

Selenium and anticarcinogenesis: underlying mechanisms

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Purpose of review

To discuss recent research related to anticarcinogenic mechanisms of selenium action in light of the underlying chemical/biochemical functions of the selenium species, likely to be executors of those effects.

Recent findings

Recent studies in a variety of model systems have increased the understanding of the anticarcinogenic mechanisms of selenium compounds. These include effects on gene expression, DNA damage and repair, signaling pathways, regulation of cell cycle and apoptosis, metastasis and angiogenesis. These effects would appear to be related to the production of reactive oxygen species produced by the redox cycling, modification of protein-thiols and methionine mimicry. Three principle selenium metabolites appear to execute these effects: hydrogen selenide, methylselenol and selenomethionine. The fact that various selenium compounds can be metabolized to one or more of these species but differ in anticarcinogenic activity indicates competing pathways of their metabolic and chemical/biochemical disposition. Increasing knowledge of selenoprotein polymorphisms has shown that at least some are related to cancer risk and may affect carcinogenesis indirectly by influencing selenium metabolism.

Summary

The anticarcinogenic effects of selenium compounds constitute intermediate mechanisms with several underlying chemical/biochemical mechanisms such as redox cycling, alteration of protein-thiol redox status and methionine mimicry.

Keywords

anticarcinogenesis, cancer prevention, carcinogenesis, protein-thiol, redox cycling, selenium

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Introduction

Selenium (Se) is a constituent of some 25 selenoproteins [1], occurring uniquely as selenocysteine. These proteins appear to discharge the nutritional functions of Se, that is, prevent dysfunction associated with deficient Se intakes. Maximal selenoprotein expression appears to require dietary levels of 0.1–0.2 mg/kg for animals and daily intakes no more than 55 µg for humans [2].

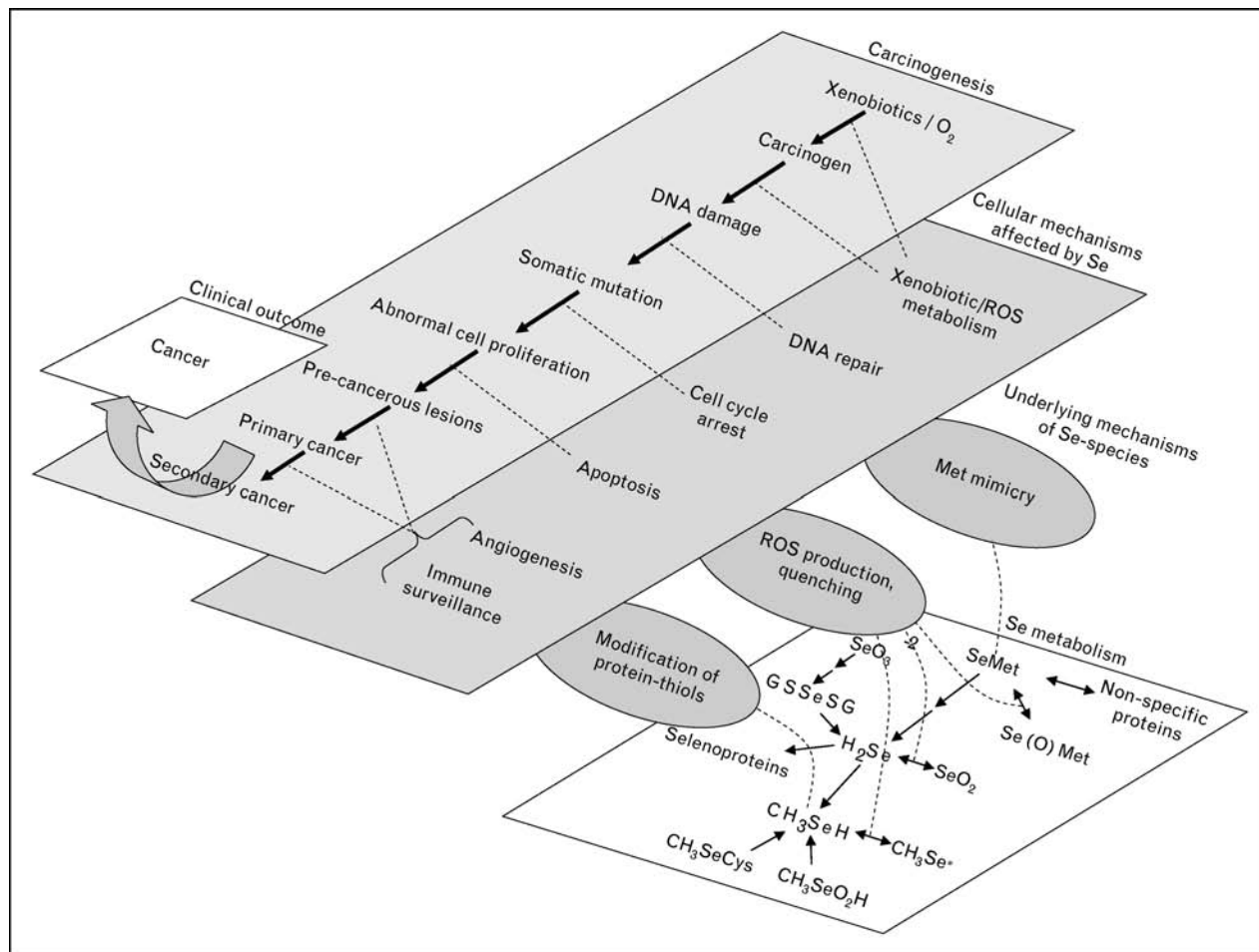
The fact that Se can also be anticarcinogenic was suggested in the 1960s based on an inverse relationship of US cancer mortality rates and crop Se contents [3]. Subsequent studies [4–7] found blood Se levels inversely associated with the prevalence of several types of cancer. Animal studies [6] have shown anticarcinogenic effects for both inorganic and organic Se compounds at doses more than is needed for maximal selenoprotein expression. The Nutritional Prevention of Cancer Trial [8] showed that supplemental Se (200 µg Se/day as high-Se yeast) reduced the risks of total cancers and prostate and colorectal carcinomas. Although only a few other

clinical trials have addressed this issue, most have indicated reduced cancer risk associated with Se treatment [5–7]; however, a recent one [9] found self-reported Se supplement use to be unrelated to prostate cancer risk.

Evidence indicates several mechanisms for Se anticarcinogenesis: altered carcinogen metabolism, cell cycle regulation, immune surveillance, cell death programming, cancer cell migration and angiogenesis [4–7]. As these effects occur at Se doses higher than those commonly encountered in diets (supranutritional), their molecular basis would appear to involve Se metabolite(s) increased under such conditions [4,6]. Studies [10,11] point to hydrogen selenide (H₂Se) and its methylated metabolite methylselenol (MeSeH) as active species, but selenomethionine (SeMet) may also have a role. Selenoproteins may also be involved, as differential cancer risk has been associated with allelic variants of some.

The efficacious use of Se for reducing cancer risk will demand knowing who can benefit from increased Se intake and what forms/levels are necessary. Answers will

Figure 1 A multi-tiered model of selenium anticarcinogenesis



This model depicts the documented effects of Se on carcinogenesis, and proposes linkages with the underlying chemical/biochemical activities of Se metabolites discussed in this article. Se, selenium.

require understanding the metabolic bases for Se anticarcinogenesis. The present article reviews recent relevant findings and presents our view of the underlying roles of Se metabolites.

Intermediate mechanisms

Most forms of Se found in foods and supplements can be metabolized to other species that can affect carcinogenesis. Se anticarcinogenesis can be conceptualized as a multi-tiered process whereby chemical/biochemical actions of Se metabolites are translated into changes in cancer risk by intermediate molecular and cellular mechanisms (Fig. 1).

Gene expression

Most of the limited gene-array studies of Se have used transformed cell lines and found treatment with SeMet or methylseleninic acid (MSA) to increase the expression of genes associated with cell proliferation and apoptosis,

and, in prostate cells, with androgen-regulated genes [12]. The few in-vivo studies have indicated increased expression of genes for xenobiotic metabolism, receptors for prostaglandin E2 and for T cells, and a T-cell transcription factor, but reduced the expression of the *Vav2* oncogene.

Recently, the first assessment of the effects of Se supplementation on gene expression in humans was reported. Pagmantidis *et al.* [13^{••}] studied adults who were given 100 μg Se/day for 6 weeks, noting increased expression of several lymphocyte genes – mostly for ribosomal protein and translation factors, which they associated with selenoprotein production. Ravn-Haren *et al.* [14^{••}] determined the effects of Se supplementation on lymphocyte genes for selected phase 2 enzymes and transcription factors containing electrophilic or xenobiotic response elements in their promoters. They found decreased expression of activator protein 1 (AP-1), Fos-regulated antigen 1 (FRA1) and the γ -glutamylcysteine ligase

catalytic subunit. This shows that Se can affect gene expression, though that process, particularly for phase 2 enzymes, is known to differ between organs.

Supranutritional intakes of Se may affect gene expression differently; however, no relevant data are available. Toxic levels of Se increased the expression of thioredoxin reductase (TRR) mRNA variants in a lung cancer cell line [15], and caused overexpression of a *Drosophila* heat shock protein gene for a protein-folding factor [16].

DNA damage and repair

Selenite treatment can cause DNA damage [10]; long-term treatment with supranutritional Se may lead to sodium selenite-induced DNA damage in both malignant and normal tissues [17]. Letavayová *et al.* [18] found selenite-induced DNA double-strand breaks and frame-shift deletions in yeast, effects not seen for SeMet or a MeSeH precursor. Selenite-induced DNA damage in malignant mammalian cells is associated with induction of p53 and p38, and caspase-independent apoptosis [19].

DNA repair is a response to such damage. Yeast growth impairment due to selenite or SeMet was enhanced in strains null for DNA repair pathways [20]. Loss of the yeast Rad52 protein increased selenite-induced DNA damage, indicating mitigation of damage involving homologous recombination [21^{••}]; but this may not be relevant to mammalian systems in which strand repair tends to occur by nonhomologous end joining. The fact that DNA repair secondary to damage can impair carcinogenesis was suggested by findings of Hu *et al.* [22] and also that a high-Se milk protein enhanced the apoptotic deletion of carcinogen-induced DNA lesions in mice, reducing the frequency of K-ras mutations. The finding that Se yeast failed to produce comparable effects suggests an active principle other than SeMet, which both sources contain.

Signaling pathways

The impact of Se on signaling varies with form: selenite treatment of tumor cells led to upregulation of some protein kinases (p27kip1 and p21cip1), reducing phosphorylation of others (Akt and ERK1/2); MeSeH precursors caused opposite effects [10]. Rudolf *et al.* [19] found selenite to activate a p53-dependent pathway, increasing p21 and phosphorylated p53, as well as a p38 pathway leading to accumulation of Bax. Lee *et al.* [23^{••}] showed that SeMet transiently activates Akt by kinase-mediated phosphorylation before inactivating it in a phosphatase and tensin homologue (PTEN) tumor suppressor-dependent fashion resulting in its degradation through both caspase and proteasome pathways. Wang *et al.* [24^{••}] showed that methylated Se produced transient upregulation of p21/CIP1 and p27/KIP1 in G1-arrested endothelial cells, with a modest increase in p16/

INK4a. These effects were accompanied by reduced turnover of p21/CIP1, and increased levels of p16/INK41.

Cell cycle and apoptosis

Cell culture and tumor studies have shown that selenium can arrest the cell cycle in different ways: selenite in S phase leading to caspase-independent apoptosis; methylated Se in G1 phase leading to caspase-mediated apoptosis [10]. Jariwalla *et al.* [25^{••}] uncovered differential sensitivity of cell types to apoptosis induced by MeSeCys or SeMet: breast carcinoma cells more than hepatoma and neuroblastoma cells more than colon cancer cells and nonmalignant mammary epithelial cells. Hu *et al.* [26] showed the response to methylated Se involves downregulated expression of two antiapoptosis proteins, Bcl-XL and survivin, presenting an opportunity to enhance effects of chemotherapeutics. Wang *et al.* [24^{••}] demonstrated that methylated Se-promoted G1 arrest in microvascular endothelial cells, indicating a basis for antiangiogenesis.

Metastasis

Both selenite and SeMet can inhibit the growth of secondary tumors in animal models [27,28]. Hurst *et al.* [29] showed that this effect involves altered collagen gene expression preferentially affected by methylated Se. Kim *et al.* [30] showed SeMet decreased tumor cell invasion by decreasing reactive oxygen species (ROS) and blunting Akt-dependent matrix metalloproteinase secretion.

Anti-angiogenesis

Jiang *et al.* [10] showed that Se treatment can impair microvascular development of tumors. The group recently demonstrated that cell cycle arrest by methylated Se in microvascular endothelial cells is associated with reduced microvessel density in tumors developing from prostate cancer cell xenografts [24^{••}]. Li *et al.* [31[•]] found methylated Se more effective than selenite in this regard, an effect that Bhattacharya *et al.* [32^{••}] showed can provide therapeutic synergy with anticancer drugs; methylselenocysteine (MeSeCys)-enhanced vascular maturation in carcinoma xenografts and tumor uptake of doxorubicin.

Roles of selenoproteins

The antioxidant functions of the Se-dependent glutathione peroxidases (GPX) and TRR are consistent with direct roles in Se anticarcinogenesis. Murawaki *et al.* [33[•]] found that tumors showed reduced expression of GPX1 and GPX3 (GPX2 was increased) and selenoprotein P (SepP), and greater oxidative protein modifications than nontumor tissues; in another study, GPX1 overexpression increased the resistance of breast carcinoma cells to UV-induced DNA damage [34]. Further, differing cancer risk has been linked with single-nucleotide polymorphisms

(SNPs) in several selenoproteins [12,35^{*}]. Carriers of the variant Leu allele of the Pro198Leu polymorphism of GPX1 were recently found to show decreased risk to prostate cancer [36^{*}]. Jablonska *et al.* [37^{*}] found lung cancer risk related to different SNP of the 15 kDa selenoprotein (Sep15); whereas plasma Se was inversely related to risk in both genotypes, individuals with the 1125 AA genotype appeared to benefit most from higher Se status. Selenoproteins may have other relevant functions is suggested by the finding that electrophilic or proteolytic removal of the selenol moiety ($-\text{SeH}$) from TRR rendered the enzyme unable to reduce substrate proteins without affecting its ability to accept electrons from nicotinamide adenine dinucleotide phosphate, reduced form (NADPH), which it transferred instead to O_2 to produce ROS and induce apoptosis [38].

Se needs for cancer risk reduction may depend on an individual's selenoprotein SNP. Méplan *et al.* [39^{**}] found SNP of SepP to be related to plasma Se level; intriguingly SNP 24731 (resulting in an amino acid change) is a predictor of presupplementation plasma Se level, whereas SNP 25191 [located in the 3' untranslated region (UTR) region responsible for Se incorporation] is a predictor of increase in plasma Se level with Se supplementation.

Underlying mechanisms

Most Se compounds used experimentally can be converted (Fig. 1) to one or more metabolites key to anticarcinogenesis: H_2Se , MeSeH and SeMet . These metabolites appear to execute several functions underlying Se anticarcinogenesis.

Redox cycling

These species can each undergo oxidation/reduction (Fig. 2). H_2Se can redox cycle, depleting GSH and

producing such ROS as superoxide (O_2^-) and hydrogen peroxide (H_2O_2) [40]. Selenite elicits biological effects through H_2Se redox cycling, this having recently been shown to decrease gene expression response in a testicular model [41]. This appears to be the basis for caspase-independent apoptosis in selenite-treated cervical cancer cells, which was suppressed by antioxidants and exacerbated by GSH depletion [19], for the DNA damage induced by long-term selenite feeding in carcinogen-treated and nontreated rats [17], and for the increase in TRR associated with hepatotoxic selenite doses [42]. Although MeSeH can also redox cycle, its putative anticarcinogenic effects are qualitatively different from those of H_2Se [10], indicating different underlying mechanisms.

It is known that free SeMet can scavenge ROS [43]. It is regenerated from Se-oxide (Se(O)Met) nonenzymatically by GSH; this process was recently shown to occur for SeMet in proteins as well [44^{*}]. The $\text{SeMet}/\text{Se(O)Met}$ couple has been shown to be an antioxidant mechanism, but little is known about how the substitution of SeMet for Met in proteins at regulatory sites may influence ROS-based sulfoxide signaling. Met oxidation can alter protein activity [45]; by this mechanism calmodulin kinase is activated in the absence of calmodulin/calcium by ROS from angiotensin signaling [46]. Because SeMet is more readily oxidized, $\text{Met} \rightarrow \text{SeMet}$ substitution in regulatory proteins may sensitize them to ROS. Reduction of peptidyl Se(O)Met is nonenzymatic [44^{*}], which would uncouple the regulation of Met sulfoxide reductase from ROS-based Met sulfoxide signaling.

Modification of protein-thiols

Protein-thiols, a common signaling response modulator to diverse stimuli, react with Se compounds [47,48]. Products derived from H_2Se and MeSeH can readily

Figure 2 Redox cycling of selenium compounds

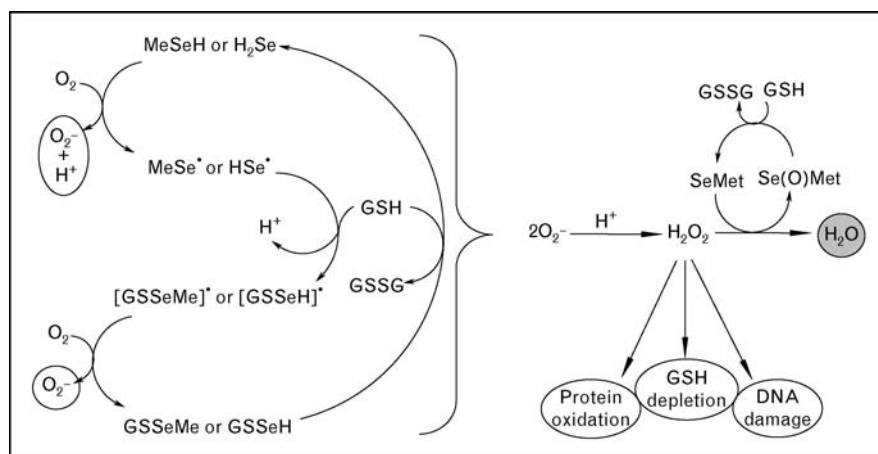
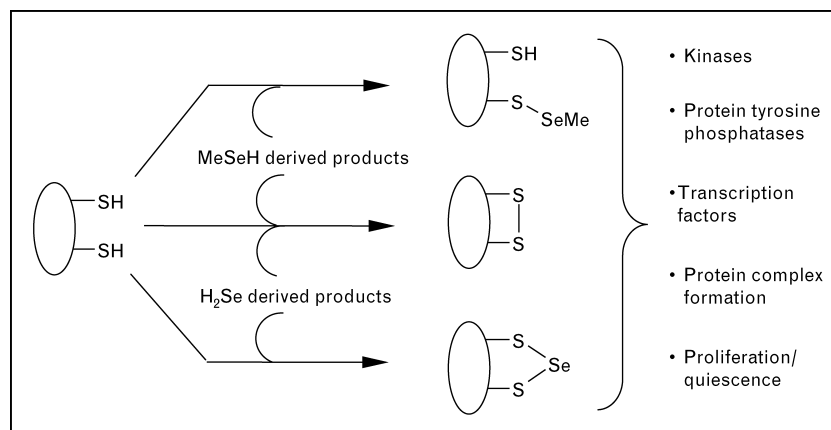
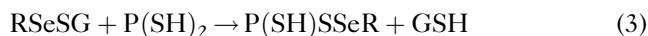
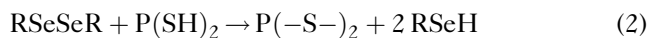


Figure 3 Modification of protein-thiols by selenium compounds



react with protein-thiols, analogous to disulfide exchange (Reaction 1); selenides can substitute for disulfides (Reaction 2, shown for protein-dithiol). Although the diselenide is thermodynamically favored, oxidation of protein-thiol and disulfide rearrangement by diselenides/selenodisulfides causes the reaction to proceed as shown [49]. Covalent adduction to form a trapped intermediate, may also affect protein activity (Reaction 3; adduction is favored at Se [50]).



Selenite is reduced to H₂Se via reduction by GSH, and peptidyl cysteines may react similarly, forming covalent adducts [48]; electrophiles produced in the course of H₂Se redox cycling may also crosslink proteins by forming protein-selenotrisulfides (P(-SSeS-)) (Fig. 3). Because intracellular levels of MeSeH would appear insufficient for bimolecular diselenide formation, the dominant species is likely to be a mixed selenosulfide of GSH, which upon ROS oxidation would produce a highly bioactive thiolating agent (MeSe(O)SG), analogous to the case recently shown for GSSG [51]. Unlike H₂Se, MeSeH cannot form trisulfides; therefore, it produces different adducts: P(SSeMe)SH from MeSeH (Fig. 3). The former mimics a disulfide and the latter a dithiol, with implications for thiol-dependent signaling. That Se species can act through protein-thiol modification was indicated by the finding of SeMet treatment altering the proteomic profile of redox-sensitive proteins in prostate cancer [52]. The induction of a *Drosophila* heat shock protein by diphenyldiselenide appears to involve altered protein conformation associated with covalent protein-thiol disruption [16]. Increased sensitivity of young animals suggests applications to proliferating cells

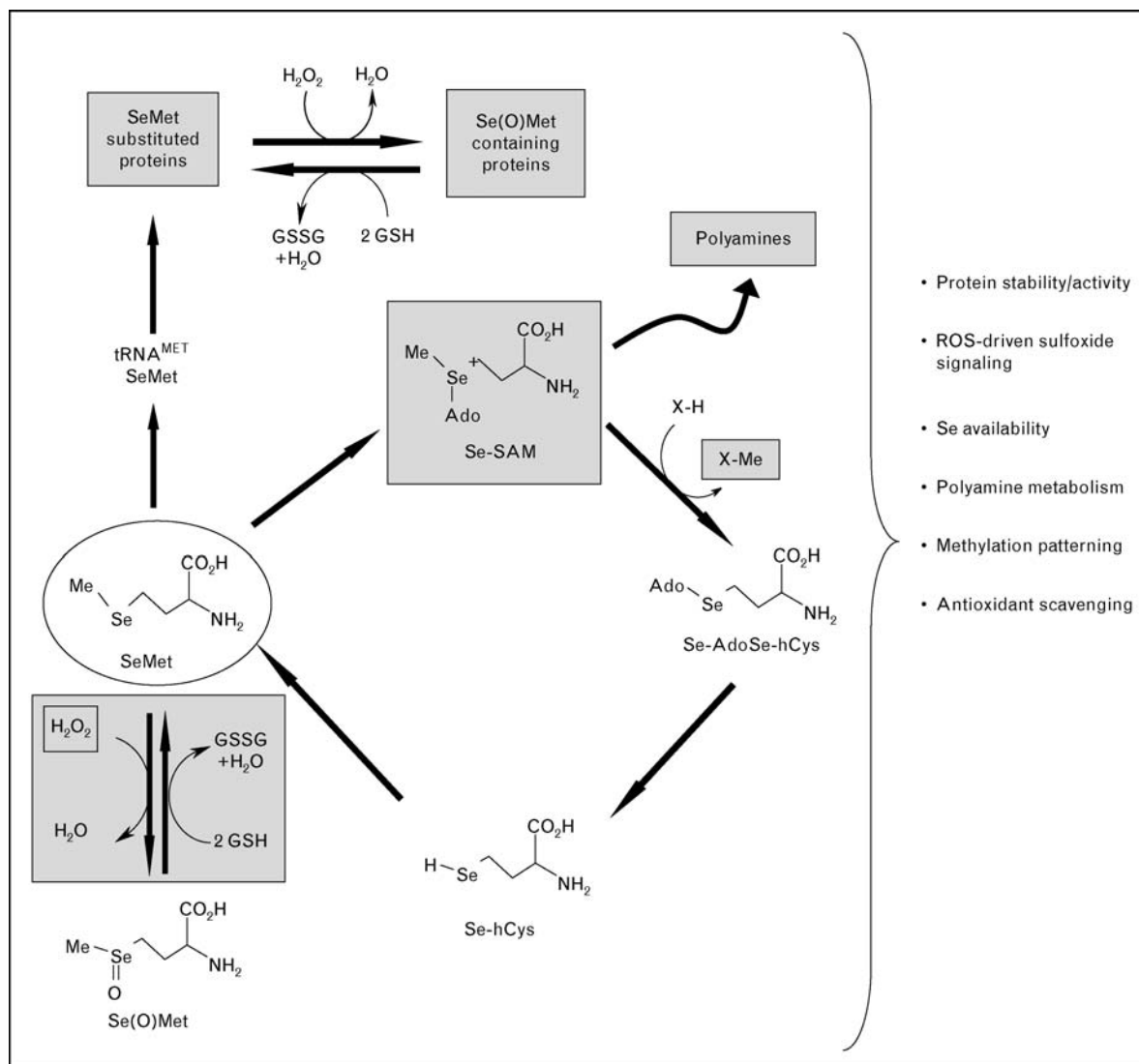
with high-protein turnover. Thus, redox cycling and covalent protein-thiol modification appear to constitute competing pathways available for H₂Se and MeSeH. The disposition of Se through each may determine their respective biological effects.

Methionine mimicry

SeMet competes with Met for metabolism including protein synthesis (Fig. 4). SeMet can charge tRNA^{Met}, resulting in substitution for Met in peptides [53], thus trapping Se and limiting its conversion to H₂Se/MeSeH. This is prominent when dietary Met is limiting, increasing the SeMet:Met ratio [54]. Release of trapped SeMet depends on protein turnover and is increased by catabolic events such as cachexia and may have toxicological implications. Li *et al.* [31[•]] demonstrated that SeMet supplementation raised tumor Se significantly more than MeSeH precursors, without reducing tumor burden. Cancer management sometimes entails dietary Met restriction [55]; selenite, MeSeCys or MSA might be more appropriate than SeMet as supplements for supporting the production of H₂Se, MeSeH, or both.

Met→SeMet substitution can affect protein stability. Substitution increased the stability of *Escherichia coli* β-galactosidase without affecting enzymatic activity [56], but decreased the stability of thymidylate synthase, also without affecting catalysis [57]. Gassner *et al.* [58] found that substitution increased the stability of lysozyme, with a gain of approximately 0.25 kcal/mol per SeMet. Stability of dihydrofolate reductase was unaffected, though the SeMet substituted enzyme was sensitized to inhibition by calcium [59]; De Bree *et al.* [60] found that insulin-like growth factor-I (IGF-I) incorporated up to 90% of Met as SeMet without altering biological potency. It may be that these substitutions affect protein turnover in a cellular context.

Figure 4 Methionine mimicry by selenomethionine



ROS, reactive oxygen species; Se, selenium.

SeMet can be converted to Met analogues [61], which may affect transmethylation and polyamine biosynthesis, and participate in transformations capable of stabilizing Se for elimination. SeMet is more effective than Met as a substrate for Met-adenosyl transferase [62], forming Se-adenosyl SeMet (Se-SAM), which can serve as methyltransferase substrate in the methylation of RNA, phosphatidyl lipids, creatine, histamine and thiols. That ratios of Se-SAM:Se-adenosylhomocysteine are decreased relative to their sulfur analogues indicates greater methylating efficiency by SeMet [63] and may be relevant to anticarcinogenesis [64], as methyltransferases play roles in gene silencing, repair of damaged proteins, activation of oncogenes and lipid metabolism. Se-SAM formation may underlay differences in bioactivity of SeMet and selenite; the toxicity of the former is

dependent on conversion of SeMet to Se-SAM [65]). Although many studies have not found SeMet to affect polyamine levels, Redman *et al.* [66] found polyamines prevent SeMet-induced apoptosis and SeMet-decreased polyamine levels in tumor cells. Conversely, Bjelakovic *et al.* [67] recently found SeMet supplementation of hepatectomized rats increased the production of spermine and spermidine, effects associated with inhibited spermine/spermidine catabolism and exposing disparate outcomes of SeMet in proliferating normal and tumor tissues.

Conclusion

Se compounds, particularly at supranutritional levels, can reduce cancer risk. This protection involves several

Table 1 Summary of chemical/biochemical activities of selenium metabolites proposed to underlie selenium anticarcinogenesis

Precursor compounds ^a	Functional species ^a	Underlying functions		
		Redox cycling	Modification of protein-thiols	Methionine mimicry
Selenite, selenate, SeMet ^{b,c} , SeCys ^b	H ₂ Se	+ (ROS-generating)	+	
SeMet ^{b,c} , SeCys ^b , MeSeCys, MSA, selenite, selenate	MeSeH	+ (ROS-generating)	+	
SeMet ^b	SeMet	+ (ROS-scavenging)		+

^a H₂Se, hydrogen selenide; MeSeCys, methylselenocysteine; MeSeH, methylselenol; MSA, methylseleninic acid; ROS, reactive oxygen species; SeCys, selenocysteine; SeMet, selenomethionine.

^b Both free and proteinyl forms.

^c Relatively less efficient.

steps in carcinogenesis. Underlying these intermediate mechanisms are the chemical/biochemical activities of Se species present in cells (H₂Se, MeSeH and SeMet), which appear to execute those effects by several means: producing ROS by redox cycling; modification of protein-thiols and mimicking Met (Table 1). Various Se compounds are capable of being metabolized to one of more of these species. Competing pathways of metabolic and chemical/biochemical disposition of ingested Se compounds appear to underlie their different relative anti-carcinogenic activities. A multitiered model of Se anti-carcinogenesis is presented.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 804).

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Together with previous findings in tumor tissues, this study indicates that there might be disparate effects of SeMet supplementation on polyamine levels between proliferating normal and cancer tissues.