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Forum Review

Redefining Oxidative Stress

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ABSTRACT

Oxidative stress is often defined as an imbalance of pro-oxidants and antioxidants, which can be quantified in humans as the redox state of plasma GSH/GSSG. Plasma GSH redox in humans becomes oxidized with age, in response to oxidative stress (chemotherapy, smoking), and in common diseases (type 2 diabetes, cardiovascular disease). However, data also show that redox of plasma GSH/GSSG is not equilibrated with the larger plasma cysteine/cystine (Cys/CySS) pool, indicating that the "balance" of pro-oxidants and antioxidants cannot be defined by a single entity. The major cellular thiol/disulfide systems, including GSH/GSSG, thioredoxin-1 (-SH_2/-SS-), and Cys/CySS, are not in redox equilibrium and respond differently to chemical toxicants and physiologic stimuli. Individual signaling and control events occur through discrete redox pathways rather than through mechanisms that are directly responsive to a global thiol/disulfide balance such as that conceptualized in the common definition of oxidative stress. Thus, from a mechanistic standpoint, oxidative stress may be better defined as a disruption of redox signaling and control. Adoption of such a definition could redirect research to identify key perturbations of redox signaling and control and lead to new treatments for oxidative stress-related disease processes. *Antioxid. Redox Signal.* 8, 1865–1879.

INTRODUCTION

AEROBIC LIFE DEPENDS upon controlled combustion for energy supply. Controlled combustion is catalyzed and regulated by metabolic machinery that can be damaged by uncontrolled oxidative reactions associated with energy production. Because of the extreme threat of such uncontrolled oxidation, aerobic life evolved a complex set of antioxidant systems to control these reactions and repair or replace the damaged machinery. At the same time, enzyme systems evolved to produce reactive species for biologic signaling, biosynthetic reactions, chemical defense, and detoxification functions. The presence of both toxic and beneficial consequences of reactive species precludes a simple definition of oxidative stress. In the following, I will present an argument that the time has arrived to redefine oxidative stress from that provided in 1985 by Helmut Sies (57) as "a disturbance in the prooxidant–antioxidant balance in favor of the former." Whereas this definition was a useful beacon for research for two decades, the accumulation of data on redox signaling pathways, antioxidant intervention trials, and oxidative stress markers, indicates that a more useful contemporary definition is "a disruption of redox signaling and control."

Abundant circumstantial evidence indicates that oxidative reactions contribute to many consequences of aging and major disease processes, including cardiovascular disease (60), pulmonary diseases (12), diabetes (10), neurodegenerative diseases (63), and cancer (9). Plausible oxidative mechanisms have been proposed and supportive data are available from chemical and biochemical systems, a broad range of studies in model organisms, and observational studies in humans. However, despite this amassed wealth of scientific evidence, large-scale interventional studies with antioxidants, based on the concept that oxidative stress is an imbalance between pro-oxidants and antioxidants, have often been inconsistent in demonstrating health benefits in terms of quan-

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Subsequent to preparation of this article, H. Sies and D.P. Jones introduced a new definition of oxidative stress in the Encyclopedia of Stress, 2nd ed. (G. Fink, Ed.) as "an imbalance between oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signaling and control and/or molecular damage."

titative measures of disease outcome (11, 14, 19, 41, 42, 49, 55, 62, 67).

Although many have argued that more or better antioxidants are needed, our research on thiol/disulfide redox states suggests that a better clinical definition and/or redefinition of oxidative stress may be needed to resolve this apparent contradiction. In this review, I first describe our studies on the use of GSH/GSSG redox and cysteine/cystine (Cys/CySS) redox to quantify oxidative stress. With this assay (31), as well as other quantitative measures of oxidative stress, prescreening to detect oxidative stress could be used to study antioxidant interventions in individuals who have a quantifiable oxidative stress. This would allow testing of antioxidants similarly to that used in drug development (*e.g.*, where an experimental anticancer drug is tested in individuals with cancer rather than in the population in general). Use of parameters such as plasma GSH redox and Cys redox to characterize oxidative stress can potentially provide a rational basis to identify individuals who may benefit from strategies designed to protect against oxidative stress.

Second, I describe studies showing that redox signaling and control occurs through discrete redox pathways within cells (18, 21, 47). This creates the possibility that oxidative stress involving the disruption of redox circuitry could occur without an overall imbalance of pro-oxidants and antioxidants. Recognition of the critical roles of redox signaling and control in fundamental homeostatic mechanisms (16) forces the conclusion that damage to macromolecular machinery is not the only way that oxidative stress can cause disease; rather, the disruption of homeostatic control and signaling can lead to metabolic pathway and organ specificity in oxidative diseases. Thus, oxidative stress can cause organ-specific and pathway-specific toxicity related to processes such as embryogenesis and development, inappropriate apoptosis, altered cell cycle control, immune dysfunction, uncontrolled fibrotic processes, altered membrane permeability, and barrier functions. The definition of oxidative stress must eventually shift from the view of a global imbalance of pro-oxidants and antioxidants to one that addresses disruption of specific redox signaling and control pathways. Because the latter can occur without a global imbalance, a re-definition of oxidative stress can be expected to enhance development of therapeutic strategies for targeted control of oxidative stress in disease prevention.

PLASMA GSH/GSSG AND CYS/CYSS REDOX STATES PROVIDE USEFUL CLINICAL MEASURES OF THE BALANCE OF OXIDATIVE REACTIONS AND ENDOGENOUS ANTIOXIDANT DEFENSES

Extensive research on products of oxidative damage and protective antioxidant systems has provided multiple assays that are useful to characterize oxidative stress. Despite considerable effort to validate these assays, consensus is not available concerning which is most suitable for routine clinical assessment of oxidative stress. A major difficulty is that most do not assess the balance of pro-oxidants and antioxidants, but rather focus on either oxidants and oxidation products or antioxidants and antioxidant systems. A simple classification of assays into five different types is given in Fig. 1. These include (clockwise from lower left) antioxidant enzyme systems, small molecule antioxidants, antioxidant/oxidant balance, reactive oxidants, and products of oxidative damage.

Disease-oriented research more frequently uses assays from the pro-oxidant side, while nutrition research is more often focused on the antioxidant side. On the pro-oxidant side of the balance, assays are available to measure reactive oxy-

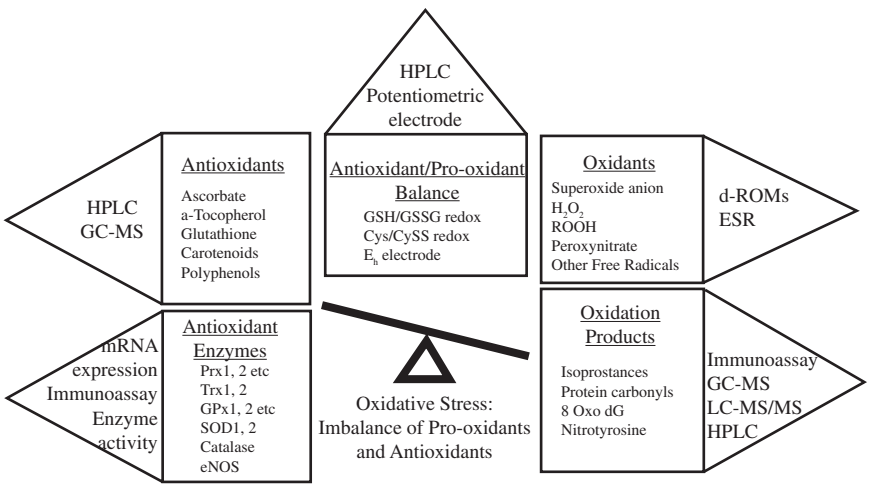

FIG. 1. Measurement of plasma GSH/GSSG redox is an example of one of five general approaches for clinical assessment of oxidative stress, including measurement of (A) antioxidant enzymes, (B) low molecular weight antioxidants, (C) the balance between pro-oxidants and antioxidants, (D) oxidants, and (E) products of oxidative damage. The GSH/GSSG redox state is calculated from measured concentrations of GSH and GSSG using the Nernst equation and expressed in mV. Cysteine redox state (Cys/CySS redox) is an analogous measure of balance between oxidants and pro-oxidants (*central panel*). GSH redox and Cys redox are not equilibrated; GSH redox is a more proximal indicator of tissue oxidative stress, while Cys redox more directly reflects oxidative processes in the extracellular fluid (32). In principle, an estimate of the antioxidant/oxidant balance could also be obtained using potentiometric electrodes.

gen species and products of lipid peroxidation, protein oxidation, and DNA damage. Free radicals can be measured by spin-trapping and electron spin resonance spectroscopy, but this is not convenient for clinical studies. On the other hand, a simple colorimetric assay to measure preformed reactive species in the blood (d-ROMs and related proprietary forms of this assay) provides a rapid and sensitive means to quantify oxidants that react with phenylenediamine (4). This assay could allow on-site screening of individuals for experimental antioxidant trials. Assays for products of oxidative damage include those for lipid peroxidation. These measure aldehyde products [*e.g.*, colorimetric assay for TBARS (15)], immunoassays for MDA-modified proteins, HNE-modified proteins, and characteristic hydrocarbons (gas chromatography of ethane, pentane; mass spectrometry of F2α-isoprostanes) (40, 45). Protein carbonyls formed by oxidative reactions can also be measured following derivatization with hydrazine (3, 39). A well-characterized method using stable isotopic dilution mass spectrometry provides accurate quantitative measures of nitrotyrosine residues in proteins (56), which are formed by reaction of proteins with peroxynitrite. Oxidative DNA damage is often measured by HPLC or ELISA of 8-hydroxyguanine or 8-hydroxydeoxyguanosine and by measurements of damage to mitochondrial DNA.

On the antioxidant side, numerous assays are also available for a broad range of antioxidants and antioxidant systems. Principal among these are analytic procedures for the dietary antioxidants vitamin C and vitamin E (tocopherols and tocotrienols). Assays are available for many other dietary chemicals that can function as antioxidants, including large groups of carotenoids and polyphenols, with hundreds of different chemical species. Assays are also available for a large number of endogenous enzymatic antioxidant systems. These include systems for elimination of peroxides (GSH peroxidases, peroxiredoxins, and catalase) and enzymes to eliminate superoxide (MnSOD, CuZnSOD). A range of endogenously generated small molecules that function as antioxidants, including coenzyme Q, glutathione, bile pigments, and uric acid, can also be measured. However, the large number of antioxidant systems limits the utility of antioxidant assays for assessment of oxidative stress under clinical conditions. This may be resolved with newer, high throughput systems, linking antioxidants to protection of specific redox-sensitive components.

Use of GSH/GSSG redox to measure the balance of pro-oxidants and antioxidants

Because the above assays do not provide a measure of the balance of pro-oxidants and antioxidants, we focused on quantification of oxidative stress in terms of the balance of the endogenous GSH/GSSG antioxidant system (31). GSH is used to eliminate peroxides, maintain thiol/disulfide redox state of proteins, and maintain the redox state of ascorbate and (indirectly) vitamin E in their reduced and functional forms. Thus, GSH has a very central role as an antioxidant. The product of GSH oxidation, GSSG, is reduced back to GSH by GSSG reductase, an NADPH-dependent enzyme that is ubiquitously distributed in tissues. Release of both GSH and GSSG from tissues to extracellular space occurs as a function of the respective tissue concentrations. Under conditions where GSH concentration is low in tissues, GSH release into the plasma decreases. Conversely, under conditions where GSSG is increased in cells, GSSG release into plasma increases. Although the steady-state concentrations of both GSH and GSSG in the plasma are not simple functions of tissue concentrations, tissue steady-state balance of GSH and GSSG in plasma can provide a useful indicator of oxidative stress because this balance contains components directly reflecting the availability of GSH to protect against oxidative reactions and the generation of GSSG from oxidative reactions.

Methodology for determination of GSH/GSSG redox in human plasma

GSSG concentration in plasma is very low (<200 μ*M*) and difficult to measure. A commonly used GSSG reductase-dependent enzymatic assay for GSSG in plasma does not discriminate between GSSG and the cysteine–glutathione disulfide (CySSG), which is also present in plasma. To allow more direct measurement of plasma GSSG, we developed an HPLC method with fluorescence detection that has adequate sensitivity to measure low nanomolar concentrations of GSSG (33). Using the measured GSSG and GSH values in plasma, we calculate the redox potential (E_h) of the GSH/ GSSG couple using the Nernst equation; we often refer to the E_h as the "redox state" in place of "redox potential" to emphasize that these are steady-state estimates and not equilibrium values. The E_h, rather than the GSH/GSSG ratio, is a preferred expression because the stoichiometry for 2-e^- transfers, such as the reduction of H_2O_2, is 2GSH:GSSG. The use of this value for GSH redox allows comparison of the reducing force (E_h) available from the GSH/GSSG couple to any other biologic redox couple. The redox state values give no information concerning the kinetics of interaction of redox systems but do provide an indication of the direction of electron flow and whether systems are close to equilibrium. Sample collection, storage, and processing have been extensively studied and are described in detail (31, 33). The calculated redox potential for plasma GSH/GSSG in healthy individuals aged 25–35 years was -137 ± 9 mV (32). Measurement of week-to-week variation within young healthy individuals showed a standard deviation of 3.2 mV.

GSH/GSSG redox association with age

In a study of age-related macular degeneration (AMD), we made the surprising finding that substantial oxidation (approximately 25 mV) was apparent in individuals >60 compared to <43 years old (51). A non-AMD control group had a large number of individuals being treated for diabetic retinopathy and these individuals were about 20 mV more oxidized than similarly aged individuals without known disease. The magnitude of difference is remarkable in that a 30 mV change is sufficient to result in a 10-fold change in ratio of a protein dithiol/disulfide motif (31) and could have significant impact on protein function.

In a follow-up study, we examined GSH/GSSG redox in 125 individuals aged 18–93 years, with approximately 20 individuals per decade and equal distribution of males and

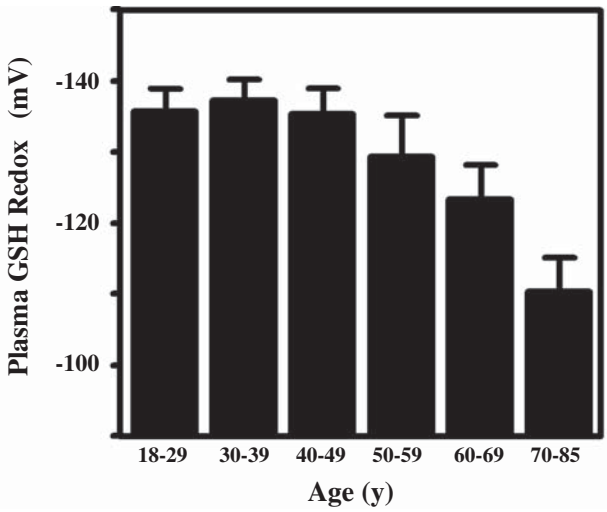

FIG. 2. Mean plasma GSH redox becomes progressively oxidized with age after 45 years. Measurements in healthy individuals show that little variation occurs among younger individuals, but after 45, oxidation occurs at about 0.7 mV per year (35). Cys/CySS redox also becomes progressively oxidized with age, but this oxidation occurs throughout the age range from 18 to 93 years and at a slower rate (0.2 mV per year).

females (35). The results showed that GSH/GSSG redox was oxidized in association with age after 45 years (Fig. 2). The average rate of change was 0.7 mV/y (31).

GSH/GSSG redox association with oxidative stress

Examination of plasma antioxidant status and GSH/GSSG redox after high-dose chemotherapy and bone marrow transplantation (29) showed that plasma tocopherols and GSH concentration decreased, and GSH/GSSG redox became more oxidized acutely and during the 3 weeks after treatment. The principal therapeutic agent in these studies was cyclophosphamide, an agent known to decrease GSH and cause oxidative stress. The extent of oxidation was greater with standard high-lipid parenteral nutrition (PN) than with the identical PN with low lipid content. The study showed that the oxidative stress induced by high-dose chemotherapy caused a significant oxidation of GSH/GSSG redox and that the lipid-rich PN preparation may induce a further oxidation. Thus, the results directly show that plasma GSH redox is oxidized during oxidative stress in humans.

Independent evidence that plasma GSH/GSSG redox state is a marker of oxidative stress in humans comes from a study of cigarette smoking (43). We examined the redox states of the GSH/GSSG and Cys/CySS couples in plasma of smokers and nonsmokers between the ages of 44 and 85 years (n = 78 nonsmokers, n = 43 smokers). The GSH concentration was lower in smokers (1.8 ± 1.3 μ*M*) than in nonsmokers (2.4 ± 1.0; $p < 0.005$), and GSH/GSSG redox was more oxidized in smokers (−128 ± 18 mV) than in nonsmokers (−137 ± 17 mV; $p = 0.01$). Cys was also decreased in smokers (9 ± 5 μ*M*) compared to nonsmokers (13 ± 6 μ*M*; $p < 0.001$), and the Cys/CySS redox in smokers (−64 ± 16 mV) was also more oxidized than nonsmokers (−76 ± 11 mV; $p < 0.001$). While the oxidation of GSH/GSSG can be explained by the role of GSH in detoxification of reactive species in smoke, the more extensive oxidation of the Cys pool shows that smoking has additional effects on sulfur amino acid metabolism. Together with the data on oxidation following chemotherapy, the results support the interpretation that plasma GSH/GSSG and Cys/CySS redox states provide useful measures of oxidative stress *in vivo* in humans.

GSH/GSSG interaction with Cys/CySS

To determine the interactions of the GSH/GSSG and Cys/CySS pools, thiol and disulfide forms were measured in plasma from 24 healthy individuals aged 25–35 years (32). In this study, GSH concentration correlated with Cys concentration, but no correlations were observed between GSSG and CySS or between the reduced and oxidized components. Redox state values (E_h) calculated using the Nernst equation showed that the plasma GSH/GSSG redox state (−137 ± 9 mV) was considerably more oxidized than values for tissues and cultured cells (−185 to -258 mV). The redox state for Cys/CySS (−80 ± 9 mV) was 57 mV more oxidized than that for GSH/GSSG. The lack of equilibration between the GSH/GSSG and Cys/CySS pools supports the interpretation that these plasma redox values are dynamic indicators of the systemic balance between oxidative and antioxidant processes (32). **Because the GSH and Cys redox systems are not in equilibrium, the data suggest that the concept of a single balance between pro-oxidant and antioxidant systems is an unacceptable simplification for consideration of oxidative stress.**

Definition of oxidative stress in terms of GSH redox or Cys redox

For young healthy individuals, 2 standard deviations is about 18 mV for both GSH and Cys redox. Thus, as a starting point for discussion, one may select a value ≥−119 for GSH redox or a value ≥−62 mV for Cys redox to identify individuals with oxidative stress (Fig. 3). Adoption of such criteria will require additional research on this concept and critical evaluation. In addition, there will be a struggle against the point of view that oxidative stress is not quantifiable (59). However, common quantitative standards would advance clinical utility of oxidative stress markers; based upon available data, GSH/GSSG and Cys/CySS redox state values provide a reasonable place to begin.

The values suggested as initial criteria are based upon a small number of studies on a small number of individuals using only one method for analysis. Clearly, additional studies are needed to obtain consensus. For instance, values of ≥−119 for GSH redox and ≥−62 mV for Cys redox may be too conservative in that only about half of healthy 70-year-old individuals would be categorized as having oxidative stress. On the other hand, essentially all smokers and type 2 diabetics older than 45 years would be classified by at least one of these criteria as having oxidative stress. An alternative approach would be to establish age-specific criteria for oxidative stress. Collection of additional data from representative populations under controlled conditions will allow better criteria to classify individuals based upon redox measurements.

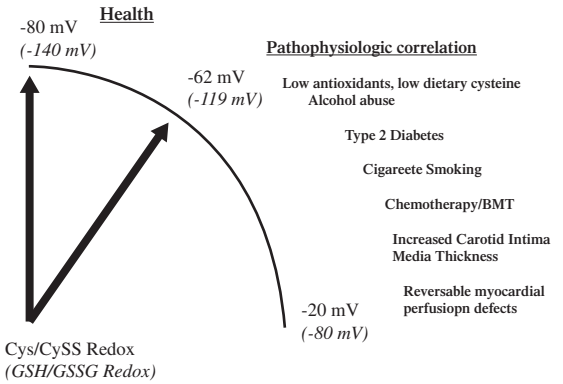

FIG. 3. Classification of oxidative stress in individuals. At present, no quantitative means is available to characterize individuals with oxidative stress, and systematic studies to do this are needed. As a starting point for discussion we may consider individuals oxidized more than 2 standard deviations from the mean of young healthy individuals to have oxidative stress. This is equivalent to ≥ -119 mV for GSH/GSSG redox state or ≥ -62 mV for Cys/CySS redox state in a small study of individuals aged 25–35 years (32). Chemotherapy, type 2 diabetes, and cigarette smoking have been associated with oxidation of GSH redox state or Cys redox state. Recent data also show that early signs of cardiovascular disease are associated with oxidation of GSH and/or Cys redox (2, 6).

Nutritional and therapeutic control of plasma redox states

The more reduced redox state of the plasma GSH/GSSG couple indicates that this pool more directly reflects pro-oxidant/antioxidant balance in tissues, while the more oxidized Cys/CySS couple more directly reflects oxidative processes ongoing in the extracellular space. Stress hormones stimulate GSH release from liver (58) and transport into circulation from the intestinal lumen (7, 20); however, there is no information on whether hormonal effects on transport could be therapeutically useful to control plasma GSH redox or to improve *in vivo* protection against oxidative stress. On the other hand, oral supplementation of Cys at three times the Recommended Dietary Allowance caused the plasma Cys to increase and the calculated redox state to become more reduced (61). Other studies show that plasma GSH can be increased by supply of Cys precursors, glutamine, and inducers of GSH synthesis, and studies are needed to determine whether these could be useful to improve plasma GSH and Cys redox states. Consequently, available data indicate that maintenance of optimal sulfur amino acid supply, as well as other nutritional factors, may be an important factor in regulation of redox state.

Studies of Bannai and co-workers (8) have provided important insight into the function of the transport system, x_c^-, in cellular Cys supply. Cells require a constant supply of Cys for protein synthesis. The liver can convert Met to Cys by the transulfuration pathway, but other cells must be supplied with either Cys or CySS. x_c^- exchanges Glu for the anionic form of CySS. The system is composed of two proteins, xCT and the heavy chain of the 4F2 cell surface antigen (64), with the former inducible by oxidants (52) and amino acid deprivation (53). Thus, in cells expressing x_c^-, either oxidative stress or amino acid deprivation cause increased uptake. CySS taken up by fibroblasts and macrophages is rapidly reduced to Cys and used for GSH synthesis. The combination of CySS uptake and release of Cys or GSH provides a means to reduce extracellular thiol/disulfide redox state, a process earlier termed a Cys–CySS shuttle mechanism (13, 48). Recent studies (54) of an x_c^- knockout mouse showed that plasma Cys/CySS redox state was more oxidized and that fibroblasts were impaired in capability to maintain GSH. Thus, the results show that the CySS transport system x_c^- is a critical transport system contributing to regulation of plasma thiol/disulfide redox state.

SYSTEMATIC VARIATION OF EXTRACELLULAR CYS/CYSS REDOX STATE CAN ALTER FUNDAMENTAL BIOLOGIC PROCESSES

Regulation of extracellular Cys/CySS redox state

Based upon the knowledge that the Cys/CySS redox couple quantitatively represents the largest pool of low molecular weight thiols and disulfides in plasma, and that Cys and CySS are used as sulfur amino acid precursors in cell culture medium, we designed experiments to determine the effects of variation in Cys/CySS redox on cell functions over the physiologic range found *in vivo* in human plasma. The experiments used total Cys and CySS at concentrations typically present in cell culture (200–400 μ*M*) and varied the concentrations of each so that the total pool size was constant in terms of cysteine equivalents and the thiol/disulfide redox potential was varied from −150 to 0 mV. The measured Cys/CySS redox range in human plasma is −120 to −20 mV (35, 44), so that this experimental range from −150 to 0 mV covers the entire physiologic range and extends to somewhat more reducing and oxidizing conditions.

Studies to evaluate the stability of Cys redox state in the culture medium showed that cells were able to control extracellular redox state over time, adjusting the redox state to a value approaching −80 mV, that is, the average value found in human plasma (30). The rate of approach to the steady state Cys/CySS redox varied considerably. Under conditions known from empirical data to promote growth, most cells achieve a steady state in the range of −60 to −100 mV within 24 h.

These observations provide strong evidence that the redox potential of the Cys/CySS pool in human plasma, which averages −80 mV, is a fundamentally important parameter for cell functions (44). At present, the only system known to function in a quantitatively important way to control extracellular redox regulation is the x_c^- system described above (54). This system is an example of one of at least four processes that could contribute to plasma GSH/GSSG and Cys/CySS redox states, which include transport of disulfides in and out of tissues, transport of thiols in and out of tissues, extracellular oxidation of thiols, and reduction of disulfides to thiols on the extracellular surface of cell membranes. A number of Cys and CySS transport systems are known (8), and GSH and GSSG transport systems have been described (50). Considerable

attention has been given to the possible role of GSH efflux as a means to reduce CySS to allow uptake of Cys in cells without CySS uptake. The latter cannot provide a complete explanation for extracellular redox regulation, however, because extracellular Cys/CySS redox was regulated in a similar manner in cells without and with depletion of cellular GSH with buthionine sulfoximine (5). A more reasonable alternative is that a plasma membrane oxidoreductase can use cellular reductants to reduce CySS to Cys without transport. Such a system could directly reduce CySS or transfer electrons through another carrier. For instance, thioredoxin-1 facilitates reduction of CySS and uptake in lymphoid cells (25). Cys and GSH oxidation can occur by auto-oxidation as well as catalyzed by ceruloplasmin and a plasma membrane thiol oxidase found in kidney and intestines (38). Considerable effort will be needed to establish the quantitative importance of these different processes to account for the relatively tight regulation of the steady-state redox of Cys/CySS and GSH/GSSG in plasma.

A potentially important *in vitro* observation is that the approach to the physiologic steady-state value is enhanced by addition of growth factors (28, 30). Studies with Caco2 cells showed that this rate of approach was enhanced by IGF-1, EGF, and KGF, growth factors that stimulate the rate of proliferation in this cell line. Furthermore, the extracellular E_h in cell culture was found to vary in association with the life cycle of CaCo2 cells (48). Thus, results suggest that the variation of the extracellular Cys/CySS redox is connected with signaling and control mechanisms that influence cell proliferation.

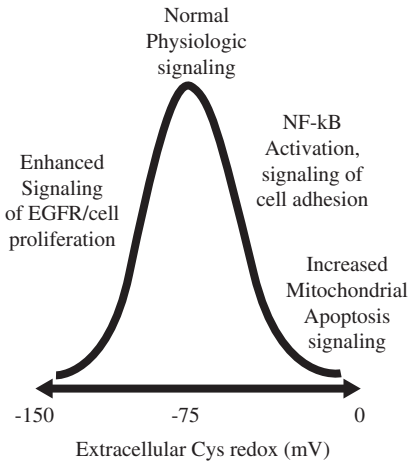

FIG. 4. *In vitro* cell studies show that variation in Cys redox state over the physiologic range found in vivo in plasma alters fundamental cell functions. More oxidized values are associated with increased adhesion of monocytes to vascular endothelial cells (18) and increased sensitivity to oxidant-induced apoptosis (27). More reduced values stimulate cell proliferation (28, 30).

Effects of variation in extracellular E_h on cell functions

Because cells control extracellular Cys/CySS redox in cell culture, yet plasma Cys/CySS varies over a range of about 100 mV in humans, we felt that it would be important to know whether variation in extracellular Cys/CySS redox had effects on cell functions. To date, we have explored three complex cell processes with controlled variations in extracellular redox, and these results show that cell proliferation, cell adhesion, and apoptosis vary as a function of extracellular E_h over the physiologic range found *in vivo* (Fig. 4). In each case, the extent of deviation of E_h from the physiologic mean value elicited cell signaling (*e.g.*, by P44/42 MAPK pathway or NF-κB).

In these studies, we used an experimental model with constant total Cys + CySS pool size, expressed in Cys equivalents, and varied concentrations of Cys and CySS to obtain initial redox state values from 0 to −150 mV (18, 27, 28, 30). Because cells regulate the extracellular redox state, these initial values changed toward the mean physiologic value with time, necessitating frequent replacement of culture medium. In these studies, distinction between extracellular events and intracellular events is not trivial. The strategies that we have used include: (a) measurement of cellular GSH concentration and GSH/GSSG redox state under all conditions to determine whether extracellular effects were mediated through this central cellular thiol/disulfide redox system; (b) pretreatment with nonpermeant alkylating reagents to determine whether effects were sensitive to modification of extracellular thiols; (c) maintenance of constant E_h with extracellular pool size set at either 100, 200, or 400 μ*M* Cys equivalents to vary concentrations of Cys and CySS without change in E_h; and (d) measurement of ROS generation as a function of extracellular E_h. The experimental model is complex in that systematic variation in Cys/CySS redox has associated changes in Cys and CySS concentrations and also in Cys/CySS ratio. To minimize this problem, relatively high Cys and CySS concentrations were used to saturate transport systems where possible, and experiments were performed with different total pool sizes but with constant E_h. None-the-less, because the concentrations of Cys and CySS changed during the course of experiments, the results do not completely distinguish between effects due to Cys concentration, CySS concentration, and E_h. On the other hand, it should be noted that both Cys and CySS concentrations vary little under physiologic conditions *in vivo*. Thus, the component of growth stimulation that is unrelated to redox (*i.e.*, that due to increased Cys or CySS uptake) is likely to be mediated principally by activity of relevant transporters and not by changes in plasma Cys and CySS concentrations. While additional studies are needed, the following summarizes the available data concerning the effects of extracellular Cys/CySS redox on proliferation and other cellular functions.

Cell proliferation as a function of extracellular Cys/CySS redox

In cell culture, O_2 partial pressure, pH, and redox potential in the culture medium determine maximal cell density (24). Hwang and Sinskey (24) showed that when O_2 and pH are controlled, maximal cell density could be obtained by controlling E_h through addition of Cys. Numerous studies show that redox systems are critical for cell proliferation and that this involves requirements for thioredoxin, GSH, and cysteine, probably at multiple sites in signaling and cell function.

Physiologically, most cells are exposed to and dependent upon Cys and CySS as the major thiol precursors for protein and GSH synthesis. Adequate supply of these precursors for protein synthesis and maintenance of cellular GSH is essential for cell division, and Cys or CySS concentration in cell culture medium can alter cellular GSH and cell proliferation rates. However, when we varied extracellular Cys/CySS redox state over the *in vivo* physiologic range with constant Cys + CySS pool size, we found that CaCo2 cell proliferation rate at −150 mV was twofold that at 0 mV, with no detectable change in cellular GSH (30). Thus, even though in other systems, Cys and/or CySS are essential for GSH synthesis and proliferation, the data were not consistent with the proliferative effect being due to limitation of Cys or CySS for GSH supply. Experiments with HT29 cells as well as fibroblasts and normal human retinal pigment epithelium showed the same pattern of response, although the magnitude of growth stimulation due to E_h was variable. Consequently, extracellular Cys/CySS redox state could be fundamentally important in control of cell proliferation rate. This effect may be small compared to potent effects of growth factors studied *in vitro*, but small effects persisting over years or decades can be important in control of cell populations *in vivo*. This regulation of proliferation by circulating Cys/CySS redox state in plasma could be important in maintaining cell populations in tissues, stimulating stem cell growth, and enhancing tissue repair. Alternatively, redox stimulation of precancerous cells could promote tumor development (44).

Redox-dependence of cell growth signaling

To investigate mechanisms involved in redox-dependent cell growth, we performed experiments with Caco2 cells in which growth stimulation was provided by changing the Cys/CySS redox potential (47). Previous research showed that stimulation of proliferation occurred with no apparent effect on cellular GSH, and that this stimulation was lost upon addition of epidermal growth factor (EGF) (30). To determine whether a more reduced extracellular Cys/CySS redox state activated the mitogenic p44/42 MAPK pathway and whether this was signaled through the EGF receptor (EGFR), Caco2 cells were exposed to the same range of extracellular redox conditions from −150 to 0 mV (47). In the absence of added growth factors, the most reduced (−150 mV) redox state induced an 80% increase in EGFR phosphorylation, and this was followed by a marked increase in phosphorylation of p44/42 MAPK. Inhibitors of EGFR (AG1478) and p44/42 MAPK (U0126) phosphorylation blocked redox-dependent p44/42 phosphorylation, indicating that −150 mV extracellular redox state induced signaling through EGFR. These effects were inhibited by pretreatment with a nonpermeant alkylating agent (4-acetamido-4'-maleimidylstilbene-2, 2′-disulfonic acid), showing that signaling involved thiols accessible to the extracellular space. Redox-dependent phosphorylation of EGFR was completely prevented by a metalloproteinase inhibitor (GM6001), and an antibody to the EGFR ligand, transforming growth factor-α (TGFα) partially inhibited the phosphorylation of p44/42 MAPK by redox. TGFα was also found to be increased in culture medium at more reduced redox states. Thus, the data show that a redox-dependent activation of metalloproteinase can stimulate the mitogenic p44/42 MAPK pathway by a TGFα-dependent mechanism (47).

Effect of oxidized extracellular Cys/CySS on monocyte adhesion to endothelial cells

Atherosclerosis is associated with Cys/CySS oxidation, and our recent data show that oxidation of Cys/CySS can potentially contribute in a causal way to atherosclerosis development (18). We examined the function of extracellular Cys/CySS redox state in regulation of the early events of atherosclerosis using cultured aortic endothelial cells and monocytes as a vascular model system. Endothelial cells were exposed to initial E_h from −150 mV (most reduced) to 0 mV (most oxidized), and molecular processes associated with cell adhesion were measured. In comparison to more reduced E_h, E_h of Cys/CySS equal to 0 mV stimulated H_2O_2 but not nitric oxide (NO) production. This condition (0 mV) also activated NF-κB, increased expression of adhesion molecules (ICAM-1, PECAM-1, P-selectin), and stimulated monocytes binding to endothelial cells. Change in extracellular E_h from 0 to −150 mV regulated thiol/disulfide redox states of extracellular membrane proteins and H_2O_2 production, indicating that variation in extracellular E_h is detected and signaled at the cell surface. The results showed that the extracellular thiol/disulfide E_h of Cys/CySS couple can play a key role in regulating early events of atherosclerosis and, therefore, suggest that Cys redox can be useful as a potential marker for vascular disease risk.

Effect of oxidized extracellular Cys/CySS redox on peroxide-induced apoptosis

Oxidative stress is known to contribute to progression of age-related macular degeneration (1). *In vitro* studies showed that oxidative stress induces apoptosis in retinal pigment epithelial (RPE) cells (26, 46), the cells lost first in development of age-related macular degeneration. Therefore, we performed experiments to determine whether RPE cells exposed to more oxidizing physiologic Cys/CySS redox potentials were more susceptible to oxidant-induced apoptosis (27). The RPE cells were incubated in culture medium with controlled E_h established over the range of −16 mV (most oxidized) to −158 mV (most reduced). Results showed that RPE cells were more sensitive to oxidant-induced apoptosis induced by *tert*-butylhydroperoxide (*t*BH) under the more oxidized extracellular conditions (E_h > −55 mV) compared to the reduced conditions (E_h < −89 mV). Data indicated that apoptosis was mediated by the mitochondrial pathway because loss of mitochondrial membrane potential ($\Delta\Psi_m$), release of cytochrome *c* and activation of caspase 3 following *t*BH treatments all increased under the more oxidized conditions. In contrast, extracellular redox state did not affect expression of key ligand-mediated apoptosis machinery, including Fas and FasL. The results show that variation of extracellular E_h, over the range found *in vivo* in human plasma, can contribute to a decline in cell populations by enhancing sensitivity to oxidant-induced apoptosis (27). Enhanced sensitivity to apoptosis could provide a general mechanism whereby a more oxidized redox state could contribute to the degenerative changes that are associated with aging.

Research needs for plasma GSH redox, Cys redox, and disease outcome

The research summarized above provides evidence that GSH redox and Cys redox are useful quantitative clinical measures of oxidative stress. The results show that redox parameters become oxidized in humans with increasing age, are oxidized in humans in association with conditions known to cause oxidative stress (*e.g.*, chemotherapy and cigarette smoking) and are oxidized in association with important pathologic processes (*e.g.*, type 2 diabetes and cardiovascular disease) (44) (Fig. 3). *In vitro* studies provide evidence that redox parameters reflect function of fundamental redox signaling and control processes (Fig. 4). Accordingly, measurement of GSH and Cys redox states can potentially provide useful information concerning individual health. However, such measurements are useful clinically only if criteria are established that indicate a need for intervention, and interventional strategies are available to correct the redox state. At present, no data are available to show that individuals with more oxidized redox state are at increased risk of disease or that interventions that may normalize an oxidized redox state provide any beneficial effect. Thus, GSH and Cys redox states are among the best available measures to quantify oxidative stress according to the current definition of oxidative stress because these parameters measure the balance of oxidative processes interacting with the central glutathione antioxidant system and the reductive processes functioning to maintain homeostasis. As discussed above, cutoff values are needed to classify healthy and unhealthy redox, and specific studies are needed to determine whether disease outcomes can be altered by interventions to stimulate reduction of plasma E_h in individuals with values more oxidized than the cutoff values.

AN IMPROVED DEFINITION: OXIDATIVE STRESS IS A DISRUPTION OF REDOX SIGNALING AND CONTROL

Limitations to the definition of oxidative stress as an imbalance of pro-oxidants and antioxidants

The lack of equilibration between the two key thiol/disulfide systems in plasma described above indicates that the concept of oxidative stress as a global shift in the balance of pro-oxidants and antioxidants, while useful, is fundamentally limiting in the quest for improved prevention and intervention in disease processes with important oxidative components. The balance concept implies that distinct biologic systems respond in the same way to decreased pro-oxidants and increased antioxidants. If mechanisms of oxidative stress were limited to free radical damage to macromolecular machinery, this concept would probably be adequate. However, oxidative stress also involves effects on redox signaling. Multiple systems are involved, and there is no reason to assume that these systems would have the same sensitivities to oxidants or respond identically to antioxidants. The failed intervention trials with antioxidant supplements in humans (11, 19, 41, 42, 49, 55, 67) show that the imbalance concept is inadequate when applied to the role of antioxidants in protection against oxidative stress in human disease.

Experimental models have long revealed this problem. For instance, addition of excess iron to biologic systems causes oxidative stress regardless of antioxidant levels. Numerous studies are available to show that antioxidants become pro-oxidants under some *in vitro* conditions. Available data indicate that the balance concept is only valid as a definition for oxidative stress under conditions of deficiency of antioxidants. Indeed, deficient concentrations of vitamin C and E, as well as conditions that limit GSH and other antioxidant systems such as NADPH supply, peroxidases, and superoxide dismutases, are associated with disease processes that can benefit from antioxidants. Such conditions may be better viewed in terms of threshold requirements for specific types of antioxidants rather than a reflection of a global pro-oxidant or antioxidant balance. Together, these different lines of reasoning suggest a need to redefine oxidative stress.

Alternative definition for oxidative stress

An alternate definition for oxidative stress is "a disruption of redox signaling and control." Considerable evidence accumulated in the past 15 years shows that the reactive oxygen species (ROS) and reactive nitrogen species (RNS) function in redox signaling. Because these reactive species are present at very low concentrations in cells and are difficult to directly measure, we used GSH/GSSG redox state as a means to quantitatively define oxidative stress in cultured cells (37). These studies provided a useful way to characterize the balance of processes in cells; however, extension of the steady-state redox measurements to the Trx-1 and Cys/CySS redox couples showed that these thiol/disulfide systems are not in redox equilibrium in cells (34, 48, 66). Consequently, the results provide mechanistic data that challenge the central concept that oxidative stress can be described in terms of a balance of pro-oxidants and antioxidants.

Redox circuitry model

A redox circuitry model with control nodes and discrete pathways integrates concepts of global redox control with specificity in redox signaling. Although most studies of signal transduction mechanisms have an underlying assumption of specificity, evidence for specificity in redox signaling mechanisms is relatively limited. Most of the ROS and RNS thought to be involved in redox signaling are relatively nonspecific in their reactivities. Moreover, conditions in which exogenously added oxidants provide evidence for redox signaling, such as studies involving addition of hydrogen peroxide, result in global oxidative changes. In other words, there is a lack of specificity in oxidation of macromolecules under conditions where peroxide addition results in altered signaling. Similarly, evidence in support of redox signaling mechanisms obtained by addition of nonspecific reductions, such as *N*-acetyl-L-cysteine (NAC), provide little evidence for specificity in redox signaling because millimolar concentrations of NAC cause global redox changes. Genetic and molecular biology studies provide evidence for requirement of specific

components in signaling pathways, and site-directed mutagenesis studies provide evidence for essential cysteines, but these two approaches do not establish whether redox processes are controlled by global redox parameters or rather by pathway-specific oxidation-reduction reactions. Consequently, even though one would like to assume that there is specificity in redox signaling, solid scientific evidence that such specificity occurs remains limited.

A redox signaling pathway, or redox circuit, involves at least three critical components, a redox-signal generator, a redox signal, and a redox signal sensor. Such a pathway could involve superoxide as a redox signal, with a specific enzyme that generates superoxide, and a protein that is oxidized or reduced by superoxide and functions as a sensor. Similarly, hydrogen peroxide could function as a redox signal, with a specific enzyme that generates peroxide and a protein that senses peroxide. If the sensors are sufficiently selective in their reactivity with hydrogen peroxide or superoxide, these circuits could exist within the same physical space and transmit biologic information independently. The pathways could be interconnected in multiple ways and respond similarly to imposed perturbations such as supply of oxygen (altering signal generation) and NAC (altering signal detection). Therefore, the individual circuits would not be truly independent pathways but rather be interacting components in a more complex network.

Thiol/disulfide systems as redox signals

An important condition for functioning as a signaling molecule or ion is that the signal usually must be present at very low concentrations (*i.e.*, submicromolar) to allow rapid and sensitive control. ROS such as superoxide and hydrogen peroxide clearly fulfill this requirement. However, thiol/disulfide components such as Cys, CySS, GSH, and GSSG, do not fulfill this criterion. In cells, GSH concentrations are millimolar and GSSG, cysteine, and cystine concentrations are micromolar. These concentrations are high so that these metabolites are not well-suited for intracellular signaling. On the other hand, change in thiol/disulfide redox state provides a mechanism that could serve in signaling because only a 30 mV change is needed to cause a 10-fold change in a dithiol/disulfide motif (31). Changes of >30 mV occur under various cellular conditions (37, 48, 65).

GSH redox during differentiation and apoptosis

Oxidation and depletion of the GSH/GSSG pool occur under toxicologic and pathologic conditions, and such changes are known to affect enzyme induction and cell proliferation. To quantify the magnitude of redox change that occurs during physiologic processes, we measured GSH, GSSG, cell volume, and pH, and used the Nernst equation to estimate the redox state of the GSH/GSSG pool in HT29 cells under different conditions of physiologic signaling (37). The results showed that the differentiating agent sodium butyrate resulted in a 60 mV oxidation of cellular GSH/GSSG redox state (from −260 to −200 mV), an oxidation sufficient for a 100-fold change in protein dithiols/disulfide ratio. The detoxification enzyme inducer benzyl isothiocyanate resulted in only a 12−16 mV oxidation in nondifferentiated cells but a 40 mV oxidation (to –160 mV) in differentiated cells. Changes in GSH redox state correlated with expression of glutathione *S*-transferase and NADPH:quinone reductase activities. The results show that redox changes in the GSH/GSSG pool are sufficient to allow this pool to regulate protein functions in response to physiologic stimuli. Studies of other cell types and tissues *in vivo* showed that GSH/GSSG redox is generally controlled over the same redox range as found in HT29 cells. Thus, the results suggested that GSH/GSSG redox could be a central component for global redox control. However, this appealing concept was shown to be overly simplistic when redox state analyses were performed for Trx-1.

Redox state of Trx-1

A study of redox states of GSH/GSSG and Trx-1 in Caco2 cells as a consequence of progression from proliferation to contact inhibition and spontaneous differentiation showed a significant decrease in GSH concentration, accompanied by a 40 mV oxidation of the cellular GSH/GSSG redox state (48). Use of Redox–Western blot methodology (65, 66) showed that the redox state of Trx-1 did not change under these conditions (48). Thus, in these cells, the two central cellular antioxidant and redox-regulating systems (GSH and Trx-1) are independently controlled and not in redox equilibrium. This observation means that the concept of a pro-oxidant/antioxidant balance cannot be unambiguously applied to central cellular antioxidant systems. The lack of equilibration provides the basis to conclude that there is independent control of redox-sensitive pathways.

Redox state of cellular Cys/CySS

The finding that GSH and Trx-1 are not in redox equilibrium prompted us to examine the redox state of Cys/CySS, another major cellular thiol/disulfide system (34). The results provided the unexpected finding that the Cys/CySS couple is substantially more oxidized than either GSH or Trx-1 couples (34). Moreover, while GSH/GSSG redox became oxidized by either inhibition of GSH synthesis with buthionine sulfoximine (BSO) or cysteine starvation, the Cys/CySS redox state changed very little. Thus, the redox state of cellular Cys/CySS is controlled independently of Trx-1 and GSH/GSSG.

Circuitry model for redox signaling

A redox circuitry model can be developed utilizing three thiol/disulfide nodes. Based upon these findings, we proposed a model for redox signaling with Cys/CySS as a distinct oxidizing node for redox signaling, along with Trx/TrxSS as a reducing node and GSH/GSSG as an intermediate, switchable node (34). The different thiol/disulfide nodes allow distinct redox signaling and control functions in analogy to the functions of the electron carriers NADH/NAD^+ and NADPH/$NADP^+$. The NADH/NAD^+ and NADPH/$NADP^+$ couples are maintained at different steady-state redox potentials in cells to provide different pathways of electron flow to support catabolism and anabolism simultaneously within the same aqueous compartment.

In the model in Fig. 5, activity of a protein can be switched by either (a) a dithiol/disulfide switch or (b) a thiol/S-thiyl

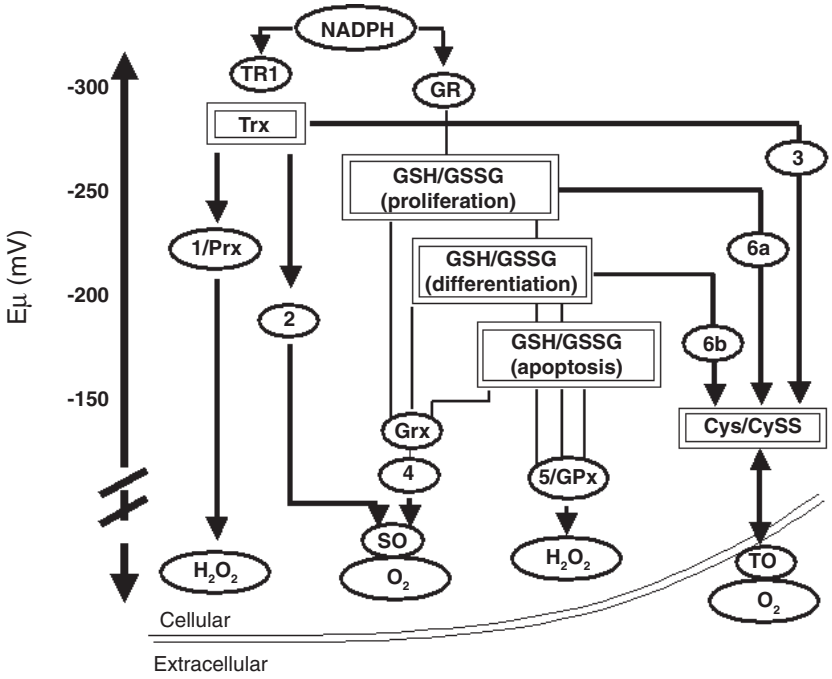

FIG. 5. Circuitry model for redox signaling and control. Measures of GSH Trx-1 and Cys redox states show that these couples are not in equilibrium in cells. Consequently, proteins that are rapidly reduced by one of these couples cannot rapidly interact with another couple, otherwise the redox couples would equilibrate. This allows for redox-sensitive proteins to function in discrete pathways. Redox switches could function by being oxidized by ROS such as hydrogen peroxide, by specific enzymes known as sulfhydryl oxidases (SO), or by the Cys/CySS couple, which is substantially more oxidized that Trx-1 or GSH/GSSG couples. Switches can thereby be classified according to reductant/oxidant combination as numbered 1–6. These classes of proteins would differ in sensitivity to changes in the major thiol/disulfide couples as well as control by specific enzymes. For instance, proteins with Trx as the donor (Classes 1–3) would all be dependent upon Trx activity and redox state, but Class 1 would respond to peroxides, while Class 2 would respond to specific O_2-dependent sulfhydryl oxidases, and Class 3 would respond to changes in oxidation of the Cys/CySS couple. Because Trx appears to be more reduced than GSH/GSSG under all conditions in cells, these switches may have a default reduced state, being switched on by one of the oxidation mechanisms. Classes 4–6 would differ in that they would be responsive to changes in GSH/GSSG redox state and may switch on or off due to the change in redox associated with the life cycle of the cell. Peroxiredoxins would be in class 1, reduced by Trx-1 and oxidized by H_2O_2. Class 2 would be proteins reduced by Trx-1 and oxidized by sulfhydryl oxidase. Class 3 switches would be proteins oxidized by Cys/CySS and reduced by Trx-1. Class 4 switches would have the characteristic of GSH peroxidases, oxidized by peroxides and reduced by GSH. Class 5 switches would be reduced by GSH, probably mediated by glutaredoxin, and oxidized by sulfhydryl oxidase. Class 6 would be oxidized by Cys/CySS and reduced by GSH/glutaredoxin. Mechanisms for regulation of Cys/CySS redox are not known but may involve a plasma membrane thiol oxidase (TO). See Ref. (34) for further description.

switch, with directionality controlled by coupling to a reduced (Trx-1 or GSH) or oxidized (ROS, O_2, or CySS) redox node:

(a) Pr-SS + reductant → Pr-$(SH)_2$ ("on" or "off", depending upon protein)

Pr-$(SH)_2$ + oxidant → Pr-SS (activity state reversed from above)

(b) Pr-SS-R + R'SH → Pr-SH + RSSR' ("on" or "off", depending upon protein)

Pr-SH + RSSR → Pr-SS-R (activity state reversed from above)

In this model, six different classes of signaling/control proteins can exist in terms of the reductant, oxidant combination: 1, Trx-1, ROS; 2, Trx-1, O_2; 3, Trx-1, CySS; 4, GSH, ROS; 5, GSH, O_2; 6, GSH, CySS (Fig. 3). Peroxiredoxins are reduced by Trx-1 and oxidized by H_2O_2, and have the character of a Class 1 redox signaling protein. Class 4 proteins include some glutathione *S*-transferases, which have a peroxidase activity that allows for sulfhydryl switching that could control processes such as binding to JNK. Sulfhydryl oxidases could function in signaling through sulfhydryl switching proteins coupled with either Trx-1 (Class 2) or GSH (Class 5). The relatively oxidized Cys/CySS redox state allows for *S*-cysteinylation of proteins to provide new classes of signaling proteins with Trx-1 (Class 3) or GSH (Class 6) as a reductant:

PrSH + CySS → PrSS-Cys + Cys (activity "on" or "off")

Pr-SS-Cys + GSH → PrSH + CySSG (activity opposite of above).

For such a scheme, CySSG, which is maintained at a very low concentration in cells, would be rapidly removed by reaction with GSH, Trx-1, or GSSG reductase. Equivalent reaction schemes in which CySS is used to oxidize dithiols to disulfides could also occur, countered by Trx-1 or GSH.

Because the three thiol/disulfide couples (Trx-1, GSH/GSSG, Cys/CySS) have different rates of reaction with different proteins, the results suggest that redox-dependent proteins exist in discrete redox circuits in cells. Hence, oxidative stress may be more appropriately defined in terms of disruption of redox circuitry rather than an imbalance of prooxidants and antioxidants.

MECHANISTIC DATA SUPPORT THE NEED FOR A NEW DEFINITION OF OXIDATIVE STRESS

Studies reviewed above show that thiol/disulfide redox state, *per se*, provides a signal affecting cell proliferation, cell adhesion, and sensitivity to apoptosis. These data alone do not suggest a need to redefine oxidative stress. However, both increased ROS and increased cellular GSH have been linked to proliferation, while numerous studies show that added ROS causes a decrease in GSH. This inconsistency is difficult to reconcile with the concept of a central balance of pro-oxidants and antioxidants because different studies associate increased ROS with both increased and decreased GSH. Research on thiol/disulfide redox states shows that apparent discrepancies can occur because there are multiple redox-sensitive pathways and specificity in redox signaling and control.

Evidence for discrete redox-signaling pathways

To investigate the roles of GSH/GSSG and Trx-1 in peroxide dependent signaling, we used cells that had been transfected with NADPH oxidase-1 (Nox1) and had constitutively high rates of H_2O_2 generation (17). The cells also had a constitutively active form of Ras, so the precise source of hydrogen peroxide generation is not known. Transfection of the cells with a redox-sensitive reporter construct containing ARE-4 from glutamate-cysteine ligase showed that hydrogen peroxide-dependent signaling occurred without detectable oxidation of either GSH/GSSG or Trx-1. Increased expression of catalase resulted in loss of detectable ROS signal, blocked activation of the reporter, and also had no effect on the GSH/GSSG or Trx-1 redox state. Thus, these experiments show that hydrogen peroxide-dependent signaling can occur through discrete redox-signaling pathways without measurable effect on the major thiol/disulfide control systems in cells (17).

Effects of high levels of H_2O_2

In contrast to the experiments with Nox-1-derived H_2O_2 generation, addition of exogenous H_2O_2 results in an extensive and parallel oxidation of both Trx-1 and GSH (65). Analysis of redox state in cell nuclei and cytoplasm with exogenously added H_2O_2 further showed that high doses of H_2O_2 oxidize nuclei as well as cytoplasm, and that the Trx-1 in these compartments recover over similar time course. Thus, high levels of oxidant are not selective in oxidation (65).

Effects of physiologic levels of ROS

Compartmentation is an important aspect of cell signaling mechanisms and recent advances allow investigation of compartmentation in redox signaling. The redox states of cytosolic and nuclear Trx-1 and mitochondrial Trx-2 were measured by Redox Western blot methodologies during endogenous ROS production induced by EGF signaling in a keratinocyte cell line (21). Glutathione redox state was measured by HPLC. Results showed that only cytosolic Trx-1 was significantly oxidized. Thus, the results demonstrate that EGF signaling involves subcellular compartmental oxidation of Trx-1 in the absence of a generalized cellular oxidation.

Compartmental redox signaling

Discrete compartmental redox signaling is demonstrated by Nrf-2-dependent activation of ARE. Nrf-2 is a redox-sensitive transcription factor that is activated by an oxidative signal in the cytoplasm but has a critical cysteine that must be reduced to bind to DNA in the nucleus. The GSH and Trx-1 systems function in thiol/disulfide redox control in both the cytoplasm and the nucleus, and previous studies suggested that these systems are overlapping in control of cytoplasmic activation of NF-κB (23, 36). To test whether GSH and Trx-1 have distinct functions in Nrf-2 signaling, we selectively modified GSH by metabolic manipulation and selectively modified Trx-1 expression by transient transfection (22). Cytoplasmic activation of Nrf-2 was measured by its nuclear translocation, and nuclear activity of Nrf-2 was measured by expression of a luciferase reporter construct containing an ARE4 from glutamate-cysteine ligase. Results showed that *tert*-butylhydroquinone (TBHQ), a transcriptional activator that functions through Nrf-2/ARE, promoted Nrf-2 nuclear translocation by a type I (thiylation) redox switch that was regulated by GSH not by Trx-1. In contrast, the ARE reporter was principally controlled by nuclear-targeted Trx-1 and not by GSH. The data show that the GSH and Trx-1 systems have unique, compartmented functions in the control of transcriptional regulation by Nrf-2/ARE (22).

Together, the results of the studies show that redox signaling occurs through specific signaling pathways without global changes in the central thiol/disulfide redox couples. Thus, extracellular Cys/CySS redox can activate EGFR signaling without altering cellular GSH/GSSG redox, cellular GSH/GSSG redox can control Keap-1 and regulate Nrf-2 translocation to the nucleus without direct input from Trx-1, and Trx-1 can control Ask-1 activity and DNA binding of Nrf-2 without effects on the GSH/GSSG couple (Fig. 6). An imbalance of pro-oxidants and antioxidants can clearly disrupt such circuitry by providing massive amounts of oxidants, allowing parallel and uncontrolled oxidation of multiple pathways. However, the existence of discrete pathways implies that disruption of specific circuits can occur without an overall imbalance in pro-oxidants and antioxidants. Consequently, disruption of redox circuitry would appear to be a more fundamental characteristic than redox imbalance and therefore provide a better way to define the concept of oxidative stress.

Implications for clinical assessment of oxidative stress

As indicated above, a large number of assays are available to measure oxidants and oxidation products. There would appear to be a clear utility for multiple assays, one that measures directly the oxidant load in the system, such as could be available from the d-ROMs assay, a second that measures products of lipid peroxidation, such as the F2-isoprostanes, a third that captures oxidation based upon RNS such as assay of nitrotyrosine, and a fourth that measures oxidative DNA

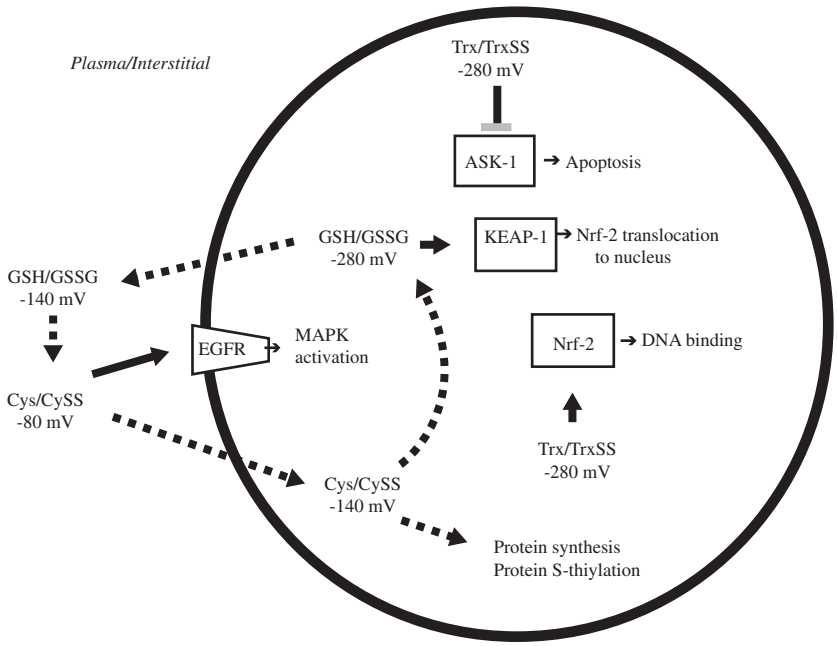

Fig 6. Specific interactions of proteins with Trx-1, GSH/GSSG, and Cys/CySS couples. Mechanistic studies have established interactions of specific signaling pathways and protein systems with specific thiol/disulfide couples. Reduced Trx-1 blocks activation of apoptosis signal-regulating kinase-1 (Ask-1) and stimulates DNA-binding of transcription factors with a critical cysteine residue. These transcription factors include Nrf-2, NF-κB, P53, Fos, Jun, and several others. Keap-1-Nrf-2 interaction is regulated by GSH/GSSG redox; oxidation of GSH/GSSG redox allows translocation of Nrf-2 to the nucleus for transcriptional activation of phase 2 detoxification enzyme expression. Extracellular Cys/CySS redox regulates phosphorylation and activation of EGFR. This activation is sensitive to pretreatment with thiol-reactive chemicals and appears to be mediated by a metalloprotease (47).

damage. There are also a number of ways to measure antioxidants and function of antioxidant systems. However, other than the common measures for vitamin C and vitamin E, so many other antioxidants are present that higher capacity/more rapid through-put methods for profiling antioxidant levels and antioxidant systems are needed. On the other hand, measures of GSH redox and Cys redox provide direct quantifiable information on the tissue pro-oxidant/antioxidant balance. As indicated above, a strong argument can be made that plasma GSH redox and plasma Cys redox provide the most useful and scientifically sound approaches available for quantitative assessment of oxidative stress in clinical research.

SUMMARY

The concept of oxidative stress as a global imbalance of pro-oxidants and antioxidant has served well for two decades, but the accumulated data now tell us that this definition is inadequate and conceptually limiting. Foremost among the data are numerous interventional trials with antioxidants that have been inconsistent and inconclusive. These studies indicate that shifting the balance by providing more antioxidants provides limited increase in protection. A simple interpretation is that oxidative stress is not adequately defined by an imbalance of oxidants and antioxidants. Human studies show that plasma GSH and Cys redox states are useful measures of oxidative stress, but GSH and Cys redox states are not equilibrated in either cells or plasma. The lack of equilibration means that oxidative stress cannot be defined by a single global balance. Recognition of the existence of multiple, discrete redox signaling pathways suggests that a more suitable definition for oxidative stress is a condition that disrupts redox signaling and control. Such a definition provides a conceptual framework for more meaningful clinical assessment of oxidative stress and development of disease-specific antioxidant therapies based upon mechanisms of organ- or pathway-specific disruption of redox processes.

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ABBREVIATIONS

AMD, age-related macular degeneration; ARE, antioxidant response element; Ask-1, apoptosis signal-regulating kinase-1; CuZnSOD, copper-zinc superoxide dismutase; Cys, cysteine; CySS, cystine; DNA, deoxyribonucleic acid; d-ROMs, derivatives of reactive oxygen metabolites; E_h, redox potential; ELISA, enzyme-linked immunosorbent assay; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; FasL, Fas ligand; GSH, glutathione; GSSG, glutathione disulfide; HNE, 4-hydroxynonenal; HPLC, high-performance liquid chromatography; ICAM-1, intercellular adhesion molecule-1; IGF-1, insulin-like growth factor-1; JNK, c-Jun N-terminal kinase; KGF, keratinocyte growth factor; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; MnSOD; manganese superoxide dismutase; NF-κβ; nuclear factor-κβ; Nox-1, NADPH oxidase-1; Nrf-2, nuclear factor-E2-related factor-2; PECAM, platelet endothelial adhesion molecule; PN, parenteral nutrition; Pr-(SH_2), protein containing reactive dithiol; Pr-SS, protein containing internal disulfide; Pr-SS-R, protein containing disulfide with other molecule; RNS,

reactive nitrogen species; ROS, reactive oxygen species; RPE, retinal pigment epithelium; SO, sulfhydryl oxidase; TBARS, thiobarbituric acid-reactive substances; t-BH, *tert*-butylhydroperoxide; TBHQ, *tert*-butylhydroquinone; TGF-α, transforming growth factor-α; TO, thiol oxidase; Trx-1, thioredoxin-1; Trx-2, thioredoxin-2; x_c^-, exchange transporter for anionic form of cystine and glutamate.

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