Inverse mRNA Expression of the Selenocysteine-Containing Proteins GI-GPx and SeP in Colorectal Adenomas Compared With Adjacent Normal Mucosa

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Abstract: Four selenocysteine-containing proteins (gastrointestinal glutathione peroxidase, plasma glutathione peroxidase, selenoprotein P, and thioredoxin reductase) are expressed in the colonic mucosa. Because of their antioxidant functions, a protective role in colon carcinogenesis is discussed. The aim of this study was to elucidate an involvement of gastrointestinal selenoproteins during the adenoma-carcinoma sequence. Matched pairs of biopsies of colorectal adenomas and adjacent normal mucosa from 11 patients were analyzed for mRNA expression, protein expression, or enzyme activity of selenoproteins by Northern blot, Western blot, or enzymatic tests. All adenomas revealed a marked reduction of selenoprotein P and a variable increase of gastrointestinal glutathione peroxidase mRNA compared with adjacent tissue. Thioredoxin reductase and plasma glutathione peroxidase mRNA expression were not altered in adenomas. The Northern blot results were confirmed by Western blot analysis or enzyme activity measurement, respectively. We conclude that gastrointestinal glutathione peroxidase and selenoprotein P play a complementary role in the antioxidative cell defense along the adenoma-carcinoma sequence. It remains to be shown whether upregulation of gastrointestinal glutathione peroxidase in adenomas represents a compensatory mechanism to reduce susceptibility for oxidative damage resulting from the loss of selenoprotein P.

Introduction

Colorectal tumorigenesis is a multistep process based on inherited or acquired molecular defects that are associated with a progressive disorganization of tissue architecture as well as derangement of regulation of normal cell replication and differentiation. Numerous mutagenic events can occur throughout colorectal carcinogenesis. For instance, activating point mutations in oncogenes such as K-ras or loss of heterozygosity in tumor suppressor genes such as APC, MCC, DCC, and p53 facilitate colorectal carcinogenesis (1,2). Additionally, mutations of the “mutator genes” hMSH2, hMLH1, hPMS1, and hPMS2 induce general genomic instability as a result of the impairment of the DNA mismatch repair system (3). A major contribution to DNA damage in tumor progression in the colon (4,5), as well as mismatch repair deficiency (6), is caused by oxidative stress due to production of H₂O₂ and other reactive oxygen species (ROS). The number of ROS-induced hits is estimated at 20,000 per cell per day (7). Several antioxidants, such as reduced glutathione (GSH) and thioredoxin (Trx), are suggested to protect cells and the genome against H₂O₂- and ROS-inducible damage. The proteinaceous tripeptide GSH occurs intracellularly in high concentrations of 0.5–12 mmol (8) and contributes to prevent oxidative decay of cellular and subcellular structures (9). Regeneration of GSH occurs enzymatically by glutathione reductase. Trx, a protein disulfide reductase, catalyzes the first unique step in DNA synthesis and is involved in regeneration of reductive enzymes as well as redox regulation of enzymes and transcription factors (10). Oxidized Trx is regenerated by the selenocysteine-containing protein thioredoxin reductase (TrxR) (11).

Reduction of hydroperoxides is catalyzed by the selenocysteine-containing protein family of glutathione peroxidases (GPx), which use GSH as a cofactor. The classical cellular GPx, cGPx (12,13), the plasma GPx, pGPx (14), and the gastrointestinal GPx, GI-GPx (15), detoxify H₂O₂ and organic hydroperoxides. The reduction of phospholipid hydroperoxide, cholesterol hydroperoxide, and linoleic acid hydroperoxide is catalyzed by phospholipid hydroperoxide GPx (16). In addition, selenoprotein P (SeP) is able to reduce phospholipid hydroperoxide, although less efficiently than phospholipid hydroperoxide GPx (17).

Recently, we identified the mRNA of four different selenocysteine-containing proteins in the mucosa of the gastrointestinal tract: pGPx, GI-GPx, TrxR-α, and SeP (18). pGPx is a secreted GPx isoform (14), which may contribute to

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extracellular neutralization of H₂O₂. In contrast, the cytosolic isoform GI-GPx is suggested to play an important role in controlling cellular redox mechanisms (12,13) and resistance against colon cancer development (19).

Although TrxR-α mRNA has been found nearly ubiquitously in the human digestive tract (18), gastrointestinal expression of the recently described isoform TrxR-β (20) is unknown. Besides control of various cellular redox-related processes such as transcription (e.g., activation of nuclear factor-κB and activator protein-1), TrxR is involved in protein-DNA interactions, growth control, and DNA synthesis (21–23). Furthermore, because of elevated TrxR and Trx gene expression in colon cancer tissue and some cell lines, an association to colon carcinogenesis has been discussed (24,25).

The biological function of SeP, the fourth gastrointestinal selenocysteine-containing protein (18), is discussed. There is increasing evidence for an important role in the antioxidant defense, as indicated by the high content of selenocysteine residues (26–28), a protective effect against diquat- or paraquat-induced liver damage (29,30), protection against peroxynitrite-inducible cell injury (31), protection against oxidative damage from glutathione depletion in selenium-deficient rats (32), and phospholipid hydroperoxide reduction (17). SeP mRNA expression is detectable in colon carcinoma cells (33). Similar to GI-GPx, particularly high SeP mRNA levels have been demonstrated in the human colon and rectum (18).

To determine a potential involvement of the gastrointestinal selenoproteins in colon cancer development, we investigated human biopsy specimens of colorectal adenomas in comparison to surrounding nonadenomatous tissue for the expression of GI-GPx, SeP, pGPx, and TrxR-α at the mRNA, protein, and functional levels.

Methods

Biopsy Sampling

With written informed consent of the patients, matched pairs of forceps biopsies from colorectal adenomas and adjacent normal mucosa were obtained during therapeutic colonoscopy before removal of the polyps (n = 10). Furthermore, biopsies from rectal adenomas were obtained from one patient with familial adenomatous polyposis (FAP) during diagnostic sigmoidoscopy before proctocolectomy. Tissue samples from patients with no pathological findings during diagnostic colonoscopies served as controls.

RNA Isolation and Northern Analyses

Total RNA was isolated by guanidine-CsCl centrifugation according to the method of Chirgwin and co-workers (34). Fifteen micrograms of total RNA were separated by electrophoresis on denaturing formaldehyde gels, transferred to nylon membranes, and fixed by ultraviolet cross-linking. The cDNA probes were hybridized in a solution containing 5× saline-sodium citrate, 50% formamide, 1× Denhardt’s reagent, 1% sodium dodecyl sulfate, 20 mM sodium phosphate, pH 6.3, 100 µg/ml denatured salmon sperm DNA, and radiolabeled cDNA (probe 0.3 MBq/ml) at 65°C overnight. cDNA probes were labeled with deoxy-[α-32P]CTP (110 TBq/mmol; Amersham, Braunschweig, Germany) by use of the random primed DNA labeling kit (Boehringer, Mannheim, Germany). Integrity and equal loading of RNA were monitored by ethidium bromide staining and hybridization with radiolabeled cDNA probes for the constitutively expressed genes glyceraldehyde 3-phosphate dehydrogenase or β-actin. Blots were exposed to Kodak X-o-mat X-ray films for one to five days at ~80°C with intensifying screen. Hybridization signal intensity was evaluated by densitometric measurement.

cDNA Probes

The hybridization probe for human SeP was a 927-bp reverse transcriptase-polymerase chain reaction product amplified from HepG2 cDNA with primers specific for the 5’-part of the published cDNA sequence (35). The full-length cDNA of the human GI-GPx (bases 1–971) was obtained from Dr. F. F. Chu (Duarte, CA) (15). The human fetal liver glyceraldehyde 3-phosphate dehydrogenase cDNA was obtained from American Type Culture Collection (no. 57091). The rat β-actin probe consisted of a 1,200-bp insert and 150 bp of the pBluescript vector obtained from Dr. Mazoub (Boston, MA). The human pGPx probe was polymerase chain reaction cloned (corresponding to bases 70–536) using primers for the published pGPx cDNA sequence (36). The hybridization probe for human TrxR was a differential display polymerase chain reaction product of 1.4 kb or the 2.3-kb 5’-product of rapid amplification of cDNA ends (37).

GPx Activity Measurement

Biopsy specimens were homogenized in a glass Teflon potter, resuspended, and sonicated in buffer containing 250 mM sucrose, 20 mM N-2-hydroxyethylpiperazine-N’-2-ethane sulfonic acid, and 1 mM EDTA, pH 7.4. GPx activity was assayed by the method of Beutler (38), with tertiary butyhydroperoxide as the substrate. Cytosols of the biopsies (50 µg) were added to the reaction mixture in a final volume of 1 ml [0.1 M tris(hydroxymethyl)aminomethane (Tris), 0.5 mM EDTA (pH 8), 200 µM NADPH, 2 mM glutathione, and 1 U/ml glutathione reductase type IV from baker’s yeast; Sigma Chemical, Deisenhofen, Germany]. The reaction was started by the addition of 7 µM tertiary butyhydroperoxide. After an initial incubation period of 1–1.5 minutes, the oxidation of NADPH was measured at 340 nm, within the linear range of the reaction for 2–3 minutes. The activity of GPx was expressed as nanomoles of NADPH oxidized per minute per milligram of protein, as determined by the Bradford Bio-Rad protein assay (39). Unspecific NADPH oxidation was meas-
ured by the complete inhibition of GPx by the addition of 100 mM mercaptosuccinate, the GPx inhibitor, to the incubation mixture before initiation of the reaction. The background values were subtracted from the obtained results.

TrxR Activity Measurement

TrxR activity was measured according to the dithionitrobenzoic acid (DTNB) method as described by Holmgren and Björnstedt (11). Cytosols were prepared as described above. The assay mixture (1 ml) consisted of 100 mM potassium phosphate, pH 7.0, 10 mM EDTA, 2 mg/ml DTNB, and 0.2 mg/ml NADPH. An aliquot of cytosol (100 µl, 1–6 µg protein/µl) was added, and the change in absorption at 412 nm was monitored for two minutes. Unspecific substrate oxidation (1–8% of the results obtained for the cytosols), as monitored in a reference cuvette containing the assay mixture (900 µl + 100 µl of suspension buffer), was subtracted. Activity was defined as micromoles of DTNB reduced to thionitrobenzoic acid (TNB) per minute (Δ412/13.6 × 2). Results are expressed as activity per milligram of cellular protein. Each measurement was performed in triplicate.

Production of Polyclonal Antibodies Against SeP

Antigenic domains of SeP were predicted by antigenicity diagrams (40–42). An antigenic peptide of 15 amino acids was chosen from the COOH region of SeP (43). The peptide was synthesized and coupled to the carrier keyhole limpet hemocyanin (Eurogentec, Seraing, Belgium). Rabbits were immunized and boosted with this conjugate. Immunoglobulins (Ig) were isolated from the rabbit sera by sodium sulfate precipitation according to Kekwick (44); then the samples were subjected to centrifugation and dialysis.

Western Blot Analysis

Biopsy samples were diluted with sample buffer [400 mM Tris, 4% lithium dodecyl sulfate (w/vol), 30% glycerin (vol/vol), 204 mM mercaptoacetic acid, and 0.02% bromphenol blue, pH 6.8]; 25 µg of protein were loaded per lane. The proteins were separated by 12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (45,46), transferred to nitrocellulose membranes, and stained with Ponceau S. Membranes were blocked with 3% nonfat milk powder, 3% bovine serum albumin (BSA), 2% horse serum, and 0.1% Tween 20 in phosphate-buffered saline (PBS) for two hours at room temperature. Membranes were incubated with the different Ig preparations (working dilution 1:750) in PBS, 1% nonfat dry milk, 1% BSA, 1% horse serum, and 0.1% Tween 20 overnight at 4°C and washed with a solution containing 10 mM Tris, 150 mM or 1 M NaCl, 0.1% t-octylphenoxypolyethoxethanol (Trition X-100), 2 mM EDTA, 1% nonfat dry milk, 1% BSA, and 1% horse serum. Finally, membranes were incubated with a peroxidase-labeled secondary antibody (anti-rabbit antibody, dilution 1:2,000, dilution 1:5,000 in PBS, 1% nonfat dry milk, 1% BSA, 1% horse serum, and 0.1% Tween 20) for one hour at 4°C and washed as described above (43). Detection was done with the enhanced chemiluminescence system according to the manufacturers’ instructions (Amersham Buchler).

Results

Patient Characteristics

Matched pairs of biopsy specimens of adenomatous polyps and normal adjacent mucosa of 10 patients were examined as well as one adenomatous tissue biopsy of a patient with FAP. Patient characteristics and the histological findings of the polyps are shown in Table 1.

Northern Blot Analyses

GI-GPx mRNA expression was elevated in the biopsy specimens of all adenomas. The mean increase in the quantified GI-GPx mRNA steady-state levels was 4.7 ± 4.6 (SE)-fold (range 1.1–17.7) compared with normal adjacent mucosa (Patients 1–10). In contrast, SeP mRNA expression was markedly decreased in all adenomas. The average reduction

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a: M, male; F, female.

b: A patient with familial adenomatous polyposis. In this case, biopsies of adjacent normal mucosa were not available. Patient underwent proctocolectomy.
was a 9.0 ± 9.5-fold decrease (range −3.2 to −32.8) of the SeP mRNA steady-state levels compared with surrounding normal mucosa. The same results were seen in the adenomatous tissue of the patient with FAP (Patient 11; Figures 1 and 2).

In contrast to the marked alterations of GI-GPx and SeP mRNA expression, neither TrxR-α nor pGPx revealed significant differences in the mRNA expression between adenomatous and adjacent nonadenomatous colorectal tissue. Compared with normal surrounding mucosa, TrxR-α and pGPx mRNA levels were only slightly increased in the adenomas: 1.4 ± 0.3-fold (TrxR-α) and 1.5 ± 0.6-fold (pGPx). The deviation of the selenoprotein mRNA levels in the adenomas from the values in the normal mucosa (100%) is shown in Figure 3.

GPx Enzyme Activity

GPx enzyme activity measurements (Patients 1–10) revealed a mean GPx activity in normal adjacent mucosa of 29.8 ± 3.9 nmol NADPH oxidized-min⁻¹·mg protein⁻¹. In adenomatous tissue, a mean GPx activity of 47.6 ± 8.9 nmol NADPH oxidized-min⁻¹·mg protein⁻¹ was determined. Therefore, in comparison to the surrounding nonadenomatous mucosa, in colorectal adenomas the enzyme activity levels were increased by a mean factor of 1.6, which is statistically not significant. GPx activities in adenomas and adjacent normal mucosa are shown in Figure 4.

TrxR Activity

In correlation with the Northern blot results, TrxR activity in adenomas was only slightly enhanced but did not differ substantially from that in normal adjacent mucosa. In adenomatous tissue the mean TrxR activity was 2.7 ± 0.4 µmol TNB-min⁻¹·mg protein⁻¹, in contrast to 2.4 ± 0.3 µmol TNB-min⁻¹·mg protein⁻¹ in surrounding nonadenomatous tissue (Figure 5).

Ponceau S Staining of Gastrointestinal Proteins and Western Blot Analysis of SeP

The Ponceau S staining showed no differences in the protein pattern or intensity of the signals for extracts of normal mucosa and adenomatous tissue (Figure 6, Lanes 1a and 2a). Variations of signal intensity and pattern of protein bands immunoreactive with SeP antisera were detected by Western blot analysis by Ig preparation of rabbit sera against a COOH regional peptide of SeP (Figure 6, Lanes 1b and 2b). Signals in the normal mucosa extract were stronger than those in the adenoma tissue extract. Several bands were detected with the polyclonal Ig antibody: normal mucosa extracts gave a broad diffuse band between 65 and 51 kDa, and adenoma tissue extracts gave a smaller band between 56 and 51 kDa and a sharp band at 61 kDa. Those molecular mass regions are in accordance with both isoforms of mature human SeP as described in the literature (61 and 55 kDa) (47–50). In both tissue extracts, two sharp bands were detected at 40 and 37 kDa; however, the 37-kDa band was stronger in the normal mucosa tissue extract than in the adenoma tissue extract. A further 34-kDa band was detectable only in the normal mucosa. An additional 24-kDa band was detected in both extracts but was of lower intensity in the adenomatous tissue. These signals in the low-kilodalton range might refer to deglycosylated or immature truncated forms of SeP (31). Furthermore, a band at 81 kDa was visible only in the adenoma tissue extract. The origin of this band is unknown.
Discussion

Epidemiological data (51,52), animal studies (53–56), and interventional studies (57) have raised an ongoing discussion about a potential chemopreventive effect of selenium against colorectal cancer. We previously described differential mRNA expression of four selenocysteine-containing proteins in the human gastrointestinal tract that may serve as molecular targets for supplemental selenium. Because of a particularly strong expression of GI-GPx and SeP in the colorectal mucosa of healthy individuals, a protective role of those proteins in the development of colorectal cancer is discussed (18). In this study, we present data on the
mRNA expression, enzyme activity, and protein expression of gastrointestinal selenoproteins in colorectal adenomas compared with normal adjacent mucosa. All adenomatous polyps revealed markedly decreased SeP and elevated GI-GPx mRNA levels. Obviously, the mRNA expression pattern of SeP and GI-GPx changes during adenomatous transition, suggesting links to colon carcinogenesis. Whether their inverse mRNA expression in adenomas is caused by a common regulating factor or represents independent phenomena must be discussed. The fact that both genes encode for selenocysteine-containing proteins raises the question regarding the role of selenium supply, particularly in reference to data suggesting a correlation between low selenium levels and adenoma and cancer development in the colon (51–59). However, the inverse expression of GI-GPx and SeP and the unchanged mRNA steady-state levels of the other selenoproteins TrxR-α and pGPx indicate that the altered expression of GI-GPx and SeP is independent of individual selenium supply.

With regard to the marked decrease of SeP mRNA in adenomatous tissue, cytokines must be discussed as potential regulatory factors. Cloning and characterization of the human SeP promoter by our group revealed downregulation of SeP expression and promoter activity by the proinflamma-
Figure 6. Ponceau S staining for whole protein and Western blot analysis for SeP of tissue extracts from colorectal adenoma and adjacent mucosa. Left: Blotted nitrocellulose membrane stained with Ponceau S: normal colorectal mucosa (Lane 1a) and colorectal adenomatous tissue (Lane 2a). Right: Western blot analysis with immunglobulin preparations from rabbit sera against synthetic COOH regional peptide of SeP: normal colorectal mucosa (Lane 1b) and adenomatous tissue (Lane 2b).

#### Cytokines and SeP Expression in Colorectal Tissues

In the context of colorectal cancer, cytokines and TGF-β play a crucial role in the regulation of SeP expression. Interferon-γ, interleukin-1β, and tumor necrosis factor-α in transient transfection experiments have been shown to affect SeP expression. However, the mechanism by which these cytokines regulate SeP expression is not fully understood.

#### SeP Expression and GI-GPx Levels

SeP expression might occur as an early event in the adenoma-carcinoma sequence, leading to increased genetic instability. The GI-GPx gene maps to chromosome 14q24.1, near Fos and TGF-β1, in the vicinity of the colon cancer susceptibility locus Ccs1 (65), suggesting a potential role in colorectal cancer susceptibility. It is hypothesized that loss of SeP expression could be a mechanism to enhance cancer resistance.

#### Antioxidant Function of GI-GPx

GI-GPx, which contains up to 10 selenocysteine residues, is an important antioxidant selenoprotein. Downregulation of SeP does not seem to be useful in conditions of potentially enhanced susceptibility for oxidative damage like adenomatous polyps. However, with the assumption that GI-GPx is the more important antioxidant selenoprotein, downregulation of SeP, which contains up to 10 selenocysteine residues, would possibly spare selenium in favor of GI-GPx. In addition, local intracellular use of selenium by incorporation into GI-GPx might be of greater benefit for the cell than synthesis and secretion of SeP, which would lead to local selenium depletion.

The Western blots confirmed the RNA expression profile for SeP. Western blot analysis revealed a decrease of the SeP signal (51–65 kDa) for adenoma tissue extracts compared with normal mucosa. The different patterns may result from changes in the distribution of several SeP isoforms in adenomatous and nonadenomatous tissue. The detection of more than one signal by polyclonal Ig preparations indicates various stages of processing of SeP. The broad diffuse bands between 65 and 51 kDa for normal mucosa and between 56 and 51 kDa for adenomatous tissue correlate with signals for highly glycosylated mature SeP isoforms (48–50). The sharp 40-, 37-, and 34-kDa signals are likely to represent deglycosylated or immature truncated forms of SeP containing fewer selenocysteine residues (31). Variations in protein pattern and signal intensity in the colorectal mucosa may be related to adenomatous transition and reflect altered functional expression.

Inverse expression patterns of SeP and GI-GPx might represent constitutive epiphenomena associated with adenomatous transition. However, mutagenic abrogation of SeP expression cannot be excluded. The SeP gene was localized to chromosome 5q31 (62), close to the APC gene locus, which is strongly linked to colon carcinoma development. Thus it appears to be intriguing to hypothesize that loss of SeP expression might occur as an early event in the adenoma-carcinoma sequence, leading to increased susceptibility to oxidative DNA damage and enhanced genetic instability. The GI-GPx gene maps to chromosome 14q24.1 (19,63,64), in the vicinity of the colon cancer susceptibility locus Ccs1 (65), near Fos and TGF-β3. Data from animal studies indicate a correlation between GI-GPx mRNA levels in the colonic mucosa and resistance against dimethylhydrazine-induced colon cancer (19). According to these data, loss of suppression of GI-GPx expression may represent a mechanism to enhance cancer resistance in an early stage of the adenoma-carcinoma sequence. GI-GPx may contribute to colon cancer resistance by catalyzing the reduction of H₂O₂ and other hydroperoxides in the colonic mucosa (66), which can cause oxidative DNA damage (5,7,67,68). Although there is no doubt about the antioxidant function of GI-GPx, the biological function of SeP is not completely elucidated, but there is increasing evidence for its potential role in antioxidant cell defense (17,26–32). Thus SeP and GI-GPx may act complementarily in the defense against oxidative injury in the colorectal mucosa. Downregulation of SeP does not seem to be useful in conditions of potentially enhanced susceptibility for oxidative damage like adenomatous polyps. However, with the assumption that GI-GPx is the more important antioxidant selenoprotein, downregulation of SeP, which contains up to 10 selenocysteine residues, would possibly spare selenium in favor of GI-GPx. In addition, local intracellular use of selenium by incorporation into GI-GPx might be of greater benefit for the cell than synthesis and secretion of SeP, which would lead to local selenium depletion. According to this hypothesis, abrogation of SeP mRNA and protein expression might be a useful mechanism to optimize defense against ROS-inducible DNA damage in a preneoplastic lesion, which is in jeopardy of forward advancement toward invasive carcinoma with every further hit.
translation factor. The 21st codon UGA, which normally represents an opal stop codon, specifies the incorporation of Sec into protein (70). Therefore, an individual or local selenium deficiency may contribute to an inadequately slight increase in GI-GPx enzyme activity in several individuals as a result of insufficient Sec incorporation during translation. This might be an explanation for several data, which indicate a correlation between low plasma selenium levels and an increased risk of colorectal cancer (51–57). In individual cases, inadequate selenium supply may cause insufficient transcription of GI-GPx mRNA, resulting in a lack of GPx. Therefore, low selenium intake may contribute to an increased colorectal carcinoma risk because of an insufficient GI-GPx translation followed by oxidative DNA damage.

In conclusion, changes in mRNA expression patterns of GI-GPx and SeP in colon adenomas suggest their complementary role in the antioxidative defense along the adenoma-carcinoma sequence. The regulating mechanism remains to be shown, but lacking modulations of the other selenoproteins pGPx and TrxR-α indicate that the altered expression of SeP and GI-GPx in adenomas is not directly related to selenium supply. To improve protection against oxidative DNA damage in a susceptible preneoplastic role, down-regulation of SeP in favor of GI-GPx upregulation may be a useful mechanism. According to this hypothesis, GI-GPx, which is associated with colon cancer resistance, seems to be the more important enzyme for antioxidant defense. Down-regulation of SeP, which contains a high amount of selenium, may ensure sufficient local and cellular selenium availability to ensure an increased GI-GPx activity. Loss of SeP mRNA expression as a primary event cannot be excluded. Lack of SeP may cause increased susceptibility to ROS- and phospholipid hydroperoxide-induced DNA damage and, therefore, facilitate tumor progression. The concomitant increase of GI-GPx mRNA levels and enhanced GPx activity in adenomas may represent a compensatory mechanism in the antioxidative cell defense.

Acknowledgments and Notes

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