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Review

Glutathione and Inflammatory Disorders of the Lung

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Abstract. Glutathione (GSH) is an essential tripeptide present in most eukaryotic cells. Because of its sulfhydryl group, GSH is a versatile molecule capable of protecting cells against oxidants and toxic xenobiotics. However, it also plays key roles in multiple metabolic pathways, such as the synthesis of certain leukotrienes, proteins, and DNA precursors as well as the activation of enzymes, the regulation of immune responses and others. Not only is GSH synthesized by cells for local use but it also participates in an elaborate intercellular exchange process regulated by the γ-glutamyl cycle. Extracellular GSH in plasma and in alveolar epithelial lining fluid is thus subject to variations according to the degree of expression of γ-glutamyl cycle enzymes and the rate of consumption of GSH by electrophilic molecules. Bronchoalveolar lavage has allowed us to observe many of these variations of GSH within the extracellular environment of the normal and diseased human lung. Studies of lung GSH have lead to a better understanding of pathogenic processes and have stimulated investigations of novel therapeutic approaches in lung inflammatory disorders.

Key words: Glutathione—Inflammation—Smoking—Idiopathic pulmonary fibrosis—Bronchoalveolar lavage disorders.

Introduction

Glutathione (L-γ-glutamyl-L-cysteinylglycine) (GSH) is a low-molecular-weight (Mr 306) tripeptide essential to the integrity of most mammalian cells (Fig. 1). The high intracellular concentration (0.5–10 mM) and the presence of a sulfhydryl group make GSH 1 of the cell's primary defenses against a wide variety of electrophilic compounds. Reaction of GSH with oxidants converts GSH to

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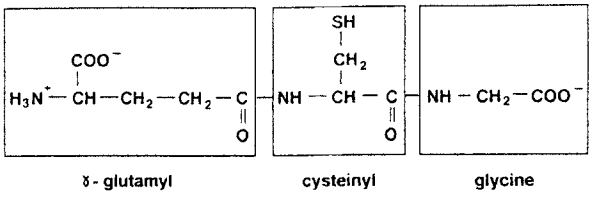

Fig. 1. Structure of glutathione.

either glutathione disulfide (GSSG; often referred to as "oxidized glutathione") or to mixed disulfides (RSSG).

In addition to its role as an intracellular antioxidant, GSH is involved in numerous other roles, both intra- and extracellularly, which are important in maintaining normal physiological functions of cells and organs. The interest in GSH is such that thousands of scientific papers concerning various aspects of GSH function have appeared in recent years [for review articles, see 27, 37, 51, 52, 60–63, 69, 70].

The current presentation will address some of the abnormalities in GSH metabolism that have been observed in various inflammatory disorders of the lung. The lung is unique in that the extracellular milieu at the alveolar epithelial surface is rich in GSH [14]. This extracellular compartment is readily sampled in humans by bronchoalveolar lavage and, therefore, much of this review relates to studies involving alveolar epithelial lining fluid GSH rather than cellular GSH.

Glutathione Synthesis, Transport, and Breakdown

The major pathways involved in glutathione synthesis and breakdown are represented by the reactions of the γ-glutamyl cycle [60–63]. The γ-glutamyl cycle involves cellular and extracellular steps, which are summarized in Fig. 2.

GSH Synthesis

Glutathione is synthesized through a 2-step reaction involving the enzymes γ-glutamylcysteine synthetase and glutathione synthetase [60]. Selective inhibition of GSH synthesis with buthionine sulfoximine, an irreversible inhibitor of γ-glutamylcysteine synthetase, is a useful method of investigating GSH biosynthesis and metabolism [60]. In an alternative fashion, cellular GSH can be depleted with diethyl maleate and the rate of subsequent GSH biosynthesis quantitated. Horton et al., using this latter approach, have demonstrated that lung macrophages, Clara cells, and type II cells synthesize GSH at a rate proportional to their initial GSH content [42].

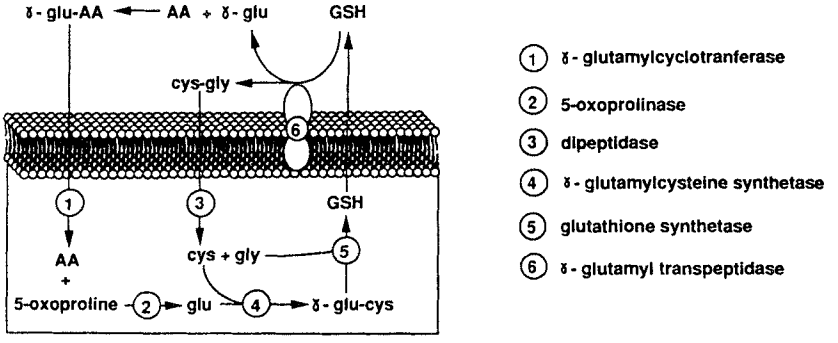

Fig. 2. The gamma-glutamyl cycle. Enzymes involved in each step are numbered and identified to the right. Conversion of 5-oxoproline to glutamate and synthesis of GSH are intracellular reactions shown in the boxed area. Transpeptidation of the γ-glutamyl moiety of GSH to an amino acid acceptor occurs at the cell surface (upper portion). GSH, glutathione; γ-glu, gamma-glutamyl; AA, amino acid; cys, cysteine; gly, glycine; glu, glutamate; cys-gly, cysteinylglycine; γ-glu-cys, gamma-glutamylcysteine.

Extracellular Transport

Once glutathione is synthesized, it can either be used in various cellular metabolic pathways or it can be exported from the cell. Glutathione disulfide export from cells, likely to occur through an active transport system, is observed in response to an oxidative stress [2, 77, 80]. However, in the absence of oxidative stress, GSH, not GSSG, is the major transport form [5, 28]. Glutathione translocation to the extracellular milieu has been observed in many cell types including fibroblasts, lymphocytes, macrophages, and epithelial cells [5, 28, 34, 76]. Although plasma GSH is approximately 3 orders of magnitude lower than cellular GSH, these relatively low levels reflect efficient extracellular catabolic pathways rather than low GSH translocation.

GSH Breakdown

The half-life of glutathione in human plasma is very short (1.6 min) [88]. Most of the plasma GSH is catabolized by the enzyme γ-glutamyl transpeptidase in the kidney, the lung, and, to a lesser degree, in other tissues [1, 34, 58]. Gamma-glutamyl transpeptidase is a plasma membrane enzyme most prevalent in secretory epithelia but also present in many cell types of the lung, such as alveolar macrophages, lymphocytes, bronchial and type I epithelial cells, and pulmonary artery endothelial cells [3, 45, 76, 84]. The heavy subunit (Mr > 60,000) of γ-GT is attached to the lipid membrane, while the light subunit (Mr 22,000) containing the active site is directed toward the extracellular milieu [60]. Its function, as its name suggests, is to catalyze the transpeptidation of the γ-glutamyl moiety of GSH to an appropriate acceptor such as certain amino acids, dipeptides,

Table 1. Metabolic functions involving glutathione

Function	Reference
Antioxidant protection of cells and molecules	19, 26, 31, 65
Conjugation with xenobiotics via GSH S-transferases	37
Conjugation with endogenous metabolites	83, 89
Conjugation with substrates for transport via ATP-dependent transport protein	46
Amino acid transport system	60–63
Support of primary antibody response	40
Regulation of T-lymphocyte proliferation	29, 55, 57, 82, 87
Maintain integrity of type II cell lamellar studies	58
Coenzyme for multiple enzymatic reactions	52
Thiol–disulfide exchange	27, 51, 52, 60–63, 70
Protein synthesis and degradation	
DNA precursor synthesis	
Enzyme activation	
Reduction of cystine	
Regulate microtubule formation	12

other γ-glutamyl compounds, or glutathione itself. As shown in Fig. 2, the γ-glutamyl-amino acid complex can be carried into the cell, where the enzyme γ-glutamylcyclotransferase converts it to the corresponding free amino acid(s) and 5-oxoproline, which is converted by 5-oxoprolinase to glutamate, an immediate substrate for the synthesis of GSH [60–63]. As a final step, the dipeptide L-cysteinylglycine may undergo rapid spontaneous oxidation in the extracellular space, especially in the presence of trace metals, and subsequently mediate the oxidation of GSH. As an alternative, L-cysteinglycine can be taken up by the cell and cleaved by cytosolic dipeptidase activity into cysteine and glycine.

Functions of Glutathione

The list of cellular and extracellular metabolic functions involving GSH has grown remarkably in recent years as understanding of this versatile tripeptide has increased (Table 1). We will review briefly some aspects of these functions to allow us to understand the potential implications of altered GSH metabolism in lung inflammatory disorders.

Antioxidant

One of the best known and well characterized functions of GSH is its role as an antioxidant [13, 26, 65]. Although GSH alone can react with a variety of peroxides, it is rendered much more efficient as an antioxidant by a metabolic

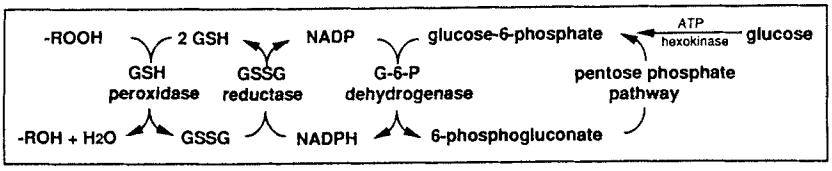

Fig. 3. The glutathione redox cycle. Glutathione converts various peroxides to nontoxic hydroxy fatty acids and/or water. Glutathione disulfide is subsequently reduced to glutathione in the presence of NADPH and glutathione reductase.

pathway that catalyzes the reaction of GSH with peroxides and restores glutathione disulfide to its reduced form, GSH (Fig. 3).

Under physiological circumstances, lung cells reduce most of the available oxygen to water through cyanide-sensitive pathways of oxidative phosphorylation. However, a fraction of the available oxygen is utilized in cyanide-insensitive metabolic pathways that generate reactive oxygen intermediates such as superoxide (O_2^-; single electron reduction of O_2) and hydrogen peroxide (H_2O_2; 2 electron reduction of O_2). Since these oxygen intermediates react readily by subtracting electrons from a wide variety of molecules (oxidation), the presence of these oxidants is a constant threat to the cell's integrity. If oxygen tensions are increased, as often occurs in the lungs of patients, the potential for oxidative damage to cells is increased [33]. However, under normal circumstances, GSH and GSH peroxidase protect the cell from oxidative damage by converting H_2O_2, lipid peroxides or other peroxides (-ROOH) to H_2O, or unreactive hydroxy fatty acids. Glutathione reductase then converts GSSG to GSH in the presence of NADPH provided by glucose-6-phosphate [19, 31]. The importance of the GSH system in protecting the lung against O_2 toxicity is supported by studies demonstrating increased O_2 toxicity in animals depleted of lung GSH by diethylmaleate [26].

GSH Conjugation

A second major function of GSH is to form conjugates with exogenous electrophilic molecules. Conjugation of GSH with various compounds can occur spontaneously or through the action of GSH S-transferases [27]. Although the principal site of exogenous compound conjugation to GSH is the liver, the lung has also been shown to catalyze the conjugation of foreign electrophilic compounds. An interesting finding is that lung uptake and utilization of extracellular GSH markedly increase the rate of cellular GSH conjugation. The mechanism by which extracellular GSH is translocated to the cytoplasm is not through uptake of intact GSH but through the γ-glutamyl cycle (Fig. 2) [7, 25]. Whether respiratory epithelial cells utilize epithelial lining fluid GSH to conjugate and detoxify inhaled xenobiotics or carcinogens is unknown.

Another essential metabolic function of GSH is the conjugation of endoge-

nous molecules. For example, GSH conjugation of leukotriene A_4 results in the formation of leukotriene C_4, which can be converted to leukotriene D_4 by γ-glutamyl transpeptidase [83, 89]. Both LTC_4 and LTD_4 are potent bronchoconstrictors and have proinflammatory effects, such as increasing vascular permeability [54].

ATP-Dependent Transport System

Ishikawa has recently provided direct evidence that glutathione-S-conjugates are transported across plasma membranes (i.e., rat heart sarcolemma) by an ATP-dependent transport system [46]. This ATP-dependent transport molecule was found to have a high affinity for LTC_4 and a much lower but definite affinity for LTD_4, LTE_4, and GSSG. Although the transport molecule is not identical to the multidrug resistance (MDR) gene product, P-glycoprotein, it may be a member of the ATP-binding cassette (ABC) superfamily of transport systems, which includes the MDR and cystic fibrosis gene products [35, 39, 73, 74]. The ABC superfamily of transport systems may prove to be a major mechanism by which cells translocate glutathione conjugates such as physiological metabolites and toxic compounds, as well as GSSG.

Amino Acid Transport

Extracellular GSH is also known to assist amino acid transport through the γ-glutamyl cycle described above (Fig. 2). Glutathione breakdown by γ-glutamyl transpeptidase results in the formation of γ-glutamyl amino acids, which are readily taken up by cells and used in various biosynthetic and metabolic pathways. The amino acids most likely to be transported by this system are L-cystine and L-glutamine, although other amino acids are known to participate as γ-glutamyl acceptors [60, 62]. Transport of GSH percursor amino acids through this system is probably the most important mechanism by which GSH is transferred from the extracellular milieu to the cytoplasm. It has recently been shown in the mouse that the lung is at least as active as the kidney in the utilization of plasma GSH by the γ-glutamyl cycle [58].

Immune Modulation

Several studies have pointed to a role for GSH in the modulation of both B- and T-lymphocyte responses. Extracellular GSH was found to correlate strongly with the capacity of culture media to support a primary antibody response in murine spleen cells [40]. In addition, GSH seems to have profound effects on other lymphocyte populations. Wedner et al. have reported that depletion of cellular GSH leads to suppression of mitogen-driven lymphocyte activation and inhibition of natural killer-cell-mediated cytotoxicity [57, 87]. Consistent with these observations, in vivo GSH administration has been found to enhance

cytotoxic T-cell activation [29]. The mechanisms by which extracellular GSH increases lymphocyte activation have recently been studied in murine and human cells. These studies indicated that extracellular GSH increased cellular GSH, probably through breakdown and uptake in the γ-glutamyl cycle described above. Cellular GSH, while not affecting the expression of the IL-2 receptor α, enhanced the binding, internalization, and degradation of IL-2 [55, 82]. As outlined by Suthanthiran et al., these observations suggest that pharmacologic manipulation of GSH synthesis, degradation, and/or translocation may provide a novel approach to immunosuppressive and immunoenhancement therapies [82].

Type II Cell Lamellar Body Integrity

One of the recently described functions of GSH is specific to an essential component of the lung, that is, surfactant [86]. Mice depleted of GSH through chronic administration of L-buthionine (S,R,)-sulfoximine show marked type II cell lamellar body swelling and disintegration [58]. Intraperitoneal administration of glutathione monoester, but not GSH, increased lung GSH levels and protected type II cells against lamellar body changes. These observations may be of particular relevance to the adult respiratory distress syndrome, an inflammatory lung disease in which an alveolar oxidant burden that may potentially deplete lung GSH is associated with abnormalities in the lung surfactant system [21, 38].

Other GSH Functions

Glutathione participates in a number of other metabolic functions essential to the cell, such as serving as a coenzyme, allowing thiol–disulfide exchanges, and regulating microtubule formation (Table 1).

Epithelial Lining Fluid GSH and the Normal Lung

The epithelial surface of the lung is exposed to potentially toxic oxidants from various sources. First, the oxygen tensions within the airways and alveolar spaces are approximately 3 times higher than in most other tissues [72]. Second, inhalation of oxidizing gases and electrophilic molecules is a common occurrence in situations such as cigarette smoking, the administration of therapeutic oxygen at high tensions, and exposure to industrial and urban pollutants [13, 33, 64, 68]. Third, inhalation of particles and microorganisms leads to the activation of airway and alveolar phagocytes, which respond by releasing large amounts of O_2^- and H_2O_2 [50]. One of the mechanisms by which the lung protects itself against extracellular oxidants is through an array of antioxidant molecules in the epithelial lining fluid (ELF). Among the known ELF antioxidants are catalase, vitamin E, vitamin C, ceruloplasmin, transferrin, lactoferrin, and GSH

[17, 24, 59, 66, 67, 79]. Whereas levels of plasma GSH are normally low (3 μM), levels of ELF GSH in normal nonsmokers are at least 100 times higher [14]. These levels are among the highest reported in any extracellular fluid.

The source of ELF GSH is not known. However, as noted above, several lung cells are capable of exporting GSH. Although many cells may contribute to ELF GSH, the alveolar macrophage is potentially a major source since it has a 9 times higher GSH content than type II cells and demonstrates an active γ-glutamyl cycle [42, 76]. Accumulation of extracellular GSH in ELF is likely to be related to 2 factors. First, the relatively impermeable alveolar–capillary barrier may limit GSH flow to the vascular compartment, where it would be rapidly catabolized by the kidney and excreted [22]. Second, the concentration of the GSH catabolic enzyme, γ-glutamyl transpeptidase, is approximately 300 times less in the lung than in the kidney, thus limiting GSH degradation [3]. In addition, much of the extracellular GSH degraded by lung cells is likely to be recycled into de novo GSH synthesis [32, 84].

Nearly all ELF glutathione is in the reduced form (GSH), the form involved in most of the metabolic functions described above. Among the potential functions of ELF GSH are immune defense enhancement, xenobiotic detoxification, amino acid transport, and antioxidant protection. The concentration of GSH in normal ELF is sufficient to protect lung fibroblasts and alveolar epithelial cells against an extracellular oxidant burden in vitro [14].

One of the striking features of ELF glutathione is the very low level of GSSG despite the potentially large lung oxidant burden. This implies an efficient mechanism of GSSG degradation, reduction, or both. Although low concentrations of enzymes involved in the GSH reduction cycle have been detected in normal ELF, their concentration does not seem sufficient to prevent GSSG accumulation. An alternative explanation would be that the γ-glutamyl cycle is responsible for GSSG degradation, cellular uptake of the corresponding amino acids, and synthesis of GSH, which is subsequently exported in the reduced form (Fig. 2).

Consistent with the concept that the γ-glutamyl cycle may contribute to the efficacy of ELF GSH as an antioxidant is a recent report by Forman and Skelton indicating that extracellular GSH protects alveolar macrophages against hyperoxia through the γ-glutamyl cycle [32]. Inhibition of γ-glutamyl transpeptidase blocked both GSH uptake and antioxidant protection provided by extracellular GSH. These observations raise the interesting point that ELF GSH may provide antioxidant protection to both the extracellular and cellular compartments.

Lung Disorders with Increased ELF GSH

Hyperoxia

Normal rats exposed for 5 days to a fraction of inspired oxygen of 0.8 were found to have marked increases in both tissue and bronchoalveolar lavage fluid

Table 2. Extracellular glutathione levels in various lung disorders

Condition	ELF[a] GSH	Plasma GSH
Normal nonsmoker	N[b]	N
Normal smoker	↑	N
Idiopathic pulmonary fibrosis	↓	N
Cystic fibrosis	↓	N
HIV seropositive	↓	↓

[a] ELF, epithelial lining fluid from the alveolar space.
[b] N, levels of GSH within the range observed in healthy nonsmokers.

(BALF) GSH [47]. Since the increase in GSH was accompanied by signs of lung injury such as increased BALF protein and LDH concentration, it was not clear whether GSH levels reflected an adaptive response or a consequence of cell injury. However, despite the high oxygen tensions to which the lung was exposed for a prolonged period, no GSSG was detected in the BALF. This latter observation again suggests that an efficient metabolic process prevents the accumulation of alveolar GSSG.

Cigarette Smoking

Another situation in which the lower respiratory tract is exposed to a high oxidant burden is cigarette smoking. Each "puff" of cigarette smoke contains free radicals in both the soluble and particular phases [68]. In addition, particular matter from the smoke is phagocytized by alveolar macrophages that subsequently proliferate, recruit neutrophils from blood, and release toxic oxidants [41, 43, 44, 71]. Normal smokers were found to have increased levels of ELF GSH, with very low levels of GSSG [14]. Plasma GSH levels were normal (Table 2). It is likely that the increased ELF GSH levels help to protect the alveolar structures against the marked oxidant burden present in the lower respiratory tract of the normal smoker.

One possible explanation for the increased ELF GSH is that smokers' alveolar macrophage GSH metabolism is altered. Smokers' macrophages actively phagocytize particulate matter from the cigarette smoke. Phagocytizing macrophages enhance their GSH synthesis, markedly increase GSH efflux, and do not express γ-glutamyl transpeptidase, thus leading to the accumulation of high GSH concentrations in their extracellular milieu [76].

Epithelial lining fluid glutathione has been found to correlate with polymorphonuclear cells and their products as well as with the antiproteases, antichymotrypsin, and secretory leukocyte protease inhibitor (SLPI) [56].

The correlation of ELF GSH with SLPI ($r = 0.831$, $p < 0.001$) is intriguing, since this serine proteinase inhibitor is very rich in sulfhydryl groups and is synthesized by bronchial epithelial cells [85]. One may speculate that bronchial epithelial cell uptake of GSH through the γ-glutamyl cycle favors SLPI synthesis.

The increased ELF GSH levels in smokers are consistent with some reports of high tissue GSH levels in animal models of cigarette smoking [20, 53]. However, Joshi et al. noted that acute cigarette smoke exposure significantly decreased lung GSH [48]. The degree to which ELF GSH changes reflect tissue GSH levels in normal smokers remains unknown.

Lung Disorders with Decreased ELF GSH

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic inflammatory lung disease characterized by increased numbers of mononuclear and polymorphonuclear phagocytes within the alveolar structures [23]. Release of O_2^- and H_2O_2 from these phagocytes is markedly increased in IPF [15], which, as in normal smokers, leads to a high alveolar oxidant burden. However, in contrast to normal smokers, patients with IPF have a marked deficiency in ELF GSH [16]. Glutathione deficiency is not observed in the plasma or in the alveolar macrophages of IPF patients, suggesting that the ELF GSH deficiency is not caused by decreased GSH synthesis. The cause of the GSH deficiency is unknown; however, several mechanisms are possible. First, GSH may be used by extracellular oxidants and/or converted to mixed disulfides. If this were the only explanation, one would also expect normal smokers to be deficient in ELF GSH, which is not the case. Second, GSH catabolism may be increased by increased epithelial cell γ-glutamyl transpeptidase activity. Alveolar epithelial cells in IPF undergo changes characterized by hyperplasia, cuboidal metaplasia, and, occasionally, dysplastic or neoplastic changes [49]. Many of these morphologic changes have been associated with increased γ-glutamyl transpeptidase activity [36, 78]. In addition, IPF alveoli are often found to be lined with ciliated cells similar to those of the bronchial epithelium [49]. Bronchial cells show much stronger γ-GT activity than normal alveolar epithelial cells [3]. Finally, in contrast to phagocytizing macrophages, *Corynebacterium parvum*-elicited macrophages demonstrate decreased GSH efflux and increased γ-glutamyl transpeptidase activity, 2 conditions that would be expected to decrease extracellular GSH [76]. It is not known whether IPF alveolar macrophage GSH metabolism is similar to that of elicited macrophages.

Regardless of the cause of ELF GSH deficiency in patients with IPF, the low levels of this antioxidant, coupled with the high oxidant burden at the IPF alveolar surface, are likely to contribute to an oxidant–antioxidant imbalance that can increase alveolar epithelial cell damage. It therefore seems rational to try to correct the relative ELF GSH deficiency in patients with IPF.

The contrast in ELF GSH concentrations between smokers and patients with IPF led us to examine the effect of extracellular GSH on proliferating lung fibroblasts. These studies demonstrated that GSH within the concentration range found in normal ELF, but not IPF ELF, suppressed fibroblast proliferation in vitro [18]. The mechanisms are not entirely clear, but seem to be related

to autoxidation of the sulfhydryl group, since proliferation was restored by the addition of catalase to the GSH. Whether GSH-mediated suppression of fibroblast proliferation occurs in vivo is unknown.

Cystic Fibrosis

Cystic fibrosis lung disease is characterized by an excessive airway burden of neutrophils and neutrophil-derived products [6, 81]. As in patients with IPF, the ELF but not the plasma GSH levels are markedly decreased [75]. The cause of this deficiency remains to be identified.

Human Immunodeficiency Virus Seropositivity

Buhl and co-workers have reported that both plasma and ELF GSH levels are significantly decreased in symptom-free human immunodeficiency virus (HIV)-seropositive persons [10]. These observations are consistent with the study of Eck et al., in which patients with acquired immunodeficiency syndrome (AIDS) were found to have low plasma cysteine and acid-soluble thiol concentrations as well as low GSH levels in peripheral blood mononuclear cells [30]. In view of the profound effects cellular and extracellular GSH can have on lymphocyte function (see above), it is conceivable that systemic GSH deficiency may contribute, at least in part, to the immune dysfunction associated with HIV infection.

Therapeutic Implications

Based on the multiple vital functions of GSH, it seems rational to pursue various strategies aimed at correcting ELF GSH deficiency. One approach that has proven effective in augmenting ELF GSH is through direct GSH aerosolization to the lower respiratory tract. Glutathione nebulization in sheep was found to increase ELF GSH more effectively and for a more sustained period of time than intravenous administration [11]. This approach is now being tested in patients with ELF GSH deficiencies. Preliminary results suggest that GSH aerosolization is a safe and feasible strategy to increase ELF GSH [9].

Another interesting approach to correcting lung GSH deficiency may be through the administration of glutathione monoethyl ester [4]. This compound, in which the glycine carboxyl group of GSH is esterified, is readily translocated into cells and de-esterified by cellular esterase activity. The resultant cellular products are GSH and ethanol. In contrast to GSH, the GSH ester administered either enterally or parenterally can effectively increase lung cellular GSH [58]. Since ELF GSH is necessarily derived from cells, repletion of lung cellular GSH by administration of GSH monoethyl ester could conceivably restore ELF GSH. Furthermore, since GSH monoethyl ester uptake does not depend on the γ-glutamyl cycle system, lung GSH restoration would be possible even in the

presence of γ-glutamyl cycle abnormalities. However, Tsan et al. have reported that GSH monoethyl ester, while increasing pulmonary artery endothelial cell GSH, did not protect cells against extracellular H_2O_2 and seemed to induce endothelial cell vacuolization [84]. The authors suggest that the apparent absence of antioxidant protection and concomitant vacuolization may have been caused by contamination of the GSH monoethyl ester by significant amounts of toxic GSH diethyl ester.

Glutathione repletion has been attempted by intravenous administration of N-acetylcysteine (NAC) in patients with the adult respiratory distress syndrome (ARDS) [8]. Preliminary results suggest that NAC-treated patients maintain higher red blood cell GSH levels than the placebo-treated group. The effect of intravenous NAC on ELF GSH levels is unknown.

Conclusion

Lung ELF GSH studies have provided us with a window through which it is possible to gain insights into GSH abnormalities associated with various inflammatory lung disorders. The intricate relationship between cellular and extracellular glutathione makes it necessary to study all aspects of lung GSH metabolism rather than limiting ourselves to the cellular or ELF compartments. Exciting new approaches to the modulation of lung GSH are currently being investigated and, it is hoped, will lead to the development of useful therapies for inflammatory lung diseases in the near future.

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