1β production via suppression of their gene expressions in lipopolysaccharide (LPS)-stimulated macrophages (33). Roflumilast inhibited the DNA binding activity of NF-κB via inhibition of IκBα phosphorylation and degradation (42). Roflumilast was further shown to inhibit p38 MAP kinase and JNK activation in macrophages. Another study on neuronal cells exposed to glutamate toxicity revealed that inhibition of IκBα degradation by using BAY 11–7082, a selective inhibitor of IκBα phosphorylation, significantly enhanced cell survival against glutamate toxicity (57). Treatment of B non-Hodgkin's lymphoma (NHL) cell lines with an anticancer agent Rituximab, was shown to inhibit the constitutive NF-κB activity and further sensitized the tumor cells to both chemotherapy and Fas-induced apoptosis (84).

Montelukast is a novel cysteinyl leukotriene 1 receptor antagonist (88). A recent study examining the effect of mon-

telukast on THP-1 cells revealed that montelukast inhibited NF-κB activation in THP-1 cells in a dose-dependent manner (47). Furthermore, montelukast significantly inhibited lipopolysaccharide-induced IL-6 (60), TNF-α (20), and MCP-1 production (47) in the peripheral blood mononuclear cells of controls and patients with asthma. However, these effects of montelukast were observed at higher doses and more studies are required to determine a lower therapeutic dose. NF-κB is a transcriptional activator of several cytokine genes such as IL-6 and TNF-α. Peroxisome proliferator-activated receptors (PPAR), alpha and gamma, are other important components believed to modulate inflammatory processes (36). Fenofibrate, a ligand for PPARα was found to inhibit cytokine production in rheumatoid arthritis synovial fluid (RSF), NF-κB activation in RSF, and osteoclast differentiation from osteoclast progenitor cells (54). Therefore, fenofibrate has been considered to be a potentially good anti-inflammatory agent. The agonists for PPARγ may be anti-inflammatory to block NF-κB and AP-1-driven genes.

The lung in cystic fibrosis (CF) expresses a profoundly proinflammatory phenotype, due to constitutive hypersecretion of IL-8 from epithelial cells lining the airways (50, 79). Systematic search for candidate drugs that might be used therapeutically to suppress IL-8 secretion from these cells have yielded no single drug that may be a complete therapeutic alternative. Recently, a class of amphiphilic pyridinium salts, the most potent of which is MRS2481, an (*R*)-1-phenylpropionic acid ester, has been identified and synthesized by Tchilibon *et al.* (79). MRS2481 acts via inhibition of NF-κB signaling and AP-1 transcription factor binding to the IL-8 promoter. MRS2481 was further found to inhibit TNF-α-induced phosphorylation and proteosomal destruction of IκBα. Since IκBα is the principal inhibitor of the NF-κB signaling pathway, preservation of intact IκBα would serve to keep the IL-8 promoter silent. MRS2481 blocks TNF-α-activated phosphorylation of JNK, the c-JUN kinase. Due to high water solubility and efficacy and requirement of lower concentrations it is anticipated that MRS2481, or an optimized derivative, may be an important tool against the inflammatory phenotype of the CF lung. Many other drugs and agents that are targeted against NF-κB and/or its modulators are being tested presently. It will be a matter of time before a safe therapy is available for immaculate control of inflammation.

## CONCLUSIONS

Glutathione and thioredoxin are the important protective antioxidants in the lungs. Regulation of intracellular redox levels in response to oxygen/nitrogen species and in inflammation has critical effects on different lung cells, activation of redox sensor/signal transduction pathways and various transcription factors such as NF-κB and AP-1. Several proteins have been identified, which respond to the redox alterations in the cells and are involved in thwarting the deleterious effects of redox imbalance. Typically these redox-sensitive proteins contain cysteines, which are the sites of action during an oxidative stress situation. Understanding of the transient form of cysteine (sulfenic or sulfinic acid) on redox sensing proteins will provide us information as to how signaling proteins are regulated during oxidative stress and inflammation. Extracellular redox environment may also affect cell signaling via transmembrane cysteine-rich receptors, (e.g., EGF receptor phosphorylation). Study of the protective role of GSH/thiol compounds on inhibition of the inflammatory response and correcting the fundamental oxidant/antioxidant imbalance in patients with chronic inflammatory diseases are an important area of further research. Novel anti-inflammatory drugs, both synthetic and dietary botanical based, have been identified which are designed to have dual role as an antiinflammatory as well as an antioxidant. Hitherto, most drugs were targeted at the cyclo-oxygenase system, which were saddled with side effects too. However, a more dynamic and specific control point component, NF-κB and its modulators, have been recently targeted in order to obtain more specific and faster effects. Moreover, such drugs also demonstrate anticancer prowess. Therefore, multifunctional drugs would be a novel therapeutic approach attracting researchers in future. Compounds with multiple functions, such as antioxidant and antiinflammatory properties can also be designed to upregulate the endogenous antioxidant defence mechanism and inhibit the proinflammatory mediator synthesis and or release. Further studies are required to understand and identify the novel plant-based antioxidant and anti-inflammatory components that may be effective agents against chronic lung inflammation.

## ABBREVIATIONS

AP-1, activator protein-1; ASK-1, apoptosis signal-regulating kinase 1; COPD, chronic obstructive pulmonary disease; ELF, epithelial lining fluid; EGF, epidermal growth factor; eGPx, extracellular glutathione peroxidase; GCL, glutamate cysteine ligase; GSH, glutathione; GSSG, glutathione disulfide; HIF-α, hypoxia inducible factor-alpha; $H_2O_2$, hydrogen peroxide; HAT, histone acetyltransferase; HDAC, histone deacetylase; HO-1, heme oxygenase-1; 4-HNE, 4-hydroxy-2-nonenal; IKK, IκB kinase; IL-6, interleukin-6; IL-8, interleukin-8; Keap1, kelch-like ECH-associated protein 1; MAPK, mitogen-activated protein kinase; NAC, *N*-acetyl-L-cysteine; NO, nitric oxide; NF-κB, nuclear factor-kappaB; Nrf2, NF-E2 related factor-2; Ref-1, redox factor –1; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-alpha.

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Received after revision October 6, 2005; accepted October 6, 2005.

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