Metabolic Regulation and Function of Glutathione Peroxidase-1

Xin Gen Lei,[1] Wen-Hsing Cheng,[2] and James P. McClung[3]

[1]Department of Animal Science, Cornell University, Ithaca, New York 14853; email: XL20@Cornell.edu

[2]Laboratory of Molecular Gerontology, National Institute on Aging, National Institutes of Health, Baltimore, Maryland 21224, and Department of Nutrition and Food Science, University of Maryland, College Park, Maryland 20742

[3]Military Nutrition Division, U.S. Army Research Institute of Environmental Medicine, Natick, Massachusetts 01760

Annu. Rev. Nutr. 2007. 27:41–61

First published online as a Review in Advance on April 27, 2007

The *Annual Review of Nutrition* is online at http://nutr.annualreviews.org

This article's doi: 10.1146/annurev.nutr.27.061406.093716

0199-9885/07/0821-0041$20.00

Key Words

selenium, reactive oxygen species, reactive nitrogen species, signaling, chronic disease

Abstract

Glutathione peroxidase-1 (GPX1) represents the first identified mammalian selenoprotein, and our understanding in the metabolic regulation and function of this abundant selenoenzyme has greatly advanced during the past decade. Selenocysteine insertion sequence–associating factors, adenosine, and Abl and Arg tyrosine kinases are potent, Se-independent regulators of GPX1 gene, protein, and activity. Overwhelming evidences have been generated using the GPX1 knockout and transgenic mice for the in vivo protective role of GPX1 in coping with oxidative injury and death mediated by reactive oxygen species. However, GPX1 exerts an intriguing dual role in reactive nitrogen species (RNS)-related oxidative stress. Strikingly, knockout of GPX1 rendered mice resistant to toxicities of drugs including acetaminophen and kainic acid, known as RNS inducers. Intracellular and tissue levels of GPX1 activity affect apoptotic signaling pathway, protein kinase phosphorylation, and oxidant-mediated activation of NFκB. Data are accumulating to link alteration or abnormality of GPX1 expression to etiology of cancer, cardiovascular disease, neurodegeneration, autoimmune disease, and diabetes. Future research should focus on the mechanism of GPX1 in the pathogeneses and potential applications of GPX1 manipulation in the treatment of these disorders.

Contents

INTRODUCTION

Discovery of Glutathione Peroxidase-1 as a Selenoprotein

Glutathione peroxidase-1 (glutathione: H_2O_2 oxidoreductase, EC 1.11.1.9; GPX1) was initially discovered by Mills in 1957 as an erythrocyte enzyme that protects hemoglobin from oxidative breakdown (103). In the early 1970s, two groups demonstrated that GPX1 is a selenium (Se)-dependent enzyme (58, 121). Subsequently, selenocysteine (Sec) was identified as the moiety of Se in the GPX1 protein (21). Today, Sec is recognized as the twenty-first amino acid, despite similar structure to cysteine. Although Se may exist in mammalian proteins in other chemical forms, such as selenomethionine via a nonspecific replacement of sulfur in methionine and other Se-binding proteins that do not contain Sec (9), this essential trace element probably confers its metabolic functions mainly in the form of Sec in selenoproteins. A unique consensus Sec-insertion sequence (SECIS) in the mRNA of selenoproteins is required for the synthesis of Sec (12). Using this unique SECIS signature to search the published genome database, Gladyshev and coworkers have reported that there are 25 selenoproteins in humans (85).

GPX1: glutathione peroxidase-1

Se: selenium

Selenocysteine-insertion sequence (SECIS): unique mRNA stem loop structure associated with the incorporation of essential micronutrient selenium into selenium-containing proteins

Incorporation of Se into GPX1 and Other Selenoproteins

As discussed above, Se is incorporated into GPX1 and other selenoproteins in the form of Sec coded by UGA and directed by SECIS (12, 21, 125). This SECIS represents an mRNA stem loop structure and serves as a platform for the recruitment of specific translation elongation factors and Sec tRNA (designated as Sec-tRNA$^{[Ser]Sec}$). As such, tRNA$^{[Ser]Sec}$ decodes the UGA codon for the entire family of selenoproteins. Targeted disruption of this tRNA gene in mice

leads to embryonic lethality (14). In bacteria, the SelB protein binds to SECIS and recruits Sec-tRNA$^{[Ser]Sec}$ (13, 48, 129). In eukaryotes, the mRNA-tRNA interaction is more complex, as the eukaryotic SECIS element is recognized by a protein complex containing SECIS-binding protein 2 (SBP2) and elongation factor EFSec (149). The most recent list of eukaryotic tRNA$^{[Ser]Sec}$-interacting proteins includes two selenophosphate synthetases, ribosomal protein L30, SECp43, and soluble liver antigen (22, 128, 145). It seems that the interaction between SBP2-binding protein and SECIS mobilizes EFsec and Sec-tRNA$^{[Ser]Sec}$ to the ribosome, while the binding of L30 protein to SECIS stimulates the completion of selenocysteine synthesis (22).

Enzyme Family of GPX1

In addition to GPX1, there are five other known GPX enzymes: GPX2–GPX6. Data from in vitro activity assays suggest that all members use GSH to catalyze the reduction of hydrogen peroxide and lipid peroxides. Whereas GPX1 is the most abundant selenoperoxidase and is ubiquitously expressed in almost all tissues (25, 26, 58, 121), GPX2 expression is most prominent in the gastrointestinal tract (30). Expression of GPX3 is greatest in the kidney, although this enzyme is expressed in various tissues and is secreted into extracellular fluids as a glycoprotein (135, 147). Different from other glutathione peroxidases, GPX4, or phospholipid hydroperoxide GPX, is not a tetramer, but rather a monomer, and is the only GPX enzyme that reduces phospholipid hydroperoxides (141). In addition, GPX4 contains a mitochondrial isoform that mediates the apoptotic response to oxidative stress (3, 112) and has a peroxidase-independent structural role after sperm maturation (142). Recently, GPX6 was identified as a selenoprotein in the human genome by homology search (85). However, GPX6 from rodents and GPX5 from both humans and rodents do not contain Sec or Se (85).

REGULATION OF GPX1 mRNA, PROTEIN, AND ACTIVITY EXPRESSION

Regulation by Se Supply

The expression of GPX1 mRNA, protein, and activity in tissues is more sensitive to dietary Se deficiency than other selenoperoxidases or selenoproteins (11). In fact, Se deficiency in rats results in a 90% loss of liver GPX1 mRNA and a 99% loss in GPX activity (122). In cells, Se deficiency results in a 60% reduction in GPX1 mRNA and a 93% loss in GPX1 activity (4). Nonsense codon-mediated decay seems to be the mechanism by which Se deficiency reduces the abundance of GPX1 mRNA, as the Sec codon reduces the abundance of cytoplasmic GPX1 mRNA by a translation-dependent mechanism under conditions of Se deprivation (106).

Injection of Se into deficient animals results in the rapid restoration of both GPX mRNA and activity (132). However, the Se-induced restoration of GPX1 activity seems to be saturable in a number of animal models and cell types (132, 133). Because of the sensitive and saturable nature of GPX1 activity in response to dietary Se, GPX1 has been used as a biomarker to assess body Se status or the nutritional requirement of Se. Furthermore, the low rank of GPX1 in the hierarchical partitioning of Se prompted the conception of the "GPX1 buffer" hypothesis (16, 131). Based on this hypothesis, GPX1 functions as a body storage form of Se, instead of as an important antioxidant enzyme, to release Se for maintaining the expression of essential selenoproteins in Se depletion and to take up Se for avoiding Se toxicity in Se repletion. However, two lines of solid evidence from GPX1 knockout or overexpressing mice do not support the GPX1 buffer hypothesis. First, alteration of GPX1 expression does not affect the mRNA or activity expression of other selenoproteins (25, 26). Second, knockout of GPX1 renders mice susceptible to severe acute oxidative stress, whereas overexpression of GPX1 confers extra protection against the insult (27).

Glutathione peroxidases: antioxidant enzymes that use glutathione as a substrate (reductant) to catalyze the breakdown of peroxides

Knockout (null): genetically delete or disrupt functional expression of selected single or multiple genes in animals

Overexpression: genetically elevate the functional expression of selected single or multiple genes above normal levels in animals

Reactive oxygen species (ROS): oxygen-containing molecules that are more active than the triplet oxygen molecule present in the air and can cause oxidative stress

Pro-oxidants: compounds that induce formation of reactive oxygen species and reactive nitrogen species

Oxidant stress: exposure to reactive oxygen or nitrogen species and (or) the loss of balance between antioxidant defense and pro-oxidant or oxidant attack

Regulation by SECIS-Associating Factors

The SECIS-associating factors may regulate selenoprotein expression in at least two ways. First, the intracellular location of SBP2 is shifted from the cytoplasm to the nucleus upon exposure to reactive oxygen species (ROS), suggesting a mechanism by which oxidative stress decreases selenoprotein expression (116). Consistently, tissue GPX1 protein and activity are decreased after administration of pro-oxidant paraquat to mice (24). Secondly, Se status modulates Sec-tRNA$^{[Ser]Sec}$ methylation at position 34 of this tRNA, and such modification alters Sec-tRNA$^{[Ser]Sec}$ secondary and tertiary structure (43). Mice engineered to express a mutant Sec-tRNA$^{[Ser]Sec}$ (Sec-tRNA$^{[Ser]Sec}$ i^6A^- transgenic mice) are unable to carry out this specific tRNA methylation, but expression of various selenoproteins in these animals is not equally affected (19). Selenoproteins such as GPX1 and GPX3, whose expression is highly responsive to Se deficiency, appear to require the tRNA methylation (2). In contrast, TR-1 and thioredoxin reductase-3 are less affected by Se deficiency, and their expression is independent of the tRNA methylation.

Adenosine-Dependent Activation of GPX1

Adenosine is a widely distributed molecule with a number of biological functions, including protection against myocardial ischemia/reperfusion injury (96). It has been hypothesized that adenosine may impart protection against ROS, as it attenuates oxidant-induced damage in cells (88) and animals (87). Because overexpression of GPX1 in mice is known to diminish tissue damage following myocardial ischemia/reperfusion (146), one recent study examined the ability of adenosine to affect GPX1 regulation. In that study, treatment of human primary pulmonary endothelial cells with adenosine in the presence of erythro-9-(2-hydroxy-3-nonyl)adenine (EHNA), an adenosine deaminase inhibitor, resulted in increased GPX1 mRNA levels, protein expression, and enzyme activity (151). The adenosine-driven induction of GPX1 expression was due to enhanced mRNA stability. The adenosine-driven induction of GPX1 conferred protection against ROS, as adenosine/EHNA-treated cells were resistant to hydrogen peroxide–induced oxidant stress. Meanwhile, inhibition of GPX1 pharmacologically or by siRNA diminished the protection by adenosine against ROS. These findings suggest that adenosine may be a potent, Se-independent regulator of GPX1 expression, and that the associated GPX1 activity change may exert important physiological functions.

Regulation Via c-Abl and Arg Tyrosine Kinases

The c-Abl and Arg nonreceptor tyrosine kinases represent another Se-independent regulator of GPX1 expression. The cytoplasmic forms of these kinases are activated in response to ROS and may be involved in the apoptotic response to oxidant stress (18). In fact, hydrogen peroxide–induced apoptosis is attenuated in cells deficient in c-Abl and Arg (18, 130). Because of the association between c-Abl and Arg and oxidant stress, one recent study explored the interactions between these proteins and GPX1 (17). In that study, it was determined that c-Abl and Arg associate with GPX1 in a yeast two-hybrid system and in 293 cells, and that the interaction is regulated by intracellular oxidant levels. Furthermore, it was demonstrated that GPX1 functions as a substrate for c-Abl- and Arg-mediated phosphorylation at Tyr-96, which induces GPX1 activity. Lastly, treatment of c-Abl- and Arg-deficient cells with hydrogen peroxide resulted in a greater apoptotic response as compared with wild-type cells, suggesting that the loss of GPX1 regulation by c-Abl and Arg results in increased sensitivity to ROS-induced apoptosis.

Furthermore, recent studies have demonstrated that other factors, including epidermal growth factor receptor (50) and homocysteine (67), may participate in the regulation of GPX1. Factors that may participate in the regulation of GPX1 gene expression and enzyme activity are summarized in **Figure 1**.

Altered Expression in Diseases

One recent report demonstrated that GPX1 expression was decreased by hyperhomocysteinemia (67), a risk factor for cardiovascular disease. In that study, homocysteine was shown to interfere with the SECIS readthrough such that GPX1 expression was reduced at the translational level. It has also been observed that GPX1 activity is diminished in lung cancers with GPX1 loss of heterozygosity (69), and GPX1 protein expression is decreased in T cells during HIV infection (64). Moreover, bone loss induced by estrogen deficiency has been shown to be associated with hydrogen peroxide formation and increased GPX1 expression (86).

ROLES OF GPX1 IN REDOX REGULATION

Protection Against ROS

Although in vitro cellular studies demonstrated that modulation of GPX1 activity expression by ectopic expression or antisense RNA down-regulation affected cell resistance to oxidative stress (104, 140), the most convincing evidence for the in vivo antioxidant role of GPX1 was attributed to the observation that GPX1-overexpressing [GPX1(+/+)] mice were more resistant, while GPX1 knockout mice [GPX1(−/−)] were more susceptible to paraquat-induced lethality than were wild-type mice (27). In fact, mouse survival time in these experiments was solely a function of tissue GPX1 activity. Furthermore, GPX1 was not only antioxidative, but also the mediator of body Se in protecting against such drastic, acute oxidative stress (24, 27). Its protection was conferred by preventing a collapse of redox status and attenuating oxidation of lipids, protein, NADPH, and NADH (24, 27). Meanwhile, the in vivo antioxidant role of GPX1 has been substantiated by a number of publications using independently developed GPX1(−/−) mouse lines and various ROS-inducing agents (41, 53, 59, 60).

The physiological essentiality of GPX1 protection against ROS-related stress depends upon Se status and the severity of the stress. After an injection of paraquat at a dose of 12.5 mg/kg, all Se-adequate mice, regardless of their GPX1 status, survived (28). Thus, GPX1 is not essential for Se-adequate mice to cope with moderate oxidant stress. However, even minute amounts of tissue GPX1 activity become important for the antioxidant defense in Se-deficient mice. Although the majority of Se-deficient wild-type and GPX1(−/−) mice died of the injection of paraquat at 12.5 mg/kg, a prior injection of Se (50 μg/kg as Na_2SeO_3) that restored only 4% of the normal GPX1 activity in wild-type mice resulted in significant reductions in mortality and severity of liver aponecrosis compared with Se-injected GPX1(−/−) mice. Liver injury was more apoptotic in GPX1(−/−) mice, but more necrotic in wild-type mice. The repletion of minute GPX1 activity in wild-type mice also attenuated activation of caspase-3 and c-Jun N-terminal kinase (JNK) and the expression of Bcl-X_s and GADD45 (28, 29).

Dual Roles Against Reactive Nitrogen Species

Although reactive nitrogen species (RNS) such as nitric oxide (NO), peroxynitrite (PN), and their reactive intermediates are produced constantly in aerobic metabolism, their distinct features are not often recognized from those of ROS. Nitric oxide is an uncharged lipophilic molecule that contains a single unpaired electron that causes it to be reactive with other molecules, including GSH.

GPX1(+/+): GPX1 overexpression

GPX1(−/−): GPX1 knockout

Reactive nitrogen species (RNS): highly reactive, nitrogen-containing molecules that can cause oxidative stress

PN: peroxynitrite

APAP: acetaminophen

SOD: superoxide dismutase

Release of NO by nitric oxide synthase (NOS) may result in the production of superoxide (76). When superoxide is produced in parallel with NO, the two react to form PN, which is highly cytotoxic (8) and is capable of oxidizing numerous biomolecules, including lipids, amino acids, and DNA (127). PN is especially harmful to proteins due to its ability to react with tyrosine residues to form 3-nitrotyrosine. This chemical modification, called protein nitration, may lock enzymes or proteins in an inactive form by preventing the phosphorylation of tyrosine residues (136).

Early in vitro studies suggested that the GPX1 enzyme and its mimetic ebselen catalyzed PN reduction and prevented tyrosine nitration in cell lysates (127). However, a recent study demonstrated a promotion, instead of a protecting, role of GPX1 in coping with the PN-induced cell death (61). In that study, primary hepatocytes isolated from GPX1(−/−) mice were more resistant than those from wild-type mice to PN-induced apoptosis, DNA fragmentation, cytochrome-c release, caspase activation, and cellular GSH depletion.

The promoting role of GPX1 in RNS-related stress and its metabolic relevance have been well illustrated in a number of animal studies with acetaminophen (APAP). As the vascular production of PN is induced by APAP overdose, PN formation has been suggested as a critical mediator of APAP-induced hepatotoxicity (81, 82, 102). Initially, Mirochnitchenko and coworkers (105) found that mice overexpressing GPX1 had reduced survival time and increased oxidant damage as compared with wild-type mice when both groups were treated with 450 mg of APAP/kg. Meanwhile, another group demonstrated that GPX1(−/−) mice were not more susceptible to an injection of 300 mg of APAP/kg, but had lower plasma alanine aminotransferase activity increases than did wild-type mice (81). Furthermore, double knockout of GPX1 and Cu,Zn-superoxide dismutase (SOD1) rendered primary hepatocytes (152) and mice (90) more resistant to APAP-induced toxicity than wild-type controls. In addition, the enhanced resistance of GPX1(−/−) mice to kainic acid–mediated mortality and seizures (75) represents another strong in vivo evidence for the promoting role of GPX1 in RNS-related stress, as kainic acid is a neurodegenerative drug that has been shown to induce PN formation in brain (117). Thus, GPX1 may play dual roles in coping with oxidative stress mediated by ROS versus RNS (**Figure 2**).

ROLE OF GPX1 IN SIGNAL TRANSDUCTION

Apoptotic Signaling Pathway

Results from early studies suggested a role of GPX1 in hydrogen peroxide–induced apoptosis in bovine renal epithelial cells (79) and in murine myeloid progenitor cells (115). More directly, primary hepatocytes isolated from GPX1(−/−) mice were more susceptible to ROS-induced apoptosis, but were more resistant to RNS-induced apoptosis than cells from wild-type mice (61). After the treatment with each of the oxidants, cells of the two genotypes displayed completely opposite profiles including cell viability, DNA fragmentation, capase-3 activation, p21WAF1/CIP1, cytochrome C release, protein nitration, and the GSH/GSSG ratio. As mentioned above, repletion of minute amounts of GPX1 activity in liver of wild-type mice exerted a significant impact on paraquat-mediated activation of caspase-3, p53 stability, and expression of Bcl-X_s and GADD45 (28, 29). In addition, increased GPX1 activity was associated with the inhibition of apoptosis induced by growth factor withdrawal from pro-B-lymphocytes (70) or by c-Myc (115). Because levels of ROS were low in such condition, GPX1 likely modulated apoptosis caused by factors other than oxygen tension. In human endothelial cells, overexpression of GPX1 alone, in the absence of exogenous stress, resulted in a significant decrease in the expression of the proapoptotic Bax, whereas that of antiapoptotic

Bcl-2 remained unchanged (57). Primary myoblasts isolated from GPX1(−/−) mice in the absence of exogenous apoptotic stimuli consistently showed increased rates of apoptosis (89). Interestingly, primary hepatocytes isolated from GPX1(−/−) mice were more resistant to APAP-induced cell death due to an attenuation in APAP-induced GSH depletion (152).

Protein Kinase Phosphorylation

The p38 mitogen-activated protein kinase (MAPK) and JNK pathways impart essential roles in ROS-induced apoptosis (95, 114). Overexpression of GPX1 in mouse embryonic fibroblasts has been shown to prevent p38 MAPK phosphorylation at Thr-180/Tyr-182 under hypoxia that presumably induces oxidative stress (52). However, decomposing endogenous ROS by expression of GPX1 in GPX1-underexpressed MCF-7 cells did not affect p38 MAPK expression and phosphorylation (110). Also, GPX1 had no significant impact on p38 MAPK phosphorylation in mice and cells treated with paraquat or diquat (29, 61). Interestingly, low GPX1 activity (4% of the adequate level) in Se-deficient mice was sufficient to attenuate JNK phosphorylation at Thr-183/Tyr-185 mediated by a low dose of pro-oxidant (29). In addition, protein kinase B (also known as Akt) phosphorylation at Ser-308 was reduced in MCF-7 cells overexpressing GPX1 (110), or in GPX1(+/+) mice following an insulin challenge (99). Meanwhile, fibroblasts from GPX1(−/−) mice showed decreased Akt phosphorylation at Ser-473 upon stimulation with hydrogen peroxide (139).

Oxidant-Mediated Activation of NFκB

NFκB is a transcriptional factor involved in regulating cellular responses to a variety of environmental stressors (78). Overexpression of GPX1 has been implicated in the reduction of hydrogen peroxide–induced NFκB activation in MCF-7 cells (92, 93). Recent evidence has suggested that GPX1 and the c-Src tyrosine kinase likely function in the same process of IκBα phosphorylation that leads to NFκB activation in response to hypoxia (56). Strikingly, both GPX1 and catalase, but not Mn-SOD (SOD2) or SOD1, modulate IκBα phosphorylation, suggesting a difference between hydrogen peroxide and superoxide in the activation of NFκB. Conversely, NFκB activation was found to be elevated in GPX1(−/−) embryonic fibroblasts treated with hydrogen peroxide (139) or GPX1(−/−) brains after stroke (36).

The effect of GPX1 expression level on the NFκB pathway has clinical implications. For instance, bone resorption depends on osteoclasts that express high levels of GPX1 protein and require NFκB activation for cell development (86). The level of GPX1 activity may also affect pathogenesis involving COX-2 up-regulation, as Se-deficient macrophages show increased NFκB activation and subsequent COX-2 up-regulation (148). The signal pathways that involve GPX1 are summarized in **Figure 3**.

ROLES OF GPX1 IN CANCER AND CHRONIC DISEASES

GPX1 Expression and Cancer

Cells from cancer patients often show defects in the regulation of proliferation, apoptosis, and senescence (40). Analysis of a long-term clinical trial concluded that daily supplementation with Se at a supranutritional dose (200 μg) resulted in significant reductions in mortality associated with total carcinomas as well as lung, prostate, and colon cancers (31, 32). It remains unclear as to how Se decreases cancer risk and whether GPX1 is involved in the action. It is also unclear whether the anticarcinogenic properties of Se are a result of pro-oxidant or antioxidant function (46, 113). The paradox is that Se compounds per se are known to initiate ROS-induced apoptosis in cancer cells, yet some selenoproteins

attenuate ROS levels in the body (24, 113). In the Sec-tRNA$^{[Ser]Sec}$ i^6A^- transgenic mouse model, GPX1 is one of the selenoproteins that demonstrate reduced expression (19). Using this line of transgenic mice that has a preference for GPX1 suppression among all selenoproteins, azoxymethane treatment resulted in aberrant crypts in the colon as compared with wild-type mice.

Although GPX1 was unlikely to be the only selenoprotein involved, these results suggested the involvement of GPX1 in the chemoprevention imparted by dietary Se. However, this finding raises a question regarding GPX2 involvement, as its expression is primarily confined to the gastrointestinal system (30). This issue was partially addressed by a recent report showing that GPX1, instead of GPX2, was expressed in selective colon locations including lymphatic tissues (47). Using a TGF$^{\alpha}$/c-Myc mouse model of cancer, Novoselov et al. (113) suggested that both selenoproteins and Se compounds contributed to the inhibition of liver carcinogenesis, although it was unclear as to the relative contribution of GPX1 to this protection. On the other hand, GPX1 expression has been found to be decreased or repressed in estrogen receptor–positive breast cancer cells (54), in a mouse model for liver tumors, and in a prostate cancer cell line (63). It will be of great interest to discern whether GPX1 expression and the associated ROS changes are directly involved in the chemopreventive effects of dietary Se.

GPX1 Polymorphisms and Allelic Changes

In the 201 amino acid–containing GPX1 protein peptide, the single-nucleotide polymorphism (SNP) that alters particular amino acid sequences is associated with certain diseases. Moscow et al. (107) first reported an SNP within the GPX1 gene that resulted in either a proline (Pro) or leucine (Leu) at codon 198 in lung cancer specimens. This SNP has also been reported to be associated with bladder cancer (73). Although the SNP was later found in some breast cancer patients (72, 118), there is no consistent evidence to support an association between the GPX1 Pro198Leu polymorphism and susceptibility to breast cancer (1, 20, 34). Likewise, another GPX1 polymorphism GCG in exon 1 was not associated with prostate cancer risk (84). Nonetheless, analysis of breast and colorectal cancer DNA revealed that 36% to 42% of GPX1 genes showed loss of heterozygosity during tumor formation (71, 72). It seems that the GPX1 Pro198Leu SNP resulted in a decreased response of GPX1 catalytic activity to Se supplementation (72), suggesting that GPX1 activity may involve the regulation of carcinogenesis via modulation of ROS levels. Consistent with this notion, a recent report using samples from alcoholic patients with cirrhosis suggested that polymorphisms in GPX1 and Mn-SOD likely collaborated to regulate carcinogenesis in liver (134). Identification of additional GPX1 SNPs and systematic evaluation of their associations with cancer will help expand our ability to diagnose and treat GPX1-related cancers.

Cardiovascular Diseases

The GPX1 protein is expressed in blood vessels and has been implicated in cardiovascular disease (83). Atherosclerosis occurs predominantly at low sheer stress areas, and such stress has been shown to enhance GPX1 mRNA levels in cultured bovine aortic endothelial cells (137). An important association between GPX1 expression and plasma homocysteine levels has been documented (67). Elevated levels of homocysteine can increase levels of ROS, leading to endothelial injury in the pathogenesis of atherogenesis (66). In cultured bovine aortic endothelial cells, overexpression of GPX1 alleviated homocysteine-induced endothelial dysfunction (144), and the addition of homocysteine suppressed GPX1 expression at the translation level (67). Homocysteine likely interrupts the UGA

read-through such that GPX1 expression is down-regulated. Moreover, a report using GPX1(−/−) mice suggested that GPX1 contributed to the protection of Se against myocarditis induced by a benign strain of coxsackievirus B3 that likely increased cellular oxidative stress (7). Taken together, these results suggest that GPX1 may protect against atherogenesis in vessels and virus-induced myocarditis by reducing ROS levels.

Neurodegenerative Diseases

Considerable evidence links GPX1 to the pathogenesis of neurodegenerative diseases, most likely through its peroxide-eliminating activity. GPX1 is known to localize primarily in glial cells (138), in which GPX1 activity is tenfold higher than in other brain regions (124). Moreover, there is an increase in GPX1 expression surrounding the damaged brain regions in Parkinson's disease patients (38). Ridet et al. (119) employed a lentivirus-based system delivering GPX1 to neuroblastoma cells in vitro, in which a twofold increase in GPX1 expression protected cells from 6-hydroxydopamine-induced neurotoxicity. Furthermore, the delivery of GPX1 to nigral dopaminergic neurons in vivo attenuated 6-hydroxydopamine toxicity in a mouse model of Parkinson's disease (119). Similarly, knockout of GPX1 rendered mouse neurons more susceptible to damage induced by neurotoxins such as malonate, 3-nitropropionic acid, and tetrahydropyridine (80, 150), whereas overexpression of GPX1 protected mice against neurotoxicity (10).

Furthermore, GPX1 may also play a role in Alzheimer's disease. Although amyloid β-peptide-induced oxidative stress has been implicated in the pathogenesis of this disease, cultured neurons from GPX1(−/−) mice are more susceptible to treatment of amyloid β-peptides (35), and overexpression of GPX1 in the PC12 pheochromocytoma cells or rat embryonic cultured cortical neurons renders these cells more resistant to the peptides (5). In stark contrast, in comparison with wild-type mice, knockout of GPX1 rendered mice more resistant to kainic acid–mediated mortality and seizures (75). As mentioned above, kainic acid is a neurodegenerative drug that induces PN formation in brain (117). It is likely that the roles of GPX1 in neurodegenerative diseases are case- or cause-specific.

DM: diabetes mellitus

Autoimmune Diseases

Low dietary Se intake has been suggested to correlate with a 20-fold increase in the risk of developing AIDS in HIV-infected individuals (6). Consistently, HIV-infected individuals have diminished total body Se content and GPX1 activity (51). Analysis of ^{75}Se-labeled human Jurkat T cells has revealed four ^{75}Se-containing proteins including GPX1, GPX4, TR1, and Sep15 (64). Based on the known function of these selenoproteins, we may speculate that Se imparts its function in the pathogenesis of AIDS via redox regulation. Similarly, a GPX protein from the *Molluscum contagiosum* virus (80% homology to human GPX1) conferred protection against hydrogen peroxide insult when expressed in HeLa cells (126). One possible mechanism is that GPX1 may protect HIV-infected individuals from loss of helper T cells by the prevention of oxidant-induced apoptosis.

Diabetes

Diabetes mellitus (DM) is a chronic state of glucose imbalance that affects 20 million Americans (39), and the prevalence will likely rise from 6% to more than 10% in the next decade (120). There are three forms of DM. Type I DM, or juvenile diabetes, is caused by an autoimmune inflammatory reaction affecting the β-cells in the pancreatic islet. Type II DM is characterized by an inability to utilize glucose in the presence of insulin, and is associated with weight gain and adiposity, hyperinsulinemia and insulin resistance, and impaired glucose tolerance (91). The third form of DM, gestational diabetes, occurs only

Antioxidant enzymes: proteins that catalyze reactions to suppress the formation of free radicals or to repair the oxidative damage. Free radicals are chemical species with unpaired electrons, in general reactive and attacking other molecules

during pregnancy and is associated with insulin resistance and, in extreme cases, β-cell insufficiency (77).

Oxidant stress has been implicated in both the pathogenesis and complications associated with all three types of DM. In humans and animals with DM, persistent hyperglycemia results in the elevated production of ROS due to the direct autoxidation processes of glucose and the nonenzymatic glycation of proteins resulting in the formation of glucose-derived advanced glycosylation end products (15). Other mechanisms that may result in the formation of ROS during DM include metabolic stress due to weight gain and changes in energy metabolism, activation of RNS (33), activation of xanthine oxidase (42), increased expression of inflammatory mediators, and altered expression of antioxidant enzymes (101).

It is likely that ROS and RNS contribute to the destruction of the pancreatic β-cell during the pathogenesis of type I DM, as these cells express low levels of antioxidant enzymes, including GPX (65). Furthermore, significant reductions in erythrocyte GPX activity and total GSH content occur in young type I DM patients as compared with age-matched controls (44, 98). Although the specific roles of GPX1 in the pathogenesis of type I DM have not been identified, Se is known to protect against the destruction of pancreatic β-cells in streptozotocin-induced diabetic mice. Treatment of these mice with sodium selenite results in nearly complete attenuation of hyperglycemia, lipid peroxidation, and plasma GSH depletion (45, 100, 108).

Although human studies have not established a direct link between GPX1 activity and type II DM, recent studies have proposed a role for ROS and altered antioxidant enzyme expression in the development of disease (55, 120). Depletion of antioxidants is associated with the pathogenesis of type II DM, as reduced vitamin E and C status is a predictor of disease (123, 143), and patients with type II DM exhibit high SOD3 (extracellular), but low GPX3 activity (101).

Insulin resistance occurs during normal pregnancy and results in gestational diabetes when women become glucose intolerant (77). One recent study investigated the association of erythrocyte GPX1 activity with insulin resistance during pregnancy (23). Interestingly, erythrocyte GPX activity increased significantly during the course of normal pregnancy, and the activity was positively associated with fasting plasma insulin and glucose concentrations and incidence of insulin resistance. The authors concluded that enhanced maternal GPX1 activity might be a protective response to pregnancy-induced increases in ROS and that there might be a link between GPX activity, insulin resistance, and β-cell function.

Transgenic mice overexpressing GPX1 have been utilized in two recent studies involving glucose homeostasis and insulin function. The first study reported the development of insulin resistance and obesity in GPX1(+/+) as compared with age-matched wild-type mice (99). The GPX1(+/+) mice developed hyperglycemia, hyperinsulinemia, and elevated plasma leptin concentrations, as well as reduced phosphorylation of Akt (a kinase downstream of the insulin receptor) in both liver and muscle after insulin stimulation. It is possible that the increased GPX1 activity might interfere with insulin function by overquenching intracellular ROS that are required for insulin signaling. This finding is supported by a recent report that β-cell-specific overexpression of catalase and metallothionein in mice resulted in accelerated spontaneous diabetes and altered insulin signaling (94).

A second study utilized pancreatic islets isolated from GPX1(+/+) mice to study the effects of oxidant injury on glucose metabolism following grafting to STZ-treated wild-type mice (109). In that study, islets that were isolated from GPX1(+/+) mice were not protected from pro-oxidant-induced cell death in vitro; however, islets isolated from animals overexpressing both GPX1 and SOD (both SOD1 and SOD2) were protected. Furthermore, when islets

from transgenic animals were grafted into streptozotocin-treated mice, overexpression with both GPX1 and SOD enzymes resulted in significantly improved control of blood glucose. However, overexpression of GPX1 alone had no significant effect.

Disruptions in insulin sensitivity often involve diminished signaling at the insulin receptor, which is a tyrosine kinase (49). The role of hydrogen peroxide and oxidant tone at the insulin receptor is controversial. Negative effects of hydrogen peroxide include the inhibition of insulin-induced tyrosine phosphorylation of the insulin receptor β subunit in NIH-B cells (68) and the inhibition of insulin-induced Akt phosphorylation in vascular smooth muscle cells (62). In contrast, early studies suggested that hydrogen peroxide could function as an insulin mimetic (37), and more recent reports suggest that insulin stimulation generates a burst of hydrogen peroxide in hepatoma and adipose cells that is associated with a reversible oxidative inhibition of overall cellular tyrosine phosphatase activity (97). Maintenance of tyrosine phosphatase activity is essential for the regulation of tyrosine phosphorylation in the insulin signaling cascade, and as such, insulin sensitivity. When considered in conjunction with the findings from GPX1(+/+) mice, it appears that the appropriate concentration of hydrogen peroxide is a key factor for insulin signaling. Likely, GPX1 plays a critical role in regulating the concentration of hydrogen peroxide through the enzyme-substrate reaction.

CONCLUSIONS AND PERSPECTIVES

Our understanding of GPX1 function and regulation has advanced significantly during the past ten years. Several new factors such as c-Abl and Arg tyrosine kinases and adenosine have been identified as Se-independent regulators of GPX1 expression. These identifications help explain responses of GPX1 gene expression and enzyme activity to changes other than Se supply in cells and tissues. It will be interesting to find out if and how these new regulators, as well as other regulators not yet identified, affect the functional coordination between GPX1 and other selenoproteins or antioxidant enzymes in various metabolic circumstances. The application of GPX1 knockout and transgenic mouse models has generated convincing evidence for the in vivo role of GPX1 in protecting against ROS-related oxidative stress. The physiological importance of that protection by GPX1 varies with severity of the employed stress and status of body Se. Strikingly, RNS-related oxidative stress is potentiated by GPX1. Knockout of GPX1 renders mice resistant to toxicities of RNS inducers acetaminophen and kainic acid. It will be scientifically fascinating and clinically important to determine how GPX1 exerts dual roles in coping with ROS and RNS. The illustration of GPX1 impact on signal transduction related to cell death, protein kinase phosphorylation, and oxidation allows us to unveil mechanisms of GPX1 functions at the cell biology level. Data from human studies and animal experiments increasingly show associations between alteration or abnormality of GPX1 expression and incidences of cancer, cardiovascular disease, neurodegeneration, autoimmune disease, and diabetes. Although it remains as a challenge to elucidate the mechanism of GPX1 in the pathogenesis of these common disorders, it will be helpful to develop novel tools and therapies to diagnose and treat these diseases through manipulation of GPX1 expression and function.

SUMMARY POINTS

1. Glutathione peroxidase-1 is the first identified and most abundant mammalian selenium-containing protein and has been considered a major intracellular antioxidant enzyme.

2. Although selenium serves as the primary regulator of GPX1 expression, selenocysteine-insertion sequence-associating factors, adenosine, c-Abl and Arg tyrosine kinase, homocysteine, and epidermal growth factor receptor may impart potent impacts on the levels of GPX1 mRNA, protein, and activity.
3. Application of GPX1-overexpressing or knockout mouse models has produced convincing evidence for the in vivo protection of GPX1 against oxidative injuries and mortality mediated by reactive oxygen species.
4. Knockout of GPX1 renders mice and their primary hepatocytes resistant to, whereas overexpression of GPX1 sensitizes mice to, oxidative injuries or death mediated by reactive nitrogen species.
5. GPX1 functions in cellular signaling pathways, including cell death and survival, protein kinase phosphorylation, and oxidant-mediated activation of NFκB.
6. Development of hyperglycemia, hyperinsulinemia, insulin resistance, and obesity in GPX1-overexpressing mice, along with the strong positive correlation between gestational diabetes and elevation of erythrocyte GPX1 activity in pregnant women, indicates the importance of maintaining normal GPX1 activity in regulating body glucose homeostasis.
7. Alteration or abnormality of GPX1 expression may be associated with etiology of a number of chronic diseases including cancer, cardiovascular disease, neurodegeneration, autoimmune disorder, and diabetes.
8. Future research should be focused on the molecular mechanisms of GPX1 in the development of chronic diseases and the potential application of GPX1 manipulation in treating the diseases.

ACKNOWLEDGMENTS

The GPX1-related research conducted in X.G. Lei's laboratory was supported in part by NIH grant DK53018. W.H. Cheng was supported in part by the Intramural Research Program of the NIH, National Institute on Aging. J.P. McClung was supported in part by the Military Nutrition Division, U.S. Army Research Institute of Environmental Medicine, Natick, Massachusetts. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the U.S. Department of the Army or Department of Defense. Any citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement of approval of the products or services of these organizations.

LITERATURE CITED

1. Ahn J, Gammon MD, Santella RM, Gaudet MM, Britton JA, et al. 2005. No association between glutathione peroxidase Pro198Leu polymorphism and breast cancer risk. *Cancer Epidemiol. Biomarkers Prev.* 14:2459–61
2. Allan CB, Lacourciere GM, Stadtman TC. 1999. Responsiveness of selenoproteins to dietary selenium. *Annu. Rev. Nutr.* 19:1–16

3. Arai M, Imai H, Koumura T, Yoshida M, Emoto K, et al. 1999. Mitochondrial phospholipid hydroperoxide glutathione peroxidase plays a major role in preventing oxidative injury to cells. *J. Biol. Chem.* 274:4924–33
4. Baker RD, Baker SS, LaRosa K, Whitney C, Newburger PE. 1993. Selenium regulation of glutathione peroxidase in human hepatoma cell line Hep3B. *Arch. Biochem. Biophys.* 304:53–57
5. Barkats M, Millecamps S, Abrioux P, Geoffroy MC, Mallet J. 2000. Overexpression of glutathione peroxidase increases the resistance of neuronal cells to Abeta-mediated neurotoxicity. *J. Neurochem.* 75:1438–46
6. Baum MK, Shor-Posner G, Lai S, Zhang G, Lai H, et al. 1997. High risk of HIV-related mortality is associated with selenium deficiency. *J. Acquir. Immune Defic. Syndr. Hum. Retrovirol.* 15:370–74
7. Beck MA, Esworthy RS, Ho YS, Chu FF. 1998. Glutathione peroxidase protects mice from viral-induced myocarditis. *FASEB J.* 12:1143–49
8. Beckman JS, Koppenol WH. 1996. Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and ugly. *Am. J. Physiol* 271:C1424–37
9. Behne D, Kyriakopoulos A. 2001. Mammalian selenium-containing proteins. *Annu. Rev. Nutr.* 21:453–73
10. Bensadoun JC, Mirochnitchenko O, Inouye M, Aebischer P, Zurn AD. 1998. Attenuation of 6-OHDA-induced neurotoxicity in glutathione peroxidase transgenic mice. *Eur. J. Neurosci.* 10:3231–36
11. Bermano G, Nicol F, Dyer JA, Sunde RA, Beckett GJ, et al. 1995. Tissue-specific regulation of selenoenzyme gene expression during selenium deficiency in rats. *Biochem. J.* 311(Pt. 2):425–30
12. **Berry MJ, Banu L, Chen YY, Mandel SJ, Kieffer JD, et al. 1991. Recognition of UGA as a selenocysteine codon in type I deiodinase requires sequences in the 3′-untranslated region. *Nature* 353:273–76**
13. Bock A. 2000. Biosynthesis of selenoproteins—an overview. *Biofactors* 11:77–78
14. Bosl MR, Takaku K, Oshima M, Nishimura S, Taketo MM. 1997. Early embryonic lethality caused by targeted disruption of the mouse selenocysteine tRNA gene (Trsp). *Proc. Natl. Acad. Sci. USA* 94:5531–34
15. Brownlee M, Cerami A, Vlassara H. 1988. Advanced glycosylation end products in tissue and the biochemical basis of diabetic complications. *N. Engl. J. Med.* 318:1315–21
16. Burk RF. 1991. Molecular biology of selenium with implications for its metabolism. *FASEB J.* 5:2274–79
17. Cao C, Leng Y, Huang W, Liu X, Kufe D. 2003. Glutathione peroxidase 1 is regulated by the c-Abl and Arg tyrosine kinases. *J. Biol. Chem.* 278:39609–14
18. Cao C, Ren X, Kharbanda S, Koleske A, Prasad KV, Kufe D. 2001. The ARG tyrosine kinase interacts with Siva-1 in the apoptotic response to oxidative stress. *J. Biol. Chem.* 276:11465–68
19. Carlson BA, Xu XM, Gladyshev VN, Hatfield DL. 2005. Selective rescue of selenoprotein expression in mice lacking a highly specialized methyl group in selenocysteine tRNA. *J. Biol. Chem.* 280:5542–48
20. Cebrian A, Pharoah PD, Ahmed S, Smith PL, Luccarini C, et al. 2006. Tagging single-nucleotide polymorphisms in antioxidant defense enzymes and susceptibility to breast cancer. *Cancer Res.* 66:1225–33
21. **Chambers I, Frampton J, Goldfarb P, Affara N, McBain W, Harrison PR. 1986. The structure of the mouse glutathione peroxidase gene: the selenocysteine in the active site is encoded by the "termination" codon, TGA. *EMBO J.* 5:1221–27**

12. Illustrates a stem-loop structure in the 3′-untranslated region of selenoprotein mRNA for translating the UGA codon into selenocysteine.

21. Reports the first cloning of GPX1 gene from mice, and unveils UGA that decodes selenocysteine.

22. Chavatte L, Brown BA, Driscoll DM. 2005. Ribosomal protein L30 is a component of the UGA-selenocysteine recoding machinery in eukaryotes. *Nat. Struct. Mol. Biol.* 12:408–16
23. Chen X, Scholl TO, Leskiw MJ, Donaldson MR, Stein TP. 2003. Association of glutathione peroxidase activity with insulin resistance and dietary fat intake during normal pregnancy. *J. Clin. Endocrinol. Metab.* 88:5963–68
24. Cheng W, Fu YX, Porres JM, Ross DA, Lei XG. 1999. Selenium-dependent cellular glutathione peroxidase protects mice against a pro-oxidant-induced oxidation of NADPH, NADH, lipids, and protein. *FASEB J.* 13:1467–75
25. Cheng WH, Combs GFJ, Lei XG. 1998. Knockout of cellular glutathione peroxidase affects selenium-dependent parameters similarly in mice fed adequate and excessive dietary selenium. *Biofactors* 7:311–21
26. Cheng WH, Ho YS, Ross DA, Valentine BA, Combs GF, Lei XG. 1997. Cellular glutathione peroxidase knockout mice express normal levels of selenium-dependent plasma and phospholipid hydroperoxide glutathione peroxidases in various tissues. *J. Nutr.* 127:1445–50

27. First demonstration of GPX1 as an in vivo antioxidant enzyme against pro-oxidant-induced oxidative stress in mice.

27. Cheng WH, Ho YS, Valentine BA, Ross DA, Combs GFJ, Lei XG. 1998. Cellular glutathione peroxidase is the mediator of body selenium to protect against paraquat lethality in transgenic mice. *J. Nutr.* 128:1070–76

28. Cheng WH, Quimby FW, Lei XG. 2003. Impacts of glutathione peroxidase-1 knockout on the protection by injected selenium against the pro-oxidant-induced liver aponecrosis and signaling in selenium-deficient mice. *Free Radic. Biol. Med.* 34:918–27
29. Cheng WH, Zheng X, Quimby FR, Roneker CA, Lei XG. 2003. Low levels of glutathione peroxidase 1 activity in selenium-deficient mouse liver affect c-Jun N-terminal kinase activation and p53 phosphorylation on Ser-15 in pro-oxidant-induced aponecrosis. *Biochem. J.* 370:927–34
30. Chu FF, Esworthy RS, Ho YS, Bermeister M, Swiderek K, Elliott RW. 1997. Expression and chromosomal mapping of mouse Gpx2 gene encoding the gastrointestinal form of glutathione peroxidase, GPX-GI. *Biomed. Environ. Sci.* 10:156–62

31. Demonstrates that daily Se supplementation reduces mortality of lung, colon, and prostate cancer in humans.

31. Clark LC, Combs GFJ, Turnbull BW, Slate EH, Chalker DK, et al. 1996. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. *JAMA* 276:1957–63

32. Combs GF Jr. 2004. Status of selenium in prostate cancer prevention. *Br. J. Cancer* 91:195–99
33. Cosentino F, Hishikawa K, Katusic ZS, Luscher TF. 1997. High glucose increases nitric oxide synthase expression and superoxide anion generation in human aortic endothelial cells. *Circulation* 96:25–28
34. Cox DG, Hankinson SE, Kraft P, Hunter DJ. 2004. No association between GPX1 Pro198Leu and breast cancer risk. *Cancer Epidemiol. Biomarkers Prev.* 13:1821–22
35. Crack PJ, Cimdins K, Ali U, Hertzog PJ, Iannello RC. 2006. Lack of glutathione peroxidase-1 exacerbates αβ-mediated neurotoxicity in cortical neurons. *J. Neural Transm.* 113:645–57
36. Crack PJ, Taylor JM, Ali U, Mansell A, Hertzog PJ. 2006. Potential contribution of NF-κβ in neuronal cell death in the glutathione peroxidase-1 knockout mouse in response to ischemia-reperfusion injury. *Stroke* 37:1533–38
37. Czech MP, Lawrence JCJ, Lynn WS. 1974. Evidence for electron transfer reactions involved in the Cu^{2+}-dependent thiol activation of fat cell glucose utilization. *J. Biol. Chem.* 249:1001–6

38. Damier P, Hirsch EC, Zhang P, Agid Y, Javoy-Agid F. 1993. Glutathione peroxidase, glial cells and Parkinson's disease. *Neuroscience* 52:1–6
39. Davidson JA. 2006. Introductory remarks: diabetes care in America—"a sense of urgency." *Endocr. Pract.* 12(Suppl. 1):13–15
40. Dawson TM, Dawson VL. 2003. Molecular pathways of neurodegeneration in Parkinson's disease. *Science* 302:819–22
41. de Haan JB, Bladier C, Griffiths P, Kelner M, O'Shea RD, et al. 1998. Mice with a homozygous null mutation for the most abundant glutathione peroxidase, Gpx1, show increased susceptibility to the oxidative stress-inducing agents paraquat and hydrogen peroxide. *J. Biol. Chem.* 273:22528–36
42. Desco MC, Asensi M, Marquez R, Martinez-Valls J, Vento M, et al. 2002. Xanthine oxidase is involved in free radical production in type 1 diabetes: protection by allopurinol. *Diabetes* 51:1118–24
43. Diamond AM, Choi IS, Crain PF, Hashizume T, Pomerantz SC, et al. 1993. Dietary selenium affects methylation of the wobble nucleoside in the anticodon of selenocysteine tRNA([Ser]Sec). *J. Biol. Chem.* 268:14215–23
44. Dominguez C, Ruiz E, Gussinye M, Carrascosa A. 1998. Oxidative stress at onset and in early stages of type 1 diabetes in children and adolescents. *Diabetes Care* 21:1736–42
45. Douillet C, Bost M, Accominotti M, Borson-Chazot F, Ciavatti M. 1998. Effect of selenium and vitamin E supplements on tissue lipids, peroxides, and fatty acid distribution in experimental diabetes. *Lipids* 33:393–99
46. Drake EN. 2006. Cancer chemoprevention: selenium as a prooxidant, not an antioxidant. *Med. Hypotheses* 67:318–22
47. Drew JE, Farquharson AJ, Arthur JR, Morrice PC, Duthie GG. 2005. Novel sites of cytosolic glutathione peroxidase expression in colon. *FEBS Lett.* 579:6135–39
48. Driscoll DM, Copeland PR. 2003. Mechanism and regulation of selenoprotein synthesis? *Annu. Rev. Nutr.* 23:17–40
49. Dupont J, LeRoith D. 2001. Insulin and insulin-like growth factor I receptors: similarities and differences in signal transduction. *Horm. Res.* 55(Suppl. 2):22–26
50. Duval C, Auge N, Frisach MF, Casteilla L, Salvayre R, Negre-Salvayre A. 2002. Mitochondrial oxidative stress is modulated by oleic acid via an epidermal growth factor receptor-dependent activation of glutathione peroxidase. *Biochem. J.* 367:889–94
51. Dworkin BM. 1994. Selenium deficiency in HIV infection and the acquired immunodeficiency syndrome (AIDS). *Chem. Biol. Interact.* 91:181–86
52. Emerling BM, Platanias LC, Black E, Nebreda AR, Davis RJ, Chandel NS. 2005. Mitochondrial reactive oxygen species activation of p38 mitogen-activated protein kinase is required for hypoxia signaling. *Mol. Cell. Biol.* 25:4853–62
53. Esposito LA, Kokoszka JE, Waymire KG, Cottrell B, MacGregor GR, Wallace DC. 2000. Mitochondrial oxidative stress in mice lacking the glutathione peroxidase-1 gene. *Free Radic. Biol. Med.* 28:754–66
54. Esworthy RS, Baker MA, Chu FF. 1995. Expression of selenium-dependent glutathione peroxidase in human breast tumor cell lines. *Cancer Res.* 55:957–62
55. Evans JL, Goldfine ID, Maddux BA, Grodsky GM. 2002. Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes. *Endocr. Rev.* 23:599–622
56. Fan C, Li Q, Ross D, Engelhardt JF. 2003. Tyrosine phosphorylation of Iκβ alpha activates NFκβ through a redox-regulated and c-Src-dependent mechanism following hypoxia/reoxygenation. *J. Biol. Chem.* 278:2072–80

57. Faucher K, Rabinovitch-Chable H, Cook-Moreau J, Barriere G, Sturtz F, Rigaud M. 2005. Overexpression of human GPX1 modifies Bax to Bcl-2 apoptotic ratio in human endothelial cells. *Mol. Cell Biochem*. 277:81–87

58. Establishes that GPX1 is an Se-containing enzyme.

58. Flohe L, Gunzler WA, Schock HH. 1973. Glutathione peroxidase: a selenoenzyme. *FEBS Lett*. 32:132–34

59. Fu Y, Cheng WH, Porres JM, Ross DA, Lei XG. 1999. Knockout of cellular glutathione peroxidase gene renders mice susceptible to diquat-induced oxidative stress. *Free Radic. Biol. Med*. 27:605–11

60. Fu Y, Cheng WH, Ross DA, Lei X. 1999. Cellular glutathione peroxidase protects mice against lethal oxidative stress induced by various doses of diquat. *Proc. Soc. Exp. Biol. Med*. 222:164–69

61. Reports the opposite roles of GPX1 in coping with reactive oxygen species versus reactive nitrogen species–induced cell death and related signaling pathways.

61. Fu Y, Sies H, Lei XG. 2001. Opposite roles of selenium-dependent glutathione peroxidase-1 in superoxide generator diquat- and peroxynitrite-induced apoptosis and signaling. *J. Biol. Chem*. 276:43004–9

62. Gardner CD, Eguchi S, Reynolds CM, Eguchi K, Frank GD, Motley ED. 2003. Hydrogen peroxide inhibits insulin signaling in vascular smooth muscle cells. *Exp. Biol. Med. (Maywood)* 228:836–42

63. Gladyshev VN, Factor VM, Housseau F, Hatfield DL. 1998. Contrasting patterns of regulation of the antioxidant selenoproteins, thioredoxin reductase, and glutathione peroxidase, in cancer cells. *Biochem. Biophys. Res. Commun*. 251:488–93

64. Gladyshev VN, Stadtman TC, Hatfield DL, Jeang KT. 1999. Levels of major selenoproteins in T cells decrease during HIV infection and low molecular mass selenium compounds increase. *Proc. Natl. Acad. Sci. USA* 96:835–39

65. Grankvist K, Marklund SL, Taljedal IB. 1981. CuZn-superoxide dismutase, Mn-superoxide dismutase, catalase and glutathione peroxidase in pancreatic islets and other tissues in the mouse. *Biochem. J*. 199:393–98

66. Handy DE, Loscalzo J. 2003. Homocysteine and atherothrombosis: diagnosis and treatment. *Curr. Atheroscler. Rep*. 5:276–83

67. Handy DE, Zhang Y, Loscalzo J. 2005. Homocysteine down-regulates cellular glutathione peroxidase (GPx1) by decreasing translation. *J. Biol. Chem*. 280:15518–25

68. Hansen LL, Ikeda Y, Olsen GS, Busch AK, Mosthaf L. 1999. Insulin signaling is inhibited by micromolar concentrations of H(2)O(2). Evidence for a role of H(2)O(2) in tumor necrosis factor alpha-mediated insulin resistance. *J. Biol. Chem*. 274:25078–84

69. Hardie LJ, Briggs JA, Davidson LA, Allan JM, King RF, et al. 2000. The effect of hOGG1 and glutathione peroxidase I genotypes and 3p chromosomal loss on 8-hydroxydeoxyguanosine levels in lung cancer. *Carcinogenesis* 21:167–72

70. Hockenbery DM, Oltvai ZN, Yin XM, Milliman CL, Korsmeyer SJ. 1993. Bcl-2 functions in an antioxidant pathway to prevent apoptosis. *Cell* 75:241–51

71. Hu Y, Benya RV, Carroll RE, Diamond AM. 2005. Allelic loss of the gene for the GPX1 selenium-containing protein is a common event in cancer. *J. Nutr*. 135:3021–24S

72. Hu YJ, Diamond AM. 2003. Role of glutathione peroxidase 1 in breast cancer: loss of heterozygosity and allelic differences in the response to selenium. *Cancer Res*. 63:3347–51

73. Ichimura Y, Habuchi T, Tsuchiya N, Wang L, Oyama C, et al. 2004. Increased risk of bladder cancer associated with a glutathione peroxidase 1 codon 198 variant. *J. Urol*. 172:728–32

74. Irons R, Carlson BA, Hatfield DL, Davis CD. 2006. Both selenoproteins and low molecular weight selenocompounds reduce colon cancer risk in mice with genetically impaired selenoprotein expression. *J. Nutr*. 136:1311–17

75. Jiang D, Akopian G, Ho YS, Walsh JP, Andersen JK. 2000. Chronic brain oxidation in a glutathione peroxidase knockout mouse model results in increased resistance to induced epileptic seizures. *Exp. Neurol.* 164:257–68

76. Juliet PA, Hayashi T, Iguchi A, Ignarro LJ. 2003. Concomitant production of nitric oxide and superoxide in human macrophages. *Biochem. Biophys. Res. Commun*. 310:367–70

77. Kaaja RJ, Greer IA. 2005. Manifestations of chronic disease during pregnancy. *JAMA* 294:2751–57

78. Karin M. 2006. Nuclear factor-κβ in cancer development and progression. *Nature* 441:431–36

79. Kayanoki Y, Fujii J, Islam KN, Suzuki K, Kawata S, et al. 1996. The protective role of glutathione peroxidase in apoptosis induced by reactive oxygen species. *J. Biochem. (Tokyo)* 119:817–22

80. Klivenyi P, Andreassen OA, Ferrante RJ, Dedeoglu A, Mueller G, et al. 2000. Mice deficient in cellular glutathione peroxidase show increased vulnerability to malonate, 3-nitropropionic acid, and 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine. *J. Neurosci.* 20:1–7

81. Knight TR, Ho YS, Farhood A, Jaeschke H. 2002. Peroxynitrite is a critical mediator of acetaminophen hepatotoxicity in murine livers: protection by glutathione. *J. Pharmacol. Exp. Ther*. 303:468–75

82. Knight TR, Kurtz A, Bajt ML, Hinson JA, Jaeschke H. 2001. Vascular and hepatocellular peroxynitrite formation during acetaminophen toxicity: role of mitochondrial oxidant stress. *Toxicol. Sci*. 62:212–20

83. Kobayashi S, Inoue N, Azumi H, Seno T, Hirata K, et al. 2002. Expressional changes of the vascular antioxidant system in atherosclerotic coronary arteries. *J. Atheroscler. Thromb.* 9:184–90

84. Kote-Jarai Z, Durocher F, Edwards SM, Hamoudi R, Jackson RA, et al. 2002. Association between the GCG polymorphism of the selenium dependent GPX1 gene and the risk of young onset prostate cancer. *Prostate Cancer Prostatic Dis.* 5:189–92

85. Kryukov GV, Castellano S, Novoselov SV, Lobanov AV, Zehtab O, et al. 2003. Characterization of mammalian selenoproteomes. *Science* 300:1439–43

86. Lean JM, Jagger CJ, Kirstein B, Fuller K, Chambers TJ. 2005. Hydrogen peroxide is essential for estrogen-deficiency bone loss and osteoclast formation. *Endocrinology* 146:728–35

87. Lee HT, Emala CW. 2001. Systemic adenosine given after ischemia protects renal function via A(2a) adenosine receptor activation. *Am. J. Kidney Dis*. 38:610–18

88. Lee HT, Emala CW. 2002. Adenosine attenuates oxidant injury in human proximal tubular cells via A(1) and A(2a) adenosine receptors. *Am. J. Physiol. Renal Physiol*. 282:F844–52

89. Lee S, Shin HS, Shireman PK, Vasilaki A, Van RH, Csete ME. 2006. Glutathione-peroxidase-1 null muscle progenitor cells are globally defective. *Free Radic. Biol. Med*. 41:1174–84

90. Lei XG, Zhu JH, McClung JP, Aregullin M, Roneker CA. 2006. Mice deficient in Cu,Zn-superoxide dismutase are resistant to acetaminophen toxicity. *Biochem. J*. 399(3):455–61

91. Leiter EH. 2002. Mice with targeted gene disruptions or gene insertions for diabetes research: problems, pitfalls, and potential solutions. *Diabetologia* 45:296–308

92. Li Q, Engelhardt JF. 2006. Interleukin-1β induction of NFκβ is partially regulated by H2O2-mediated activation of NFκβ-inducing kinase. *J. Biol. Chem*. 281:1495–505

93. Li Q, Sanlioglu S, Li S, Ritchie T, Oberley L, Engelhardt JF. 2001. GPx-1 gene delivery modulates NFκβ activation following diverse environmental injuries through a specific subunit of the IKK complex. *Antioxid. Redox Signal*. 3:415–32

75. Demonstrates that knockout of GPX1 actually protects mice from kainic acid–induced epileptic seizures and mortality.

85. Concludes that there are a total of 25 selenoproteins in the human genome by searching for SECIS in the entire genome.

94. Li X, Chen H, Epstein PN. 2006. Metallothionein and catalase sensitize to diabetes in nonobese diabetic mice: reactive oxygen species may have a protective role in pancreatic β-cells. *Diabetes* 55:1592–604
95. Lin A. 2003. Activation of the JNK signaling pathway: breaking the brake on apoptosis. *Bioessays* 25:17–24
96. Liu GS, Thornton J, Van Winkle DM, Stanley AW, Olsson RA, Downey JM. 1991. Protection against infarction afforded by preconditioning is mediated by A1 adenosine receptors in rabbit heart. *Circulation* 84:350–56
97. Mahadev K, Wu X, Zilbering A, Zhu L, Lawrence JT, Goldstein BJ. 2001. Hydrogen peroxide generated during cellular insulin stimulation is integral to activation of the distal insulin signaling cascade in 3T3-L1 adipocytes. *J. Biol. Chem*. 276:48662–69
98. Martin-Gallan P, Carrascosa A, Gussinye M, Dominguez C. 2003. Biomarkers of diabetes-associated oxidative stress and antioxidant status in young diabetic patients with or without subclinical complications. *Free Radic. Biol. Med*. 34:1563–74

99. Presents physiological evidence that overexpression of GPX1 disturbs glucose metabolism in mice.

99. McClung JP, Roneker CA, Mu W, Lisk DJ, Langlais P, et al. 2004. Development of insulin resistance and obesity in mice overexpressing cellular glutathione peroxidase. *Proc. Natl. Acad. Sci. USA* 101:8852–57

100. McNeill JH, Delgatty HL, Battell ML. 1991. Insulinlike effects of sodium selenate in streptozocin-induced diabetic rats. *Diabetes* 40:1675–78
101. Memisogullari R, Taysi S, Bakan E, Capoglu I. 2003. Antioxidant status and lipid peroxidation in type II diabetes mellitus. *Cell Biochem. Funct*. 21:291–96
102. Michael SL, Mayeux PR, Bucci TJ, Warbritton AR, Irwin LK, et al. 2001. Acetaminophen-induced hepatotoxicity in mice lacking inducible nitric oxide synthase activity. *Nitric Oxide* 5:432–41
103. Mills GC. 1957. Hemoglobin catabolism. I. Glutathione peroxidase, an erythrocyte enzyme which protects hemoglobin from oxidative breakdown. *J. Biol. Chem*. 229:189–97
104. Mirault ME, Tremblay A, Beaudoin N, Tremblay M. 1991. Overexpression of selenoglutathione peroxidase by gene transfer enhances the resistance of T47D human breast cells to clastogenic oxidants. *J. Biol. Chem*. 266:20752–60

105. Demonstrates that overexpression of GPX1 sensitizes mice to acetaminophen toxicity.

105. Mirochnitchenko O, Weisbrot-Lefkowitz M, Reuhl K, Chen L, Yang C, Inouye M. 1999. Acetaminophen toxicity. Opposite effects of two forms of glutathione peroxidase. *J. Biol. Chem*. 274:10349–55

106. Moriarty PM, Reddy CC, Maquat LE. 1998. Selenium deficiency reduces the abundance of mRNA for Se-dependent glutathione peroxidase 1 by a UGA-dependent mechanism likely to be nonsense codon-mediated decay of cytoplasmic mRNA. *Mol. Cell. Biol*. 18:2932–39
107. Moscow JA, Schmidt L, Ingram DT, Gnarra J, Johnson B, Cowan KH. 1994. Loss of heterozygosity of the human cytosolic glutathione peroxidase I gene in lung cancer. *Carcinogenesis* 15:2769–73
108. Mukherjee B, Anbazhagan S, Roy A, Ghosh R, Chatterjee M. 1998. Novel implications of the potential role of selenium on antioxidant status in streptozotocin-induced diabetic mice. *Biomed. Pharmacother*. 52:89–95
109. Mysore TB, Shinkel TA, Collins J, Salvaris EJ, Fisicaro N, et al. 2005. Overexpression of glutathione peroxidase with two isoforms of superoxide dismutase protects mouse islets from oxidative injury and improves islet graft function. *Diabetes* 54:2109–16
110. Nasr MA, Fedele MJ, Esser K, Diamond AM. 2004. GPx-1 modulates Akt and P70S6K phosphorylation and Gadd45 levels in MCF-7 cells. *Free Radic. Biol. Med*. 37:187–95
111. National Research Council. 1989/1983. *Selenium Nutrition*. Washington, DC: Nat. Acad. Press

112. Nomura K, Imai H, Koumura T, Arai M, Nakagawa Y. 1999. Mitochondrial phospholipid hydroperoxide glutathione peroxidase suppresses apoptosis mediated by a mitochondrial death pathway. *J. Biol. Chem*. 274:29294–302
113. Novoselov SV, Calvisi DF, Labunskyy VM, Factor VM, Carlson BA, et al. 2005. Selenoprotein deficiency and high levels of selenium compounds can effectively inhibit hepatocarcinogenesis in transgenic mice. *Oncogene* 24:8003–11
114. Ono K, Han J. 2000. The p38 signal transduction pathway: activation and function. *Cell. Signal*. 12:1–13
115. Packham G, Ashmun RA, Cleveland JL. 1996. Cytokines suppress apoptosis independent of increases in reactive oxygen levels. *J. Immunol*. 156:2792–800
116. Papp LV, Lu J, Striebel F, Kennedy D, Holmgren A, Khanna KK. 2006. The redox state of SECIS binding protein 2 controls its localization and selenocysteine incorporation function. *Mol. Cell. Biol*. 26:4895–910
117. Parathath SR, Parathath S, Tsirka SE. 2006. Nitric oxide mediates neurodegeneration and breakdown of the blood-brain barrier in tPA-dependent excitotoxic injury in mice. *J. Cell Sci*. 119:339–49
118. Ravn-Haren G, Olsen A, Tjonneland A, Dragsted LO, Nexo BA, et al. 2006. Associations between GPX1 Pro198Leu polymorphism, erythrocyte GPX activity, alcohol consumption and breast cancer risk in a prospective cohort study. *Carcinogenesis* 27:820–25
119. Ridet JL, Bensadoun JC, Deglon N, Aebischer P, Zurn AD. 2006. Lentivirus-mediated expression of glutathione peroxidase: neuroprotection in murine models of Parkinson's disease. *Neurobiol. Dis*. 21:29–34
120. Rosen P, Nawroth PP, King G, Moller W, Tritschler HJ, Packer L. 2001. The role of oxidative stress in the onset and progression of diabetes and its complications: a summary of a Congress Series sponsored by UNESCO-MCBN, the American Diabetes Association and the German Diabetes Society. *Diabetes Metab. Res. Rev*. 17:189–212
121. Rotruck JT, Pope AL, Ganther HE, Swanson AB, Hafeman DG, Hoekstra WG. 1973. Selenium: biochemical role as a component of glutathione peroxidase. *Science* 179:588–90
122. Saedi MS, Smith CG, Frampton J, Chambers I, Harrison PR, Sunde RA. 1988. Effect of selenium status on mRNA levels for glutathione peroxidase in rat liver. *Biochem. Biophys. Res. Commun*. 153:855–61
123. Salonen JT, Nyyssonen K, Tuomainen TP, Maenpaa PH, Korpela H, et al. 1995. Increased risk of noninsulin-dependent diabetes mellitus at low plasma vitamin E concentrations: a four-year follow up study in men. *BMJ* 311:1124–27
124. Savolainen H. 1978. Superoxide dismutase and glutathione peroxidase activities in rat brain. *Res. Commun. Chem. Pathol. Pharmacol*. 21:173–76
125. Shen Q, Chu FF, Newburger PE. 1993. Sequences in the 3′-untranslated region of the human cellular glutathione peroxidase gene are necessary and sufficient for selenocysteine incorporation at the UGA codon. *J. Biol. Chem*. 268:11463–69
126. Shisler JL, Senkevich TG, Berry MJ, Moss B. 1998. Ultraviolet-induced cell death blocked by a selenoprotein from a human dermatotropic poxvirus. *Science* 279:102–5
127. Sies H, Sharov VS, Klotz LO, Briviba K. 1997. Glutathione peroxidase protects against peroxynitrite-mediated oxidations. A new function for selenoproteins as peroxynitrite reductase. *J. Biol. Chem*. 272:27812–17
128. Small-Howard A, Morozova N, Stoytcheva Z, Forry EP, Mansell JB, et al. 2006. Supramolecular complexes mediate selenocysteine incorporation in vivo. *Mol. Cell. Biol.* 26:2337–46

121. Establishes that GPX1 is an Se-containing enzyme.

122. Shows that dietary Se deficiency in rats resulted in dramatic reduction of liver GPX1 mRNA levels and provides evidence for the regulation of Se on GPX1 gene expression.

129. Stadtman TC. 1996. Selenocysteine. *Annu. Rev. Biochem.* 65:83–100
130. Sun X, Majumder P, Shioya H, Wu F, Kumar S, et al. 2000. Activation of the cytoplasmic c-Abl tyrosine kinase by reactive oxygen species. *J. Biol. Chem.* 275:17237–40
131. Sunde RA. 1994. Intracellular glutathione peroxidases-structures, regulation, and functions. In *Selenium in Biology and Human Health*, ed. RF Burk, 10:45–77. New York: Springer-Verlag
132. Sunde RA, Saedi MS, Knight SAB, Smith CG, Evanson JK. 1989. Regulation of expression of glutathione peroxidase by selenium. In *Selenium in Biology and Medicine*, ed. A Wendel, 4:8–13. Heidelberg: Springer-Verlag
133. Sunde RA, Thompson BM, Palm MD, Weiss SL, Thompson KM, Evenson JK. 1997. Selenium regulation of selenium-dependent glutathione peroxidases in animals and transfected CHO cells. *Biomed. Environ. Sci.* 10:346–55
134. Sutton A, Nahon P, Pessayre D, Rufat P, Poire A, et al. 2006. Genetic polymorphisms in antioxidant enzymes modulate hepatic iron accumulation and hepatocellular carcinoma development in patients with alcohol-induced cirrhosis. *Cancer Res.* 66:2844–52
135. Takahashi K, Avissar N, Whitin J, Cohen H. 1987. Purification and characterization of human plasma glutathione peroxidase: a selenoglycoprotein distinct from the known cellular enzyme. *Arch. Biochem. Biophys.* 256:677–86
136. Takakura K, Beckman JS, Millan-Crow LA, Crow JP. 1999. Rapid and irreversible inactivation of protein tyrosine phosphatases PTP1B, CD45, and LAR by peroxynitrite. *Arch. Biochem. Biophys.* 369:197–207
137. Takeshita S, Inoue N, Ueyama T, Kawashima S, Yokoyama M. 2000. Shear stress enhances glutathione peroxidase expression in endothelial cells. *Biochem. Biophys. Res. Commun.* 273:66–71
138. Takizawa S, Matsushima K, Shinohara Y, Ogawa S, Komatsu N, et al. 1994. Immunohistochemical localization of glutathione peroxidase in infarcted human brain. *J. Neurol. Sci.* 122:66–73
139. Taylor JM, Crack PJ, Gould JA, Ali U, Hertzog PJ, Iannello RC. 2004. Akt phosphorylation and NFκβ activation are counterregulated under conditions of oxidative stress. *Exp. Cell Res.* 300:463–75
140. Taylor SD, Davenport LD, Speranza MJ, Mullenbach GT, Lynch RE. 1993. Glutathione peroxidase protects cultured mammalian cells from the toxicity of adriamycin and paraquat. *Arch. Biochem. Biophys.* 305:600–5
141. Thomas JP, Maiorino M, Ursini F, Girotti AW. 1990. Protective action of phospholipid hydroperoxide glutathione peroxidase against membrane-damaging lipid peroxidation. In situ reduction of phospholipid and cholesterol hydroperoxides. *J. Biol. Chem.* 265:454–61
142. Ursini F, Heim S, Kiess M, Maiorino M, Roveri A, et al. 1999. Dual function of the selenoprotein PHGPx during sperm maturation. *Science* 285:1393–96
143. Vijayalingam S, Parthiban A, Shanmugasundaram KR, Mohan V. 1996. Abnormal antioxidant status in impaired glucose tolerance and noninsulin-dependent diabetes mellitus. *Diabet. Med.* 13:715–19
144. Weiss N, Zhang YY, Heydrick S, Bierl C, Loscalzo J. 2001. Overexpression of cellular glutathione peroxidase rescues homocyst(e)ine-induced endothelial dysfunction. *Proc. Natl. Acad. Sci. USA* 98:12503–8
145. Xu XM, Mix H, Carlson BA, Grabowski PJ, Gladyshev VN, et al. 2005. Evidence for direct roles of two additional factors, SECp43 and soluble liver antigen, in the selenoprotein synthesis machinery. *J. Biol. Chem.* 280:41568–75

146. Yoshida T, Watanabe M, Engelman DT, Engelman RM, Schley JA, et al. 1996. Transgenic mice overexpressing glutathione peroxidase are resistant to myocardial ischemia reperfusion injury. *J. Mol. Cell. Cardiol.* 28:1759–67
147. Yoshimura S, Watanabe K, Suemizu H, Onozawa T, Mizoguchi J, et al. 1991. Tissue specific expression of the plasma glutathione peroxidase gene in rat kidney. *J. Biochem. (Tokyo)* 109:918–23
148. Zamamiri-Davis F, Lu Y, Thompson JT, Prabhu KS, Reddy PV, et al. 2002. Nuclear factor-κβ mediates overexpression of cyclooxygenase-2 during activation of RAW 264.7 macrophages in selenium deficiency. *Free Radic. Biol. Med.* 32:890–97
149. Zavacki AM, Mansell JB, Chung M, Klimovitsky B, Harney JW, Berry MJ. 2003. Coupled tRNA(Sec)-dependent assembly of the selenocysteine decoding apparatus. *Mol. Cell* 11:773–81
150. Zhang J, Graham DG, Montine TJ, Ho YS. 2000. Enhanced N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine toxicity in mice deficient in CuZn-superoxide dismutase or glutathione peroxidase. *J. Neuropathol. Exp. Neurol.* 59:53–61
151. Zhang Y, Handy DE, Loscalzo J. 2005. Adenosine-dependent induction of glutathione peroxidase 1 in human primary endothelial cells and protection against oxidative stress. *Circ. Res.* 96:831–37
152. Zhu JH, Lei XG. 2006. Double null of selenium-glutathione peroxidase-1 and copper, zinc-superoxide dismutase enhances resistance of mouse primary hepatocytes to acetaminophen toxicity. *Exp. Biol. Med. (Maywood)* 231:545–52

152. Demonstrates that double knockout of GPX1 and Cu,Zn-superoxide dismutase does not potentiate but actually enhances resistance of mouse primary hepatocytes to acetaminophen toxicity.

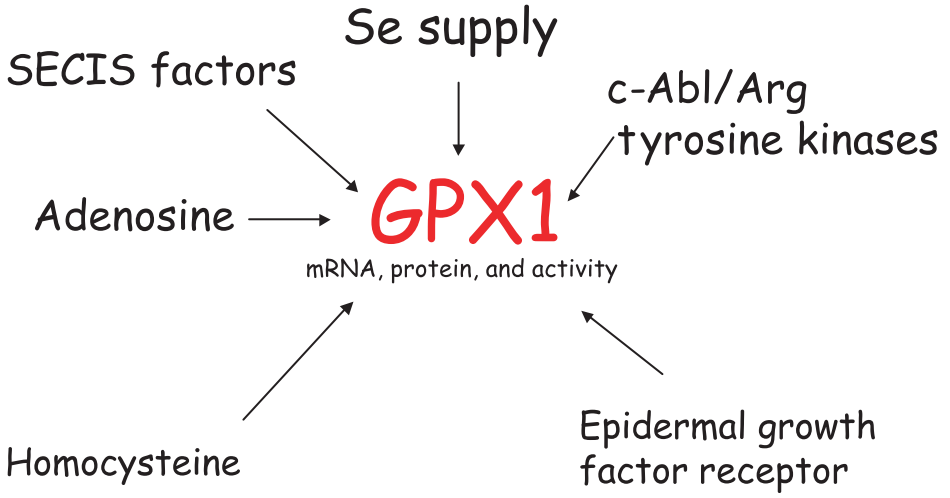

Figure 1

Regulators of GPX1 expression and activity.

Figure 2

Dual roles of GPX1 in ROS- versus RNS-related oxidative stress.

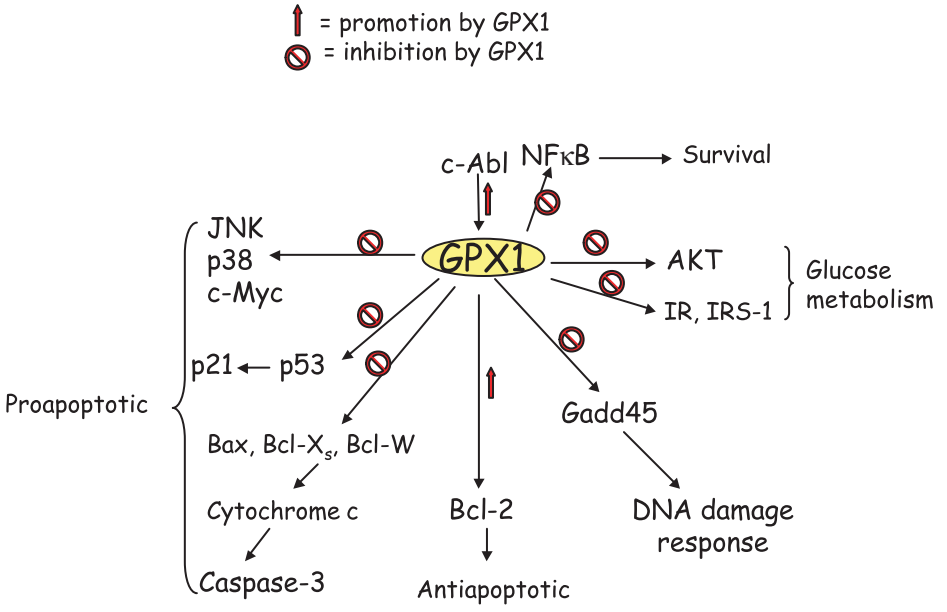

Figure 3

Roles of GPX1 in ROS-induced signal transduction; ↑ = promotion by GPX1; ⊘ = inhibition by GPX1.

Annual Review of Nutrition
Volume 27, 2007

Contents

Indexes

Errata

An online log of corrections to *Annual Review of Nutrition* chapters (if any, 1997 to the present) may be found at http://nutr.annualreviews.org/errata.shtml