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Forum Editorial

Redox Signaling in the Lungs

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THE LUNGS contain the largest epithelial/endothelial surface area of any organ and are therefore at risk from oxidant injury by inhalation of high concentrations of oxygen or the circulating oxidants and xenobiotics. However, the human lung contains very well developed antioxidant defense systems, *e.g.,* antioxidant enzymes and antioxidants, such as glutathione (GSH) and thioredoxin, which not only function as antioxidants in their redox systems, but also modify other proteins during redox signaling. GSH and thioredoxin 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 (20, 21).

Lung cells, in particular alveolar epithelial type II cells, are directly susceptible to the injurious effects of oxidants. It has been shown that lung epithelial type II cells release inflammatory mediators and cytokines/chemokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1, IL-8 in response to oxidative stress, which induce neutrophil recruitment and the activation of key redox-sensitive transcription factors such as nuclear factor-κB (NF-κB) and activator protein-1 (AP-1), thereby augmenting the inflammatory response and tissue damage (21), and hence, oxidative stress and intracellular redox regulators such as GSH and thioredoxin, direct cell signaling, transcription of proinflammatory genes, cell survival, and 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.

This exciting forum issue on redox signaling comprehensively brings together the recent findings in the context of redox signaling during inflammation, pathology, and treatments with redox-modulating drugs/dietary interventions either to inhibit abnormal signaling or to induce/boost the endogenous antioxidant systems. The topics covered are extensive and informative and have covered many aspects of redox signaling, *e.g.,* the role of cellular thiols (GSH and thioredoxin) in redox regulation of inflammation, role of hypoxia and hyperoxia in apoptosis, lung development, and redox-mediated gene transcription, modulation of redox-sensitive transcription factors by nitration and *S*-thiolation, aldehyde- and ceramide-mediated cell signaling and gene transcription, redox regulation of proinflammatory, antioxidant, and stress response genes, and redox regulation of mitogen-activated protein (MAP) kinase signaling pathways in lung cell proliferation and inflammation. This issue also provides information as to how antioxidants are involved in redox signaling to control inflammatory and oxidative stress in lung cells. However, there are numerous questions that are still unanswered and require further research:

- What are the mechanisms by which reactive oxygen species (ROS) and GSH/thioredoxin participate in intracellular redox signaling?
- What are the transient intermediates on redox sensing proteins that signal downstream events?
- Why and how do ROS and reactive aldehydes differentially regulate various redox signaling pathways?
- How do cells keep the balance between oxidant-induced proinflammatory mediators and antioxidant enzymes and what happens when this balance is disturbed?
- How do ROS modulate cellular proliferation or apoptosis?
- What are the mechanisms of redox signal transduction by polyphenols? How do redox-regulating agents mediate abnormal signaling and/or induce endogenous defense system?

Knowledge of various key redox molecules and their regulation advanced in this forum issue is aimed at providing answers to the above questions and setting a platform for not only dissecting the redox-regulated signal transduction mechanisms, but also providing directions for future research on redox signal transduction in inflammation and cell/tissue injury.

It is known that highly conserved cysteine-sulfhydryl (Cys-SH) residue(s) present in many proteins can regulate protein structure and function during redox signaling. GSH and most protein cysteines are nonreactive toward hydrogen peroxide (H_2O_2) unless they are in close association with a metal (5) or exist in the form of a thiolate anion ($-S^-$) (26). Depending on the oxidant potential, cysteine residues can be oxidized to form a disulfide bond (R-SS-R), sulfenic acid ($-SOH$), sulfinic acid ($-SO_2H$), or sulfonic acid ($-SO_3H$) (26). Whereas irreversibility of sulfinic and sulfonic acids is generally associated with oxidative injury, reversible reduction of disulfides and protein sulfenic acid moieties is often considered as the

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mediator of redox signaling (5, 31). However, Woo and colleagues have recently shown that sulfinic acid may undergo reversible reduction, suggesting that oxidatively damaged proteins can be repaired (33). Thus, understanding of the transient and short-lived ionized form of cysteine (sulfenic or sulfinic acid) on redox sensing proteins will enhance our knowledge in the field of redox sensors and signaling.

The intracellular redox state [GSH/glutathione disulfide (GSSG) levels] of the cell plays a key role in the regulation and potentiation of the inflammatory responses in lung cells (9). Altered redox states have been implicated in increased gene expression of several proinflammatory mediators (9), regulation of heat-shock factor, and induction of heme oxygenase-1 (HO-1) (15). Depletion of intracellular GSH after TNF-α exposure in epithelial and endothelial cells *in vitro* can lead to activation of NF-κB and the release of proinflammatory mediators. Transforming growth factor-β_1, an inflammatory cytokine released during inflammation, can also decrease GSH levels in lung cells and is regulated by a redox-sensitive mechanism. Similarly, a single conserved cysteine in the DNA-binding domain of Fos-Jun heterodimer is redox-sensitive and modulates the heterodimer binding to the DNA (1). Furthermore, inhibition of AP-1 binding to DNA by GSSG and enhancement by thioredoxin and a nuclear redox protein, Ref-1, suggest a possible role that cysteine-disulfide may play in such interactions (12). Recently, Delaunay and co-workers have identified a novel thiol peroxidase, which acts as an H_2O_2 receptor and redox transducer in gene transcription in yeast (7). Identification of such a sensor in eukaryotes will lead to further understanding of redox signal mechanisms. Expression of stress proteins, such as heat-shock factor, and HO-1 has been associated with the GSH/GSSG ratio, and Bundy and co-workers have added further insight by showing that HO-1 and intercellular adhesion molecule expression is redox-modulated via p38 MAP kinase in human alveolar epithelial (A549) cells (4). Carbon monoxide, a product of HO-1, has also been shown by Ryter and Choi (28) to modulate redox signaling during oxidative stress and lung inflammation. Hence, it is evident that maintenance of the 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, inhibit TNF-α-induced generation of proapoptotic factors and regulate the expression of proinflammatory genes (10, 16). Goldkorn et al. (10) have demonstrated that generation of ceramide, an apoptotic mediator, and epidermal growth factor (EGF) receptor trafficking may be modulated by oxidative stress and the redox GSH/GSSG status of the cells. Tyrosine phosphorylation of EGF-receptor in lung epithelial cells by oxidative stress is thought to influence inflammatory processes, *e.g.,* hyperplasia and proliferation in lungs (10). Certain aldehydes and quinones may also regulate EGF receptor phosphorylation in lung cells. It is likely that ROS aberrantly phosphorylate the EGF receptor, thereby enabling the recruitment of 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 extracellular epithelial lining fluid (ELF) is rich in the antioxidant GSH and its redox system, which detoxifies oxidants, free radicals, organic polyaromatic hydrocarbons, and electrophilic compounds. There is increasing evidence to suggest that many inflammatory lung diseases are associated with airway/airspace inflammation and/or oxidant/antioxidant imbalance leading to alteration in GSH levels in the ELF (23). Comhair and Erzurum show that the ROS modulation of GSH and extracellular antioxidants, in particular extracellular glutathione peroxidase (eGPx), are important for redox signaling in the lungs (6). The imbalance of the redox system may lead to abnormal signaling associated with lung tissue damage and fibrosis. eGPx can also participate in airway inflammation and is undoubtedly an important defense against oxidative injury to the airway surface. The importance of redox modulation has been further elaborated by Land and Wilson (14), who have reported that perinatal lung development and epithelial function are influenced by redox modulation in response to hypoxia and hyperoxia. Oxygen tensions in fetal and perinatal lungs can differentially influence lung morphogenesis through oxygen- and redox-responsive signaling pathways by hypoxia-regulated transcription factors (hypoxia-inducible factor-α), GSH/GSSG ratio, activation of NF-κB-dependent increase in transepithelial Na^+ transport, and lung luminal fluid clearance.

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 (27). The role of nitrosation of NF-κB subunit has also been discussed. This may be an important mechanism for redox sensing of NF-κB under some pathological conditions.

Thioredoxin, a small ubiquitous protein with a conserved sequence of -Cys-Gly-Pro-Cys- in the active site (two redox-active cysteine residues), is one of the key redox molecules. These cysteines undergo oxidation–reduction reactions in response to the redox status of the environment. The importance of thioredoxin has recently been highlighted in signal transduction, inflammatory response, and other biological functions, such as cell growth, apoptosis, and proliferation (17). Equally important for redox-signaling reactions are glutaredoxins, thiol disulfide oxidoreductases responsible for GSH-dependent thiol-disulfide oxidoreduction reactions. Apoptosis signal-regulating kinase 1 (ASK1), which is activated in response to proinflammatory and stress signals, is regulated by thioredoxin. ASK1 activates c-Jun N-terminal kinase and p38 MAP kinase pathways and has been implicated in various cell functions, including cell survival, differentiation, and inflammation. Furthermore, it has been shown that thioredoxin and glutaredoxin associate with ASK1 at the N-terminus and inhibit ASK1 activity and subsequent ASK1-dependent apoptosis by reduction/oxidation regulation (29). One of the best examples for redox sensor-mediated reactions involves, Nrf2, a member of the NF-E2 family of nuclear basic leucine zipper 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 (8). Oxidative modification of Keap1 thiol dissociates Nrf2 from the Nrf2–Keap1 complex. Nrf2 then translocates to the nucleus, binds with the 5'-upstream regulatory antioxidant response element regions of phase 2 genes, and accelerates their transcription. Thus, it is possible that many of the redox-sensitive transcription factors that are regulated by GSH can also be regulated by thioredoxin in both the cytoplasm and nucleus.

The cell cycle inhibitor $p21^{Cip1/WAF1/Sdi1}$ is regulated by redox signaling and involved in DNA replication, repair, and apoptosis (18), and may be directly involved in the 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 $p21^{Cip1/WAF1/Sdi1}$. H_2O_2 at low concentration regulates cell proliferation of primary epithelial cells that is mediated by MAP kinases (30). This suggests that changes in intracellular oxidant concentrations can modulate downstream signaling pathways controlling alveolar type II cell proliferation.

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 (19). 4-HNE is increased in lungs of patients with chronic obstructive pulmonary disease (COPD) and probably involved in many pathological reactions during lung inflammation (24). F_2-isoprostanes and other cyclopentenone prostaglandins (15-deoxy-$\Delta^{12,14}$-prostaglandin J_2) can react with the sulfhydryl group of GSH and with various GSH transferases. 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.* (32) 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. As 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.

Recently, it has been shown that redox regulation of signaling events can also occur in the nucleus. 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 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. Oxidants can reduce glucocorticoid function by inhibiting histone deacetylase activity by posttranslational modification of histone deacetylases with aldehydes and NO metabolites. Thus, oxidant stress, acting through changes in chromatin structure, can enhance inflammation and induce a state of relative glucocorticoid-insensitivity (2, 22). This may account for the lack of glucocorticoid sensitivity in patients with COPD where oxidative stress and altered redox status have been shown to occur (22). Thiol antioxidants may reduce the inflammation and restore glucocorticoid sensitivity in these subjects.

Recent studies have demonstrated that low amounts of phenolic (antioxidant) compounds can regulate redox signaling in lung cells. Curcumin (diferuloylmethane), a dietary phenolic compound, has been shown to possess both antioxidant and antiinflammatory properties in cultured alveolar epithelial cells (3). Similarly, the red wine polyphenol, resveratrol, and pomegranate wine can act as antioxidant and antiinflammatory agents by some novel mechanisms and even prolonged aging (13). Small redox molecules, such as β-strand mimetic template MOL 294 and PNRI-299, and thiol antioxidants, such as *N*-acetyl-L-cysteine, Nacystelyn, and ergothioneine, 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 (11, 20, 21, 25). However, studies are needed to validate the bioavailability of these compounds to regulate redox signaling in lung inflammation/chronic lung diseases.

CONCLUSIONS

GSH and thioredoxin are important protective antioxidants in the lungs. Regulation of intracellular redox GSH and thioredoxin levels in response to 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 such as NF-κB and AP-1. Understanding of the transient form of cysteine (sulfenic or sulfinic acid) on redox sensing proteins will provide us information on how the signaling proteins are regulated during oxidative stress and inflammation. The 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 in inhibition of the inflammatory response and correction of the fundamental oxidant/antioxidant imbalance in patients with chronic inflammatory diseases is an important area of further research. Further, understanding of the cellular and molecular redox regulating mechanisms in inflammation/proinflammatory gene transcription is urgently needed to design effective antioxidant therapeutic strategies for the treatment of various inflammatory lung conditions. Compounds with multiple functions, such as antioxidant and anti-inflammatory properties, can be designed to up-regulate the endogenous antioxidant defense mechanism and inhibit the proinflammatory mediator release. Furthermore, studies are required to understand the novel antioxidant and antiinflammatory polyphenols or dietary

antioxidants in the prevention or amelioration of chronic lung inflammation.

ABBREVIATIONS

AP-1, activator protein-1; ASK-1, apoptosis signal-regulating kinase 1; COPD, chronic obstructive pulmonary disease; EGF, epidermal growth factor; eGPx, extracellular glutathione peroxidase; ELF, epithelial lining fluid; GSH, glutathione; GSSG, glutathione disulfide; 4-HNE, 4-hydroxy-2-nonenal; H_2O_2, hydrogen peroxide; HO-1, heme oxygenase-1; IKK, IκB kinase; IL, interleukin; MAP, mitogen-activated protein; NF-κB, nuclear factor-κB; NO, nitric oxide; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α.

REFERENCES

1. Abate C, Patel L, Rausher FJ, and Curran T. Redox regulation of fos and jun DNA-binding activity in vitro. *Science* 249: 1157–1161, 1990.
2. Adcock IM, Cosio B, Tsaprouni L, Barnes PJ, and Ito K. Redox regulation of histone deacetylases and glucocorticoid-mediated inhibition of the inflammatory response. *Antioxid Redox Signal* 7: 144–152, 2005.
3. Biswas SK, McClure D, Jimenez LA, Megson IL, and Rahman I. Curcumin induces glutathione biosynthesis and inhibits NF-κB activation and interleukin-8 release in alveolar epithelial cells: mechanism of free radical scavenging activity. *Antioxid Redox Signal* 7: 32–41, 2005.
4. Bundy RE, Hoare GS, Kite A, Beach J, Yacoub M, and Marczin N. Redox regulation of p38 MAPK activation and expression of ICAM-1 and heme oxygenase-1 in human alveolar epithelial (A549) cells. *Antioxid Redox Signal* 7: 14–24, 2005.
5. Claiborne A, Yeh JI, Mallett TC, Luba J, Crane EJ 3rd, Charrier V, and Parsonage D. Protein-sulfenic acids: diverse roles for an unlikely player in enzyme catalysis and redox regulation. *Biochemistry* 38: 15407–15416, 1999.
6. Comhair SAA and Erzurum SC. The regulation and role of extracellular glutathione peroxidase. *Antioxid Redox Signal* 7: 72–79, 2005.
7. Delaunay A, Pflieger D, Barrault MB, Vinh J, and Toledano MB. A thiol peroxidase is an H_2O_2 receptor and redox-transducer in gene activation. *Cell* 111: 471–481, 2002.
8. Dinkova-Kostova AT, Holtzclaw WD, Cole RN, Itoh K, Wakabayashi N, Katoh Y, Yamamoto M, and Talalay P. Direct evidence that sulfhydryl groups of Keap1 are the sensors regulating induction of phase 2 enzymes that protect against carcinogens and oxidants. *Proc Natl Acad Sci U S A* 99: 11908–11913, 2002.
9. Filomeni G, Rotilio G, and Ciriolo MR. Glutathione disulfide induces apoptosis in U937 cells by a redox-mediated p38 MAP kinase pathway. *FASEB J* 17: 65–66, 2003.
10. Goldkorn T, Ravid T, and Khan EM. Life and death decisions: ceramide generation and EGF receptor trafficking are modulated by oxidative stress. *Antioxid Redox Signal* 7: 119–128, 2005.
11. Henderson WR Jr, Chi EY, Teo JL, Nguyen C, and Kahn M. A small molecule inhibitor of redox-regulated NF-κB and activator protein-1 transcription blocks allergic airway inflammation in a mouse asthma model. *J Immunol* 169: 5294–5299, 2002.
12. Hirota K, Matsui M, Iwata S, Nishiyama A, Mori K, and Yodoi J. AP-1 transcriptional activity is regulated by a direct association between thioredoxin and Ref-1. *Proc Natl Acad Sci U S A* 94: 3633–3638, 1997.
13. Howitz KT, Bitterman KJ, Cohen HY, Lamming DW, Lavu S, Wood JG, Zipkin RE, Chung P, Kisielewski A, Zhang LL, Sherer B, and Sinclair D.A. Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan. *Nature* 425: 191–196, 2003.
14. Land SC and Wilson SM. Redox regulation of lung development and perinatal lung epithelial function. *Antioxid Redox Signal* 7: 92–107, 2005.
15. Lautier D, Luscher P, and Tyrrell RM. Endogenous glutathione levels modulate both constitutive and UVA radiation/hydrogen peroxide inducible expression of the human heme oxygenase gene. *Carcinogenesis* 13: 227–232, 1992.
16. Liu B, Andrieu-Abadie N, Levade T, Zhang P, Obeid LM, and Hannum YA. Glutathione regulation of neutral sphingomyelinase in tumour necrosis factor-alpha-induced cell death. *J Biol Chem* 273: 11313–11320, 1998.
17. Nakamura T, Nakamura H, Hoshino T, Ueda S, Wada H, and Yodoi J. Redox regulation of lung inflammation by thioredoxin. *Antioxid Redox Signal* 7: 60–71, 2005.
18. O'Reilly MA. Redox activation of $p21^{Cip1/WAF1/Sdi1}$: a multifunctional regulator of cell survival and death. *Antioxid Redox Signal* 7: 108–118, 2005.
19. Parola M, Bellomo G, Robino G, Barrera G, and Dianzani MU. 4-Hydroxynonenal as a biological signal: molecular basis and pathophysiological implications. *Antioxid Redox Signal* 1: 255–284, 1999.
20. Rahman I. Inflammation and regulation of glutathione in lung cells. *Antioxid Redox Signal* 1, 425–447, 1999.
21. Rahman I. Oxidative stress, transcription factors and chromatin remodelling in lung inflammation. *Biochem Pharmacol* 64: 935–942, 2002.
22. Rahman I. Oxidative stress, chromatin remodeling and gene transcription in inflammation and chronic lung disease. *J Biochem Mol Biol* 36: 95–109, 2003.
23. Rahman I and MacNee W. Lung glutathione and oxidative stress: implications in cigarette smoke-induced airways disease. *Am J Physiol* 277: L1067–L1088, 1999.
24. Rahman I, van Schadewijk AA, Crowther A, Hiemstra PS, Stolk J, MacNee W, and De Boer WI. 4-Hydroxy-2-nonenal, a specific lipid peroxidation product, is elevated in lungs of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 166: 490–495, 2002.
25. Rahman I, Gilmour PS, Jimenez LA, Antonicelli F, Biswas SK, and Aruoma OI. Ergothioneine inhibits oxidative stress and TNF-α induced NF-κB/AP-1 binding and interleukin-8 release in alveolar epithelial cells. *Biochem Biophys Res Commun* 302: 860–864, 2003.
26. Rahman I, Biswas SK, Jimenez LA, Torres M, and Forman HJ. Glutathione, stress responses, and redox signaling in lung inflammation. *Antioxid Redox Signal* 7: 42–59, 2005.

27. Reynaert NL, Ckless K, van der Vliet A, K, Wouters EFM, and Janssen-Heininger YMW. Nitric oxide and redox signaling in allergic airway inflammation. *Antioxid Redox Signal* 7: 129–143, 2005.
28. Ryter SW and Choi AMK. Heme oxygenase-1: redox regulation of a stress protein in lung and cell culture models. *Antioxid Redox Signal* 7: 80–91, 2005.
29. Saitoh M, Nishitoh H, Fujii M, Takeda K, Tobiume K, Sawada Y, Kawabata M, Miyazono K, and Ichijo H. Mammalian thioredoxin is a direct inhibitor of apoptosis signal-regulating kinase (ASK) 1. *EMBO J* 17: 2596–2606, 1998.
30. Sigaud S, Evelson P, and González-Flecha B. H_2O_2-induced proliferation of primary alveolar epithelial cells is mediated by MAP kinases. *Antioxid Redox Signal* 7: 6–13, 2005.
31. Stamler JS and Hausladen A. Oxidative modifications in nitrosative stress *Nat Struct Biol* 5: 247–249, 1998.
32. Valacchi G, Pagnin E, Phung A, Nardini M, Schock BC, Cross CE, and van der Vliet A. Inhibition of NFκB activation and IL-8 expression in human bronchial epithelial cells by acrolein. *Antioxid Redox Signal* 7: 25–31, 2005.
33. Woo HA, Chae HZ, Hwang SC, Yang KS, Kang SW, Kim K, and Rhee SG. Reversing the inactivation of peroxiredoxins caused by cysteine sulfinic acid formation. *Science* 300: 653–656, 2003.

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2. Feng Zhang, Xinying Wang, Liya Pan, Weiya Wang, Ning Li, Jieshou Li. 2009. Glutamine attenuates lipopolysaccharide-induced acute lung injury. *Nutrition* **25**:6, 692-698. [CrossRef]
3. Srikanth Pendyala , Peter V. Usatyuk , Irina A. Gorshkova , Joe G.N. Garcia , Viswanathan Natarajan . 2009. Regulation of NADPH Oxidase in Vascular Endothelium: The Role of Phospholipases, Protein Kinases, and Cytoskeletal Proteins. *Antioxidants & Redox Signaling* **11**:4, 841-860. [Abstract] [Full Text PDF] [Full Text PDF with Links]
4. Adel Boueiz, Paul M. Hassoun. 2009. Regulation of endothelial barrier function by reactive oxygen and nitrogen species. *Microvascular Research* **77**:1, 26-34. [CrossRef]
5. Ian M. Adcock, Gaetano CaramoriTranscription Factors 373-380. [CrossRef]
6. Feng Zhang, Xinying Wang, Weiya Wang, Ning Li, Jieshou Li. 2008. Glutamine Reduces TNF-# by Enhancing Glutathione Synthesis in Lipopolysaccharide-Stimulated Alveolar Epithelial Cells of Rats. *Inflammation* **31**:5, 344-350. [CrossRef]
7. Jacky Jacquot, Olivier Tabary, Philippe Le Rouzic, Annick Clement. 2008. Airway epithelial cell inflammatory signalling in cystic fibrosis. *The International Journal of Biochemistry & Cell Biology* **40**:9, 1703-1715. [CrossRef]
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