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SULFUR AND SELENIUM IN OXIDATION PROTECTION

SELENIUM IS AN ESSENTIAL TRACE ELEMENT AND PLAYS A KEY ROLE IN SOME PROTEINS THAT REMOVE RADICALS AND OXIDANTS AND THEREBY REDUCE OXIDATIVE STRESS. THIS ARTICLE HIGHLIGHTS THE POTENTIAL OF SELENIUM COMPOUNDS IN MODULATING DAMAGE INDUCED BY RADICAL AND MOLECULAR OXIDANTS IN INFLAMMATION AND DISEASE

Introduction

Mammals have an absolute requirement for selenium. This is usually present in plasma at between 70-140 µg/L, with this acquired through food or supplements in either organic (e.g. seleno-L-methionine, Se-methylseleno-L-cysteine, seleno-L-cysteine, selenocystine) or inorganic forms (e.g. selenite, selenate).

Seleno-L-methionine is the predominant form in most diets [1]. Deficiency (intake <20 µg/day) is associated with an increased incidence of some cancers, infections, Alzheimer's and Parkinson's diseases, decreased function of the immune system and thyroid, and male infertility [2]. Severe deficiency is strongly associated with fatal cardiomyopathy (Keshan's disease [2]). Supplementation does not show benefit against prostate cancer in selenium-deficient men, and may even increase risk [3]. High plasma selenium (>140 µg Se/L) has also bee associated with an increased risk of type 2 diabetes, though this is not universally agreed upon [4]. Both low and high selenium levels therefore appear to have potential risks. Most selenium is incorporated into selenoproteins, via a coding system that allows incorporation of seleno-L-cysteine (Sec) into certain enzymes [2].

In contrast, selenomethionine (SeMet) is incorporated into proteins in a random manner in place of Met, and dependent on the amino acid levels. Humans express >25 selenium-containing proteins with a range of tissue and cell distributions [2]. Well-characterised species include glutathione peroxidase (GPx), thioredoxin reductase (TrxR), selenoprotein P and some isoforms of methionine sulfoxide reductases (Msrs). Each of these is linked with defences against oxidative stress, including direct detoxification (GPx, TrxR, selenoprotein P), and repair (Msrs). Selenoproteins K, M, N, and H have also been linked to redox homeostasis [5].

Sulphur species critical to human health, with the major *in vivo* pools being the tripeptide glutathione (GSH; γ-Glu-Cys-Gly) and protein-bound cysteine (Cys), cystine and methionine (Met). GSH is usually present in cells at 2-10 mM, with cytosolic and mitochondrial protein-bound thiols being ~40 mM and 70-90 mM respectively [6, 7]. Extracellular thiol levels are lower, with the plasma low-molecular-mass pool being <25 µM and protein thiols ~600 µM (mainly Cys34 of HSA) [7]. Major contributors to the cellular protein pool are thioredoxins, glutaredoxins and peroxiredoxins [8-10], all of which are involved in oxidative defence and redox homeostasis. The cellular selenol pool is low, with the major selenoenzyme GPx 2 µM [11].

Inflammation and oxidant formation

Oxidants are generated continually in aerobic biological systems as a result of respiration and normal physiological processes (Fig. 1). These species can be formed at elevated levels during disease and aging [12]. Some of these species are generated intentionally to carry out biological functions (e.g. peroxidases, NADPH oxidases, nitric oxide synthases, lipoxygenases and prostaglandin synthases) whereas in other cases oxidants are formed as byproducts (e.g. by monoamine oxidases) or accidentally (electron leakage from mitochondria) [12].

Stimulated leukocytes (white blood cells) use enzyme complexes including NADPH oxidases (NOxs, particularly NOX-2) and nitric oxide synthases to generate radicals and two-electron oxidants (Fig. 2) [12-16]. These oxidants are critical to the human immune response and are powerful bacteriostatic or bactericidal agents [17], but can also damage host tissue [18], especially when the immune system is inappropriately stimulated. Consequently chronic inflammation is strongly associated with many human pathologies involving inflammation (e.g. cardiovascular diseases, rheumatoid arthritis, asthma, cystic fibrosis, Alzheimers and Parkinson's disea-

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ses, some cancers etc.), and involves a wide variety of different oxidants often generated concurrently (Fig. 2).

Antioxidant and protective systems

Oxidant formation in biological systems is tightly regulated and controlled by defensive and repair systems (Fig. 3). Despite this, oxidative damage is widespread in most organisms [12], with this due to increased oxidant generation, a failure or decrease in defence systems, or both. This imbalance is often termed "oxidative stress" [19].

Many of these protective systems require sulfur or selenium. Selenium is typically more reactive with oxidants due to its more favourable redox and nucleophilic properties [20]. At physiological pH (7.4), thiols (RSH) are usually present in the less-reactive neutral form (cf. pK_a for Cys of ~8.7, though this varies considerably) whereas selenols (RSeH) are usually present as the anion (RSe^-, pK_a 5.2) [21]. Thus sulfur- and selenium- species should readily scavenge oxidants, and provide protection against inflammation-induced damage; this is briefly reviewed below with an emphasis on selenium species (see also [22, 23]).

Endogenous	Exogenous
Electron transport chains (mitochondria, endoplasmic reticulum, plasma membrane)	Radiation (high energy, UV, visible light + sensitizer, thermal)
Heme protein / enzyme reactions	Sulphur oxides
Peroxidases	Nitrogen oxides
Nitric oxide synthases	Particulates (e.g. diesel particles)
NADPH oxidases	Mineral fibres and dusts (e.g. asbestos)
Xanthine oxidase	Ozone
Prostaglandin synthases	Oxidised foodstuffs
Autooxidation of glucose, thiols, catecholamines, metal ions	Metabolism of chlorinated hydrocarbons, drugs, nitro compounds, paracetamol, ethanol
Lipoxygenases	

Fig. 1
Examples of endogenous and exogenous factors that result in oxidation formation

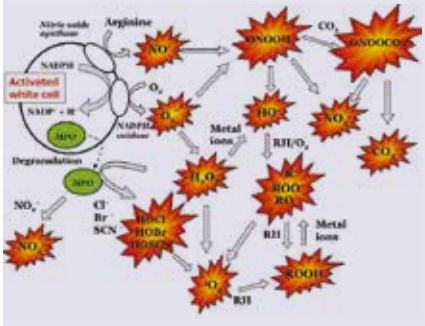

Fig. 2
Oxidant formation by activated leucocytes

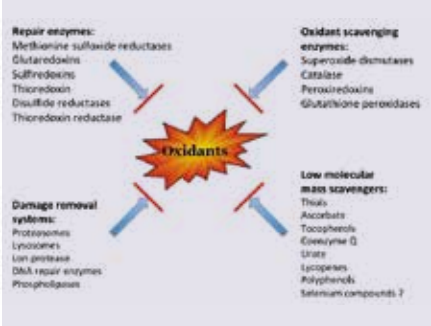

Fig. 3
Damage removal and repair systems in cells

Oxidative chemistry of sulfur and selenium compounds

Rate constants have been determined for reaction of oxidants with many sulfur- and selenium-species. For low-molecular-mass compounds, the rate constants, *k*, for selenium species are typically 10- to 100-fold greater than for their sulfur analogues (Figs. 4, 5). With proteins other factors such as structure, environment and local amino acid interactions can modulate reactivity [24].

SeMet reacts with ONOOH with a rate constant that is comparable to that for Cys, and higher than for Trp or Met (Fig. 4) [25]. SeMet can therefore compete effectively for ONOOH with other targets when present at similar concentrations. The major product is the selenoxide, SeMetO (analogous to a sulfoxide). It should be noted however that SeMet levels *in vivo* are lower than most biological targets.

HOCl reacts with SeMet with k 3.2×10^8 $M^{-1}s^{-1}$ [26], ~10-fold higher than for Met, and similar to Cys [27]. HOSCN and secondary chloramines (RNHCl, generated from HOCl and amines) also react with SeMet faster than Met (Fig. 5) [23, 28, 29]. The major products are the selenoxide and sulfoxide respectively, though with HOCl dehydroselenomethionine is also formed [30]. Photochemical systems, H_2O_2, and amino acid- and protein-bound hydroperoxides also convert SeMet to SeMetO [31, 32].

Reaction of Met and SeMet with $HO^\bullet$ occurs at diffusion-controlled rates [33, 34], with formation of short-lived adducts that decay to the radical-cations ($Met^{\bullet+}$ or $SeMet^{\bullet+}$). Hydrogen atom abstraction at neighbouring C-H bonds also occurs with Met, and to a lesser extent for SeMet [33-35]. The radical-cations can be stabilised *via* 3-electron bonds with suitable N or O atoms, or S or Se atoms of another parent molecule. This stabilisation is greater for $SeMet^{\bullet+}$, with this resulting in a ~300-fold increase in lifetime [36], which results in significant

Compound	k / $M^{-1}s^{-1}$ (seleno compound)	k / $M^{-1}s^{-1}$ (sulphur analogue)
Selenocysteine (Sec)	$(1.6 \pm 0.1) \times 10^5$	$(2.4 \pm 0.1) \times 10^3$
Sec methyl ester	$(1.3 \pm 0.2) \times 10^5$	$(3.8 \pm 0.3) \times 10^3$
Selenocysteamine	$(1.1 \pm 0.1) \times 10^5$	$(2.1 \pm 0.1) \times 10^3$
3-Selenopropionic acid	$(1.1 \pm 0.1) \times 10^5$	ND
Selenomethionine (SeMet)	$(2.4 \pm 0.1) \times 10^3$	$(1.8 \pm 0.1) \times 10^2$
Selenotalose (SeTal)	$(2.3 \pm 0.2) \times 10^3$	ND
Selenogulose (SeGul)	$(2.2 \pm 0.2) \times 10^3$	$(1.9 \pm 0.05) \times 10^2$
3-(Selenomethyl)cysteine	$(1.8 \pm 0.1) \times 10^3$	ND
3,3'-Diselenodipropionic acid	$(1.1 \pm 0.1) \times 10^3$	ND
3,3'-Diselenocysteine methyl ester	(650 ± 60)	ND
Selenocystamine	(540 ± 50)	ND

Fig. 4
Second order rate constants for the reaction of ONOOH with seleno compounds and sulphur analogues (from [42])

reaction with O_2, and SeMetO formation. With $Met^{\bullet+}$, other reactions such as decarboxylation occur, with this limiting reaction with O_2 and MetO formation [37]. SeMet may therefore be a more effective antioxidant against radical-mediated damage than Met [36].

Selenols and thiols

Kinetic data for free selenols (RSeH) is limited due to their rapid auto-oxidation to diselenides (RSeSeR). Computational studies suggest only small (~3-fold) differences between thiols and selenols [38], whereas experimental data for Sec and Sec-containing peptides indicate that these are 16-100 fold faster than for thiols (Fig. 5) [28, 39]. ONOOH also exhibits higher reactivity with selenols compared to thiols (Fig. 4) [40-42]. The active site Sec of GPx is more reactive than parent Sec, with k for H_2O_2, ONOOH, and HOSCN being 10^5-10^7 $M^{-1}s^{-1}$ [28, 43-45]. These higher rate constants has been ascribed to hydrophobic effects and hydrogen bonding interactions [46].

Reaction of thiols with $HO^{\bullet}$ occurs at the diffusion limit [47] and selenols are likely to do likewise. The phenoxyl radical from *N*-Ac-Tyr-amide oxidises Sec and selenium-substituted glutathione, GSeH, ~1,000-fold faster than for Cys [48]. Tyr phenoxyl radicals on insulin react with Sec with lower rate constants, and GSeH is slower still, though these are still ~400-fold faster than for GSH [48]. Selenols are therefore potent scavengers of protein-bound radicals, with rate constants similar to those of ascorbate and urate [48, 49].

With two-electron oxidants (e.g. ONOOH and HOCl), thiols give sulfenic acids (RSOH) [50], and selenols are believed to yield selenenic acids (RSeOH). In some cases, intermediates (e.g. RS-Cl and RSeCl) may be formed that undergo rapid subsequent hydrolysis. RSOH and RSeOH react further to give disulfides/diselenides (RSe-SeR), mixed seleno-sulfur species (RSe-SR), and oxyacids (i.e. sulfinic, RSO_2H; sulfonic, RSO_3H; seleninic $RSeO_2H$; selenonic, $RSeO_3H$) [51]. These reactions are particularly rapid for selenium species in aqueous solution [52], but selenenic acids have been detected in organic solvents [53], and in the active site of bovine GPx1, probably as a result of steric shielding [54]. Selenonic ($RSeO_3H$) acid undergoes fragmentation to give dehydroalanine (DHA) and selenite [51].

One-electron oxidation of RSH gives thiyl radicals ($RS^{\bullet}$) which have a complex chemistry, including reversible reaction with O_2 to form a peroxyl radical [55], and with GS^- to form $GSSG^{\bullet-}$ [56]. The latter undergoes rapid electron transfer with O_2 to give $O_2^{\bullet-}$ [57]. Thiyl radicals can abstract hydrogen atoms from suitable C-H bonds, [58], with this resulting in damage propagation. Thiyl radical dimerization generates reducible protein disulphide cross-links [59, 60]. Thiyl radicals can also undergo reversible addition to fatty acid double bonds, which can lead to *cis-trans* isomerisation that can perturb cellular metabolism, membrane structure and signalling [61].

Selenyl radicals ($RSe^{\bullet}$) formed from selenols are less reactive and have a lower reduction potential than $RS^{\bullet}$, and hence do not readily abstract hydrogen atoms [62]. Evolution may therefore have favoured (energetically-costly) Sec residues in proteins as a means of protecting proteins from damage by unwanted thiyl radicals [62, 63].

Thiyl radicals can undergo desulfonisation to form dehydroalanine (DHA), providing an alternative route to this species [58, 64]. This may be of biological relevance, as DHA can undergo Michael addition with thiols to form thioether adducts [65].

These have been detected in lens proteins, where protein catabolism is minimal, with the amounts correlating with the incidence and severity of age-related cataract [66].

Diselenides and disulfides

Disulfide and diselenide oxidation is slower than for thiols/selenols and thio-/seleno- ethers [39, 41], but this may be important in the depletion of GSH and mitochondrial α-lipoic acid and α-lipoamide [41, 67].

Diselenides have been examined as pro-drugs for selenols and selenoethers as antioxidants and GPx mimetics [68]. In contrast, HOCl and HOBr react readily with disulfides [27, 69, 70], and one electron oxidation of disulfides by $HO^{\bullet}$ occurs at diffusion controlled rates [47].

Disulfide oxidation by H_2O_2 [71], $^1O_2$ [72] and ONOOH [73] gives mono- (RS(O)SR) and di-oxides ($RS(O_2)SR$). The mono-oxides are weak oxidants that can oxidise thiols and disrupt zinc-sulfur clusters [74, 75], as well as inducing thionylation of proteins [76]. The latter can inhibit kinases modulate cell signalling [77]. Diselenide oxidation by two-electron oxidants is also slow and limited kinetic data is available [42]. Both GSeSeG and other diselenides consume H_2O_2 *via* enzyme-coupled reactions that can prevent oxidant-induced damage *in vitro* [78, 79]. This is unlikely to be due to direct H_2O_2 reaction, as this is slow, with a stabilised seleno species (RC=Se) being the reactant; the latter may arise via diselenide re-

Substrate	k (HOSCN+RSeH)		k (HOSCN+RSH)
	$M^{-1}s^{-1}$	Difference	$M^{-1}s^{-1}$
Selenocysteine / Cysteine	1.24×10^6	16-fold	7.8×10^4
Selenocystamine / cystamine	5.8×10^6	100-fold	5.8×10^4
γ-Glu-Sec-Gly / GSH	1.7×10^6	68-fold	2.5×10^4
Selenomethionine / methionine	2.8×10^3		$<< 10^3$

Fig. 5
Second order rate constants for the reaction of HOSCN with seleno compounds and sulphur analogues (from [28, 39])

duction by GSH [80]. Non-bonding interactions between Se and nucleophiles can modulate this reactivity [81, 82].
Selenocystine reacts with $HO^{\bullet}$ with k $8.1x10^9$ $M^{-1}s^{-1}$ [34], and 3,3 -diselenodipropionic acid reacts with a model peroxyl radical ($CCl_3OO^{\bullet}$) with similar rate constants to those for α-tocopherol and ascorbate, suggesting that diselenides may be effective scavengers [83].
These reactions involve a radical-cation ($RSeSeR^{\bullet+}$) that can be stabilised by carboxylates [34]; these species are stabilised relative to the disulfides, and have slower first order decay rate constants [34].

Recycling and repair of selenium and sulfur oxidation products

The initial products of thiol and selenium oxidation are often easily reduced back to the parent, though over-oxidation can occur. This reversibility can result in catalytic activity.
MetSO is not reduced rapidly by thiols, but is recycled by the methionine sulfoxide reductase enzyme family (Msrs) [84, 85]. These enzymes are stereospecific, with MsrA and B reducing the S and R stereoisomers respectively. MsrA can reduce free and protein-bound MetSO, though with a preference for the latter. MsrB reduces peptide-bound MetSO particularly on unfolded proteins. A third Msr from *E. coli* reduces free, but not peptide-bound MetSO; isotype is however limited to prokaryotes or unicellular eukaryotes [85]. Selenoxides are more readily reduced than sulfoxides, and this is the basis for GPx mimetic activity, in which oxidation is followed by reduction by 2 GSH equivalents to give the parent selenium compound and GSSG [68]. SeMetO is reduced by Cys, ascorbic acid and some drugs [86], as well as the thioredoxin/thioredoxin reductase system [32].

Selenols and thiols

Many protective enzymes contain active site Cys residues (e.g. peroxiredoxins, thioredoxins, glutaredoxins) and utilise the high reactivity of Cys to remove oxidants. With 2-Cys peroxiredoxins, initial conversion of the catalytic Cys to a sulfenic acid is followed by rapid reaction with a neighbouring (resolving) Cys to give a disulphide. This is then efficiently reduced by the Trx/TrxR/NADPH system. GPx and TrxR [87] use a Sec residue to rapidly reduce H_2O_2 (with GPxs) or disulfides, hydroperoxides [10, 32, 87, 88] and HOSCN (for TrxR) [89]. Mutation of the Sec residue in TrxR to Cys decreases its ability to detoxify oxidants [90].
Over-oxidation of sulfenic acids gives sulfinic (RSO_2H) and sulfonic acids (RSO_3H). Most sulfinic acids are irreversible products but some, including those in peroxiredoxins, can be reduced by sulfiredoxin [91]. In contrast, sulfonic acid formation is irreversible [92]. Sec is more resistant to over-oxidation than Cys, as both the selenenic (RSeOH) and seleninic ($RSeO_2H$) acids are readily reduced by free thiols [52, 93]. This may be a further evolutionary advantage for using Sec in proteins [93].

Diselenides and disulfides

Disulfides are readily reduced by glutathione reductases (GR), Trxs, glutaredoxins, disulfide isomerases and TrxR. GR is the major enzyme responsible for reducing GSSG to GSH [94], whereas Trx reduces protein disulfides [95]. Both enzymes employ utilise a Cys-X-X-Cys motif [95]. Mammalian TrxRs utilise a similar principle but contain a Gly-Cys-Sec-Gly motif [96, 97], allowing the reduction of a greater range of substrates. The efficacy of TrxR is at least partly due to the increased nucleophilicity of RSe- compared to RS- [62], and mutation of the Sec to Cys decreases the disulfide reductase activity of TrxR [90, 98].

Conclusions

The redox chemistry of sulfur- and selenium-containing compounds is critical to maintaining a redox balance in living organisms. Recent data indicate that low molecular mass selenium-containing compounds offer significant potential as protective agents due to their favourable kinetic, nucleophilic and reduction / recycling properties, and may have significant therapeutic potential in a range of inflammatory diseases where one- and two-electron oxidants may contribute to the disease pathology.

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Zolfo e selenio nei processi di protezione ossidativa

Il selenio è un oligoelemento essenziale e svolge un ruolo chiave in alcune proteine che rimuovono i radicali e gli ossidanti e, quindi, riduce lo stress ossidativo. Questo articolo mette in evidenza il potenziale di composti del selenio nel modulare i danni indotti da radicali e ossidanti molecolari nelle infiammazioni e nelle malattie

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