Role of Copper, Zinc, Selenium and Tellurium in the Cellular Defense against Oxidative and Nitrosative Stress[1,2]

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ABSTRACT The trace elements copper, zinc and selenium are linked together in cytosolic defense against reactive oxygen and nitrogen species. Copper, zinc–superoxide dismutase catalyzes the dismutation of superoxide to oxygen and hydrogen peroxide. The latter and other hydroperoxides are subsequently reduced by the selenoenzyme glutathione peroxidase (GPx). Cytosolic GPx can also act as a peroxynitrite reductase. The antioxidative functions of these trace elements are not confined to being constituents of enzymes: *1*) copper and zinc ions may stimulate protective cellular stress-signaling pathways such as the antiapoptotic phosphoinositide-3-kinase/Akt cascade and may stabilize proteins, thereby rendering them less prone to oxidation; and *2*) selenium does not only exist in the cell as selenocysteine (as in GPx) but also as selenomethionine, which is regularly present in low amounts in proteins in place of methionine. Selenomethionine catalyzes the reduction of peroxynitrite at the expense of glutathione. Also, low-molecular-weight organoselenium and organotellurium compounds of pharmacologic interest catalyze the reduction of hydroperoxides or peroxynitrite with various cellular reducing equivalents. J. Nutr. 133: 1448S–1451S, 2003.

KEY WORDS: • *oxidative stress* • *nitrosative stress* • *glutathione peroxidase* • *zinc finger* • *stress signaling*

One important function of metal ions in biology is to stabilize proteins. An impressive illustration of the stability of a metalloenzyme is the isolation of an enzymatically active core fragment of copper, zinc–superoxide dismutase (CuZn–SOD)[4] from the brain of a > 3,000 y-old air-dried mummy (1). Similarly, another metalloenzyme was isolated from mummies: alkaline phosphatase, a Zn^{2+}- and Mg^{2+}-containing enzyme, was recovered from rib samples of a 2,300-y-old ptolemeic mummy. This enzyme was active, immunologically indiscernible from freshly prepared enzyme and of similar molecular mass (2,3). Copper and zinc are two of the most abundant trace elements found in the human body and are intricately involved in the metabolism of oxygen and the biochemistry of redox reactions. CuZn–SOD catalyzes the dismutation of superoxide, which is constantly formed during aerobic metabolism, to oxygen and hydrogen peroxide (4). Copper and zinc are joined in cellular defense against oxidants by the semimetal selenium to form a triad of trace elements that are involved in cytosolic antioxidant defense (**Fig. 1**): hydroperoxides, including H_2O_2, are reduced to the respective alcohols or water in a reaction that is catalyzed by the selenoenzyme glutathione peroxidase (GPx) with glutathione (GSH) as the electron donor (5,6). These three trace elements play roles in the cellular defense against oxidative stress beyond those outlined: copper and zinc are not only cofactors of CuZn–SOD, and being a constituent of GPx is not the only way that selenium exerts an antioxidative function.

Prooxidant and antioxidant properties of copper ions

Copper ions are involved in both the generation of and the defense against reactive oxygen species (ROS) in cells. The generation of superoxide and hydrogen peroxide is due to the interaction of intracellular copper ions with thiols such as GSH and oxygen, which is present intracellularly in high micromolar concentrations (as indicated in reactions 1 and 2, the latter of which is the sum of reactions 2a and 2b).

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[4] Abbreviations used: CuZn–SOD, copper, zinc-superoxide dismutase; GPx, glutathione peroxidase; GSH, glutathione; MAPK, mitogen-activated protein kinase; MTF, metal transcription factor; PI3K, phosphoinositide-3-kinase; ROS, reactive oxygen species.

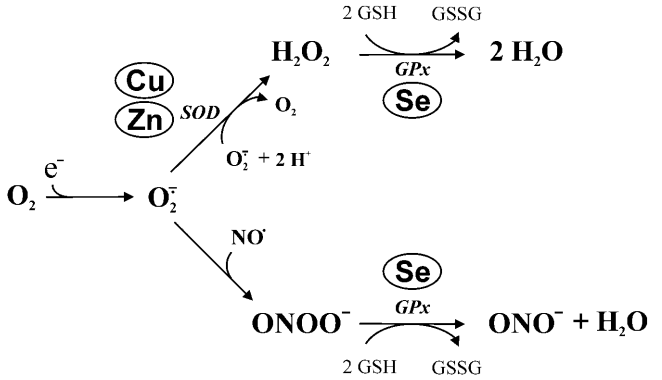

FIGURE 1 Copper, zinc and selenium in the cytosolic defense against reactive oxygen and nitrogen species. Superoxide is generated by reduction of molecular oxygen. The electrons required may leak out of the mitochondrial respiratory chain or may be derived from reactions such as the oxidation of (hypo-) xanthine as catalyzed by xanthine oxidase. Copper, zinc–superoxide dismutase (CuZn–SOD) catalyzes the dismutation of superoxide; this reaction is competed for by nitrogen monoxide, if generated in sufficient amounts, to form peroxynitrite. Both the hydrogen peroxide from superoxide disproportionation and the peroxynitrite may be reduced at the expense of glutathione (GSH) in reactions that are catalyzed by glutathione peroxidase (GPx).

$$2Cu^{2+} + 2R - SH \longrightarrow 2Cu^{+} + R - SS - R + 2H^{+} \quad (1)$$

$$2Cu^{+} + O_2 + 2H^{+} \longrightarrow 2Cu^{2+} + H_2O_2 \quad (2)$$

$$2Cu^{+} + 2O_2 \longrightarrow 2Cu^{2+} + 2O_2^{-}\cdot \quad (2a)$$

$$2O_2^{-}\cdot + 2H^{+} \longrightarrow O_2 + H_2O_2 \quad (2b)$$

Once generated intracellularly, Cu^+ may further interact with hydroperoxides to generate hydroxyl or alkoxyl radicals in Fenton-type reactions (reaction 3). This, however, is likely to occur only under conditions where cellular hydroperoxide concentrations are well above basal levels; for H_2O_2, these are estimated to be in the range of 10^{-9} mol/L (7).

$$ROOH + Cu^{+} \longrightarrow RO\cdot + OH^{-} + Cu^{2+} \quad (3)$$

Copper-induced generation of ROS may be the reason that cellular defense mechanisms have evolved that both depend on copper and scavenge ROS. The best-known antioxidative role of copper is that of being the major cofactor in CuZn–SOD, which catalyzes the dismutation of superoxide (reaction 2b). However, defense against stressful stimuli such as ROS does not only consist of the direct scavenging of the species but also of the initiation of long-term precaution: it is known that ROS such as hydrogen peroxide and peroxynitrite activate signaling pathways that regulate cellular proliferation and cell death and in part are regarded antiapoptotic including mitogen-activated protein kinases (MAPK) and the phosphoinositide-3-kinase (PI3K)/Akt pathway (8–11). Activation induced by H_2O_2 indeed renders cells more resistant against the oxidant (8,10).

Similarly, metal ions activate signaling cascades that are known to protect cells against oxidative stress-induced apoptosis. Copper ions strongly activate the antiapoptotic PI3K/Akt pathway (12) which, albeit to a minor extent, also holds for zinc. Interestingly, activation of PI3K/Akt by Cu^{2+} is independent of the intermediate generation of ROS, and thus is a feed-forward activation of a cascade: the pathway is already activated when cellular ROS levels start to significantly increase (12).

Also, metal ions such as copper, zinc and cadmium are known to induce the expression of metallothioneins (13), which are cysteine-rich metal-binding and -detoxicating proteins. In the case of copper, this would imply that metallothionein scavenges Cu^+ and prevents ROS formation. In mammalian cells, the induction of thionein by metal ions occurs in part via activation of metal transcription factor (MTF)-1, which then binds to metal-responsive elements (MRE) in the regulatory regions of associated genes [for reviews, see (14,15)]. Although Zn^{2+} may directly bind to and activate MTF-1, the mechanism of activation is not precisely known for copper ions. It has been hypothesized that intracellular Cu^+ may displace Zn^{2+} from metallothionein and result in MTF-1 activation (16). Zn^{2+} displacement is also proposed to be the mechanism by which copper ions lead to the alteration of the activities of two other well-known zinc-dependent proteins, the xeroderma pigmentosum A zinc-finger protein, which is involved in nucleotide-excision repair (17,18), and p53 (19,20).

Zinc ions as antioxidants

Similar to Cu^{2+}, Zn^{2+} is a cofactor of CuZn–SOD. However, Zn^{2+} is redox inert in biological systems. Thus, the role of zinc in CuZn–SOD is generally thought to be that of a stabilizing component (21). Yet, like Cu^{2+}, Zn^{2+} is capable of inducing a stress response in terms of *1*) the stimulation of MTF-1–dependent transcription (14,16), and *2*) the activation of stress-responsive signaling cascades such as MAPK and PI3K/Akt (12,22,23). One additional mechanism that is being discussed to explain the antioxidative action of Zn^{2+} is the binding to and stabilization of protein thiols. This was thoroughly investigated with δ-aminolevulinate dehydratase, which is an enzyme involved in porphyrin biosynthesis that is dependent on intact sulfhydryl groups for its activity. These thiols are stabilized by Zn^{2+}, and the enzyme is rendered less prone to inactivation by oxygen [for review, see (24)]. Zn^{2+} may also stabilize thiols in other zinc proteins including metallothioneins and zinc-finger transcription factors.

Exposure of these proteins to oxidants in concentrations that are sufficient to significantly oxidize the thiols leads to Zn^{2+} release; this was demonstrated for metallothionein exposed to glutathione disulfide (25) or nitrogen oxides (26).

Exposure of the vitamin D receptor/retinoid X receptor heterodimer (a Zn^{2+}-finger transcription factor of the nuclear receptor superfamily) to ROS impedes its biological activity in terms of impairing DNA binding and transcriptional regulation. Various ROS including nitric oxide, hydrogen peroxide, singlet oxygen, peroxyl radicals or peroxynitrite have this effect (27,28). Although zinc-finger oxidation is reversible in the case of nitric oxide, it appears to be irreversible after exposure to the other reactive species mentioned above. This indicates that nitric oxide potentially serves as a regulatory molecule for zinc-finger–dependent gene transcription (28). In a similar fashion, exposure of copper thiolate cluster-containing proteins to nitrogen monoxide and oxygen is proposed to result in structural changes and inactivation with copper ions being released. Examples are yeast Cu^+-metallothionein (29) and the yeast transcription factor ACE1 with its "copper fist" configuration (30). Interestingly, the low-molecular-weight organoselenium compound ebselen is capable of inducing Zn^{2+} release from Zn^{2+}-metallothionein possibly via formation of a selenodisulfide (31).

Selenium and tellurium: reduction of hydroperoxides and peroxynitrite

Ebselen is a GPx mimic not only with respect to peroxidase activity (32). Similar to GPx (vide infra), it reacts efficiently with peroxynitrite and exhibits the highest second-order rate constant known thus far for a low-molecular-weight compound

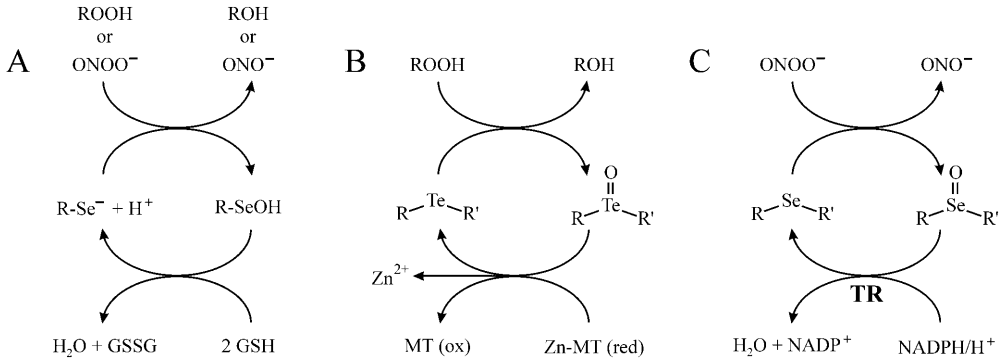

FIGURE 2 Proposed catalytic mechanisms for the reduction of hydroperoxides and peroxynitrite in the presence of seleno- and tellurocompounds. (*A*) The selenocysteine at the active site of GPx is oxidized to the corresponding selenenic acid by hydroperoxides or peroxynitrite, which in turn are reduced to the corresponding alcohol and nitrite, respectively. The reduced form of the enzyme is restored at the expense of GSH (5,6,37). (*B*) Several low-molecular-weight organoselenium and -tellurium compounds mimic the GPx reaction. The transiently formed respective selenoxide or telluroxide may be reduced by thiols other than glutathione including zinc-metallothionein (MT), which upon oxidation releases Zn^{2+} (42). (*C*) Mammalian thioredoxin reductase (TR) is a selenoenzyme and may reduce the oxidized forms of certain selenocompounds that are formed after interaction with peroxynitrite, such as the ebselen selenoxide, at the expense of NADPH (47).

with peroxynitrite (33,34). Also, it was shown that other low-molecular-weight selenocompounds such as selenomethionine are effective as well (and more effective than the corresponding sulfur compounds) in protecting plasmid DNA from peroxynitrite-induced single-strand breaks (35) and in preventing model compounds from being oxidized or nitrated by peroxynitrite (36). The selenoprotein GPx is capable of efficiently reducing peroxynitrite and preventing oxidation and nitration of model compounds as well as nitration of proteins (37). The system of GPx plus GSH works catalytically in a manner that resembles the detoxication of hydroperoxides by GPx at the expense of GSH (**Fig. 2***A*): the selenocysteine residue at the active site of the enzyme is oxidized by peroxynitrite (or peroxynitrous acid) to the selenenic acid and reduced back to the selenol at the expense of two reducing equivalents provided by GSH. The second-order rate constant for the reaction of reduced GPx with peroxynitrite is reported to be 8×10^6 $M^{-1} \cdot s^{-1}$ per tetramer (38), which on a selenium basis is similar to the rate constant of 2×10^6 $M^{-1} \cdot s^{-1}$ reported for ebselen (34).

A similar mechanism applies for selenomethionine (39,40), which is present in proteins in place of methionine and organotellurium compounds with peroxidase activity (41,42). Interestingly, although the enzyme methionine sulfoxide reductase (43) is required for the reduction of methionine oxide, methionine selenoxide is reduced nonenzymatically by GSH (39). To some extent, other thiols may act as reductants in a peroxidase reaction as well: Zn^{2+}-metallothionein was employed to reduce several organoselenium and organotellurium compounds that were oxidized by tert-butyl hydroperoxide (42). Oxidation of metallothionein coincides with Zn^{2+} release from the protein (Fig. 2*B*).

Selenoprotein P in human plasma also protects against peroxynitrite (44), which suggests that it may serve as a protectant in human blood. The heparin-binding domains of selenoprotein P enable surface coating of cellular membranes, which may serve as a protective barrier against peroxynitrite [(45); for review, see (46)].

Mammalian thioredoxin reductase is a third selenoprotein that is capable of reducing peroxynitrite (47). The enzyme uses NADPH to reduce the oxidized forms of selenocysteine or ebselen (Fig. 2*C*).

Most of the selenocompounds mentioned here have been shown to protect cells or cell lysates from protein nitration (9,37). This would also prevent cells from impairments in phosphotyrosine signaling, which is necessary for growth and survival [for review, see (48)]. Peroxynitrite is capable of activating p38 MAPK in liver epithelial cells. This activation is prevented by preincubation of the cells with selenite, which is shown to increase specific GPx activity (9). However, recent observations of hepatocytes from GPx-1 knockout mice that show a paradoxical protection against peroxynitrite (49) illustrate that the intricate network of cellular antioxidant defense is far from being fully resolved.

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