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Selenium as an anticancer nutrient: roles in cell proliferation and tumor cell invasion☆

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Abstract

Selenium is an essential dietary component for animals including humans, and there is increasing evidence for the efficacy of certain forms of selenium as cancer-chemopreventive compounds. In addition, selenium appears to have a protective effect at various stages of carcinogenesis including both the early and later stages of cancer progression. Mechanisms for selenium-anticancer action are not fully understood; however, several have been proposed: antioxidant protection, enhanced carcinogen detoxification, enhanced immune surveillance, modulation of cell proliferation (cell cycle and apoptosis), inhibition of tumor cell invasion and inhibition of angiogenesis. Research has shown that the effectiveness of selenium compounds as chemopreventive agents in vivo correlates with their abilities to affect the regulation of the cell cycle, to stimulate apoptosis and to inhibit tumor cell migration and invasion in vitro. This article reviews the status of knowledge concerning selenium metabolism and its anticancer effects with particular reference to the modulation of cell proliferation and the inhibition of tumor cell invasion.
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Keywords: Selenium; Cell proliferation; Cancer; Invasion

1. Introduction

Selenium (Se), an essential trace element for animals including humans, has been shown to affect the functions of several specific intracellular selenoproteins by being a component of their essential constituent selenocysteine (SeCys) [1]. These selenoproteins include glutathione peroxidase (GPx) and thioredoxin reductase (TrxR), which have important antioxidant and detoxification functions [1]. It was first suggested in the late 1960s that Se might also be anticarcinogenic, based on an inverse relationship of Se status and risks of some kinds of cancer [2,3]. Since then, a substantial body of persuasive evidence indicates that Se can indeed play a role in cancer prevention [4–6]. Interest in this area was stimulated by the landmark finding that supplementation of free-living people with Se-enriched brewer's yeast with predominantly selenomethionine (SeMet) decreased the overall cancer morbidity by nearly 50% [7]. That finding came from the Nutritional Prevention of Cancer (NPC) trial, a prospective, double-blinded, randomized, placebo-controlled trial involving 1312 patients

Abbreviations: AP-1, activating protein-1; ASK1, apoptosis signal-regulating kinase 1; CDK, cyclin-dependent kinase; GPx, glutathione peroxidase; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; MSeA, methylseleninic acid; NF-κB, nuclear factor-kappa B; NPC, Nutritional Prevention of Cancer; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; ROS, reactive oxygen species; SELECT, Se and Vitamin E Chemoprevention Trial; Se, selenium; SeCys, selenocysteine; SeMet, selenomethionine; SeMSC, Se-methylselenocysteine; SOD, superoxide dismutase; TIMP, tissue inhibitor of metalloproteinase; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; TrxR, thioredoxin reductase; VEGF, vascular endothelial growth factor.

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recruited because of histories of nonmelanoma skin cancers, i.e., basal cell and/or squamous cell carcinomas.

To follow-up on that finding, the Se and Vitamin E Chemoprevention Trial (SELECT) was launched in the fall of 2001. This is a randomized, double-blind, 12-year trial designed to determine whether Se (as SeMet) and vitamin E, alone or in combination, can reduce the risk of prostate cancer among 32,400 healthy men [8].

Although epidemiological studies, preclinical investigations and clinical intervention trials have supported a role of Se compounds as cancer chemopreventive agents, the mechanisms for such actions have not been elucidated. A better understanding of the underlying mechanisms will provide insights useful in interpreting the data anticipated from SELECT, as well as in considering issues such as chemical form, dose level and duration in planning future interventions.

Recent advances have led to several mechanisms being proposed for the anticancer activity of Se. These include antioxidant protection (via selenoproteins), altered carcinogen metabolism, enhanced immune surveillance, regulation of cell proliferation and tumor cell invasion and inhibition of neoangiogenesis [6–12]. Because effects on cell proliferation and tumor cell invasion are central events of each of these mechanisms, the review focuses on the roles of Se in affecting these cellular processes.

2. Selenium metabolism

With a chemistry similar to that of sulfur, Se is biologically active in a variety of covalent compounds including inorganic salts, amino acids and methylated compounds. The compounds available for use as Se supplements include the inorganic forms (sodium selenite and sodium selenate) and the organic forms [SeMet, Se methylselenocysteine (SeMSC) and Se-enriched yeast which contains mostly SeMet] [13]. Not all of these forms are metabolized alike. Humans have been found to absorb and retain Se better from SeMet and Se yeast than from the inorganic Se salts [14–16]; however, the metabolism of both organic and inorganic Se forms shows certain similarities (Fig. 1). Unlike the organic forms of Se, in which Se is in the reduced state (selenide: Se^{2-}), the inorganic salts contain Se in oxidized forms (selenite: Se^{4+}; selenate: Se^{6+}). Upon absorption, the higher-valence forms are reduced to the selenide state using reducing equivalents from reduced glutathione and reduced nicotinamide adenine dinucleotide phosphate (NADPH). In contrast, the organic forms (SeMet, SeCys) release Se in the selenide state as a result of catabolism. The Se from SeMet, consumed in the form of food proteins and/or dietary supplements, is thus transferred to form SeCys. Alternatively, SeMet can be incorporated nonspecifically into proteins, as it freely substitutes for Met in protein synthesis. Intact SeCys from the diet is not used for synthesis; instead, it is cleaved to form selenide (H_2Se) [16].

Selenide has a central role in Se metabolism, being the branch point of two metabolic pathways. One pathway results in selenoprotein production; this involves the cotranslational biosynthesis of SeCys and its incorporation into specific selenoproteins. This process involves the charging of a specific transfer RNA (tRNA) with the amino acid serine by seryl-tRNA synthase, followed by the SeCys synthase-catalyzed replacement of the serinyl hydroxyl with a selenol moiety (−SeH) from selenophosphate to form tRNA-bound SeCys [17,18]. The process is unique in that the tRNA involved is recoded, such that UGA, normally a

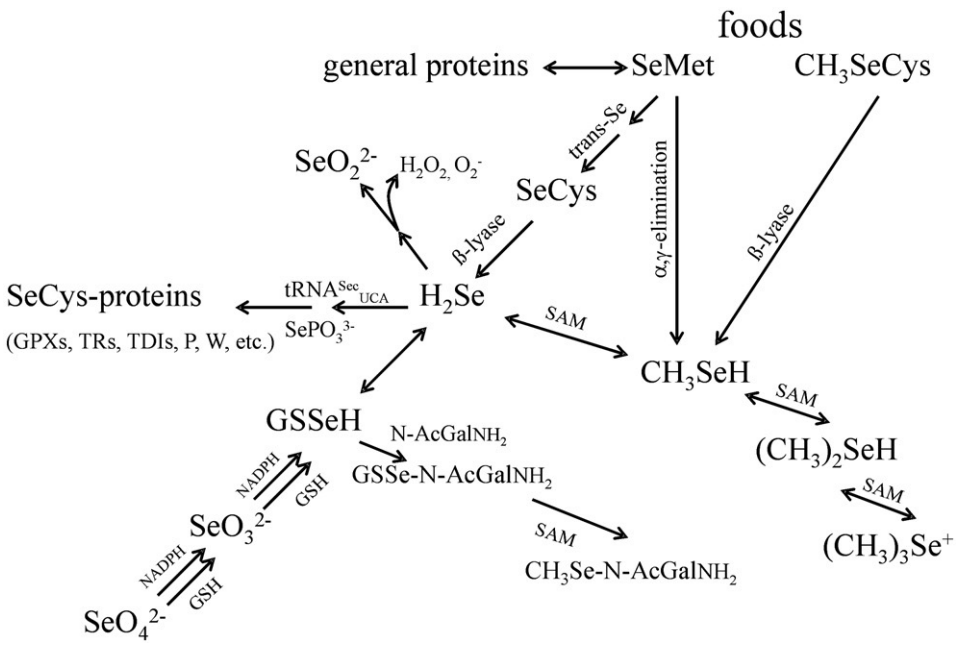

Fig. 1. Proposed pathways for the metabolism of biologically important selenomolecules.

termination codon, specifies the cotranslational insertion of SeCys. This recoding process requires the assembly of complexes, termed SeCys insertion sequence elements at selenoprotein mRNAs [1,17]. Because selenoprotein expression is tightly regulated, Se in excess of these needs enters an excretory pathway (Fig. 1).

The excretion of Se occurs by the methylation or sugar derivation of selenides. This produces a series of metabolites: methylselenol (CH_3SeH) and dimethylselenide ($[CH_3]_2SeH$), which are excreted across the lungs, and trimethylselenonium ion ($[CH_3]_3Se^+$) and 1-β-methylseleno-*N*-acetyl-D-galactosamine (CH_3Se-GalN), which are excreted across the kidney [18,19]. The pattern of these excretory forms as well as the total amount of Se excreted are influenced by both the level of Se intake and the physiological Se status. Under physiological conditions, Se homeostasis appears to be regulated mostly by the form of the dose and the rate of Se excretion [18] (Fig. 1).

Evidence suggests that CH_3SeH produced in the excretory pathway may be a key anticarcinogenic metabolite [6,20]. When arsenic was used as a blockade of Se methylation, it reduced the capability of metabolic precursors of CH_3SeH to support selenoprotein expression but enhanced the antitumorigenic activities of such precursors in animal models [21,22]. These experiments also showed that methylation blockade by dietary arsenic did not affect the utilization of selenite for supporting selenoprotein expression but inhibited the antitumorigenic effect of that form of Se [21,22]. Thus, these studies demonstrated that Se antitumorigenesis, at least in the murine mammary tumor model, depends on the metabolic production of a methylated Se metabolite.

3. The effect of Se on cell proliferation

3.1. Essential nutritional role on cell growth

Selenium is a potent effector of cell growth with a relatively narrow window of tolerance. In the form of selenite, SeMet or SeCys, it functions as an essential micronutrient at levels of ~0.1–0.2 ppm (mg/kg) in the diets of experimental animals and livestock, but it becomes toxic at levels exceeding 5 ppm [23]. The recommended daily allowance for Se is 55 μg/day for both men and women. Doses of 100–200 μg Se per day inhibit genetic damage and cancer development in human subjects and about 400 μg Se per day is considered an upper safe limit [5]. At nutritional levels, Se is the defining component of the SeCys-containing selenoproteins, a family the members of which exhibit a wide range of functions, including roles in cellular antioxidative protection, redox regulation, male fertility and thyroid function. In addition, Se has been shown to mediate a number of insulinlike actions including the stimulation of glucose uptake and regulation of glycolysis, gluconeogenesis, fatty acid synthesis and the pentose phosphate pathway [24].

Selenium, at concentrations of nanomoles per liter, is also essential for the growth of cells in culture [25,26]. The control of cell cycle progression plays a key role in terminal differentiation, growth and development [27,28]. The connections between cancer and the "check point" at the G1-S and the G2-M transitions of the cell cycle have become apparent [27–29]. Because of the conserved nature of cell cycle control mechanisms [27–29], the elucidation of the Se effect on cell cycle control will provide a better understanding of the nutritional roles of the element. When HL-60 cells were optimized in serum-free culture conditions to maximize the effects of Se on cell growth, low levels of Se (nmol/L) enhanced cell proliferation and up-regulated the expression of numerous cell cycle-related genes, including as c-Myc, cyclin C, proliferating cell nuclear antigen, cyclin-dependent kinase (CDK) 1, CDK2, CDK4, cyclin B and cyclin D2 mRNA and total cellular phosphorylated proteins [30]. This led to the promotion of cell cycle progression, particularly G2/M transition and/or the reduction of apoptosis, primarily in G1 cells [30]. Furthermore, when Jurkat cells were cultured in a serum-free (Se-deficient) medium, selenoenzyme activities such as GPx and TrxR decreased significantly within cells and subsequently induced cell death [31]. Interestingly, a lipid soluble radical-scavenging antioxidant (vitamin E) but not the water-soluble antioxidants (ascorbic acid, *N*-acetyl cysteine and glutathione), completely blocked Se deficiency-induced cell death, although vitamin E could not restore Se-dependent enzyme activity [31]. Further studies suggested that cellular reactive oxygen species (ROS), especially lipid hydroperoxides, are involved in the cell death caused by Se deprivation, in which Se and vitamin E cooperate in the defense against oxidative stress in cells by detoxifying and inhibiting the formation of lipid hydroperoxides [31]. In addition to the ability to scavenge ROS, GPx and TrxR control the redox status of their substrates, glutathione and thioredoxin; therefore, reduced selenoprotein expression due to Se deprivation can result in a compensatory increase of other dependent cellular antioxidants, such as heme oxygenase 1, that may help counteract the damaging effects of oxidant stress [32].

Although the importance of nutritional levels of Se in cell proliferation has been documented, the role of Se in cell signaling is not well understood. In several recent studies, Se has been shown to mediate insulinlike actions both in vivo and in vitro [24,33]. Insulin or insulin mimetics are necessary to promote the uptake of glucose into tissue where it can be converted into energy or stored for future use. The insulinlike actions of Se include increasing glucose uptake and adenosine triphosphate generation through the activation of glycolysis, up-regulation of antiapoptotic protein Bcl-2, maintenance of mitochondrial membrane potential, stimulation of fatty acid synthesis and pentose phosphate pathway activity. The mechanism underlying these responses appears to involve the activation of key proteins involved in the insulin signal cascade and the indirect

stimulation of tyrosine phosphorylation and activation of mitogen-activated protein kinase (MAPK) [24,33]. Selenium also directly regulates the activities of many proteins crucial for various intracellular signaling pathways. The activities of nuclear factor-kappa B (NF-B), activating protein-1, c-Jun N-terminal kinase (JNK) [34–36] and caspase-3 [37] are inhibited by Se through the redox regulation of their reactive cysteine residues. Nutritional levels of Se have also been shown to suppress apoptosis signal-regulating kinase 1 (ASK1) activities to induce cell survival through the activation of focal adhesion kinase–phosphatidylinositol 3-kinase (PI3K)–AKt kinase pathway by Rac1 activation [38] and to inhibit the apoptotic ASK1-JNK pathway both by activating focal adhesion kinase and PI3K–Akt kinase and by modifying the sulfhydryl groups of ASK1 [39].

While the deprivation of Se can reduce the protection against oxidative stress and impair immunocompetence [31–40], certain cancer cells appear to have acquired a selective survival advantage that is apparent under conditions of Se deficiency and oxidative stress [41]. A recent report showed that most hepatocellular carcinoma cell lines (10 of 13), breast cancer cell lines (11 of 14), colon cancer cell lines (8 of 10) and all melanoma cell lines tested were resistant to Se deficiency-induced cell death [41]. This suggests that at least some cancer types are relatively insensitive to Se deprivation, a prospect that warrants further investigation.

3.2. The effect of Se on cell cycle and apoptosis

Both inorganic and organic Se compounds can be antitumorigenic in animal models at "supranutritional" doses, i.e., nontoxic doses greater than those required to support the maximal expression of the selenoenzymes [4–6]. This observation has been cited as evidence for Se anticarcinogenesis involving Se metabolites, which may accumulate in significant amounts at such doses. It has been suggested that such doses of Se may affect the later stages of carcinogenesis, perhaps stimulating apoptosis, based on the finding from the NPC trial that cancer risk reductions due to Se treatment were observed after only a couple of years of intervention [7].

In cultured cell models, Se compounds have been shown to inhibit cancer cell growth by decreasing cell proliferation through cell cycle arrest and/or increasing in apoptosis [5,6,20,42]. Chemopreventive efficacy has been found to vary among Se compounds [6]. Hydrogen selenide (H_2Se) and CH_3SeH are major pools of Se metabolites that induce distinct types of biochemical and cellular responses [10,11]. The H_2Se precursors selenite and SeCys induced DNA single-strand breaks (genotoxicity) [43–45], and selenite at 5–10 μmol/L caused extensive cytoplasmic vacuolization of cells, cell detachment and cell membrane leakage. That a superoxide dismutase (SOD)-mimetic (copper dipropylsalicylate/Cu^{++}) blocked DNA single-strand breaks and apoptosis [42,46] suggested that these effects directly involved redox-mediated effects of selenite. Subsequently, the role of superoxide generation by the H_2Se pool was confirmed using SOD or SOD mimetics [47,48], and the generation of ROS was detected in in vitro models by the reaction of selenite with GSH and other thiol compounds [49,50]. The consequence of sodium selenite or selenocysteine treatment of cancer cells in vitro was S phase/G_2 cell cycle arrest and the induction of apoptotic cell death [10,35,42]. Cell death, DNA apoptotic fragmentation and DNA double-stranded breaks were preceded by the occurrence of DNA single-stranded breaks detected using a filter elution assay [51,52].

Earlier studies had found that metabolic precursors of CH_3SeH (methylselenocyanate, SeMSC) exerted moderate antiproliferative effects, as assessed by ^{3}H-thymidine incorporation into DNA of the cells at the G1 phase of the cell cycle, whereas selenite rapidly blocked DNA synthesis and arrested cells in the S phase [6,53,54]. These methylated Se compounds induced cell apoptosis without inducing DNA single-strand breaks [10,53,54]. These effects are consistent with CH_3SeH being a key anticarcinogenic metabolite [20].

The effects of Se compounds on cell cycle progression suggest mechanisms involving cyclin-dependent kinases which are known to orchestrate that process. Methylselenol appears to inhibit specific protein kinases, cyclin-dependent kinases, and target a growth control mechanism during mid- to late G1 in a manner similar to that of PI3K inhibitors [20,55–57].

Selenium also plays several other key roles in anticancer cellular signaling. Methylseleninic acid (MSeA), which can be generated locally by the reaction of membrane CH_3SeH with protein kinase C (PKC)-bound tumor-promoting fatty acid hydroperoxides, selectively inactivated PKC [58]. The redox-mediated inactivation of PKC may be responsible, at least in part, for the antioxidant-induced inhibition of tumor promotion and cell growth, as well as for the induction of cell death [58]. Several studies have also demonstrated selenite-induced apoptotic DNA laddering in the p53-mutant cancer cells without the cleavage of poly(ADP-ribose) polymerase (i.e., caspase-independent apoptosis); whereas metabolic precursors of CH_3SeH induced caspase-mediated apoptosis in those cells [47,59]. However, selenite activated the caspase-mediated apoptosis involving both the caspase-8 and the caspase-9 pathways in the p53 wild-type cancer cells [60]. Further studies indicated that selenite induced a rapid superoxide burst and p53 activation, leading to Bax up-regulation and translocation into mitochondria, which restored the cross-talk with stalled tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) signaling for a synergistic caspase-9/3 cascade-mediated apoptosis execution [61]. In contrast, MSeA, another CH_3SeH precursor, inhibited PI3K or other components of this pathway. This study demonstrated the inhibitory effects of MSeA on other protein kinase pathways, including phospho-extracellular signal-regulated kinase 1/2 and phospho-JNK.

Activation of p38 MAPK may also be involved in vascular endothelial apoptotic responses in a pharmacological or therapeutic context of MSeA exposure [62,63].

The results of microarray profiling analyses have indicated that Se treatment can alter several genes related to cell cycle/apoptosis in a manner related to cancer prevention [64]. Treatment with Se resulted in the up-regulation of genes involved in phase II detoxication enzymes, in certain Se-binding proteins and in some apoptotic genes [64]. Selenium treatment also resulted in the down-regulation of genes related to phase I activating enzymes and cell proliferation [64]. In all tissues tested, Se treatment arrested cells in the G1 phase of cell cycle and inhibited the expression of the cyclin A, cyclin D1, CDC25A, CDK4, PCNA and E2F genes while inducing the expressions of P19, P21, P53, GST, SOD, NQO1, GADD153 and certain caspase genes [64].

4. The effect of Se on tumor cell invasion

Carcinogenesis is a multistep process that includes tumor initiation, promotion and progression and the importance of cancer cell migration, proliferation and extracellular matrix degradation in this process is well known [65,66]. Studies have shown dietary supplementation with high-Se soy protein to reduce pulmonary metastasis of melanoma cells in mice [67]. Results obtained with the gene therapy approach clearly demonstrate that CH_3SeH can inhibit tumor growth and prolong host survival [68]. Because the prevention of tumor cell adhesion and migration is related to inhibition of tumor cell invasion into the basement membrane [69], factors that inhibit cell attachment in vitro are likely to decrease the invasiveness and/or metastatic potential of tumor cells in vivo [70,71]. It was reported that brief pre-exposure of HeLa cells to micromolar concentrations of selenite resulted in a dose-dependent decrease in the rate of their subsequent attachment to a solid matrix [72]. Similar concentrations of selenite have also been found to inhibit colony formation but only when the cells were exposed prior to their attaching to the dish [72]. Further studies demonstrated that these effects involved the reduction of cell surface fibronectin receptor activity, inhibiting the attachment of tumor cells to the extracellular matrix [73]. Recent data indicate that selenite inhibits the invasion of tumor cells by reducing their adhesion to the collagen matrix [74]. These effects may involve matrix metalloproteinases (MMPs) and serine proteases, the proteolytic enzymes involved in the tumor invasion. A serine protease, urokinase-type plasminogen activator (uPA), can convert plasminogen to plasmin, which is capable of degrading extracellular matrix proteins and activating latent forms of MMPs [75]. Studies have suggested that selenite can suppress the expression of both MMPs and uPA while up-regulating the expression of a tissue inhibitor of metalloproteinase (TIMP) 1, an effect directly related to the inhibition of tumor cell invasion [74]. Interestingly, treatment with CH_3SeH precursors increased the expression of both prometastatic genes, MMP-2 and MMP-9 and antimetastatic genes, TIMP-1 and TIMP-2; the net effect was inhibition of pro-MMP-2 activation and tumor cell migration and invasion capacity [12]. Therefore, both selenite and methylselenol inhibit tumor cell invasion through various molecular targets, only some of which they both affect.

Consistent with the above findings, CH_3SeH would appear to have antiangiogenic effects on the chemoprevention of cancer [11,42,76]. Methylselenol precursors exert rapid, inhibitory effects on the expression of key molecules involved in angiogenesis regulation. For example, it was demonstrated that subapoptotic doses of MSeA inhibited the expression and secretion of vascular endothelial growth factor (VEGF, an angiogenic factor), in several cancer cell lines and inhibited MMP-2 and VEGF expression in vascular endothelial cells [76]. These effects point to CH_3SeH as a key inhibitor of the angiogenic switching in early lesions and in tumors [11]. The osteopontin gene, which is mainly involved in metastasis, was recently reported to be down-regulated by Se treatment; this finding demands attention as a prospective molecular markers for chemoprevention trials [77].

5. Conclusion

Selenium is an essential nutrient with anticarcinogenic potential, particularly at supranutritional doses. The dominant forms of the element are found in foods and dietary supplements, SeMet and SeCys, with smaller amounts of methylated selenides. Inorganic Se salts, selenite and selenate, are widely used experimentally as well as in livestock feeding. Any of these forms can support the nutritional requirements for the element; however, their bioefficacy depends on both dose and chemical form. At

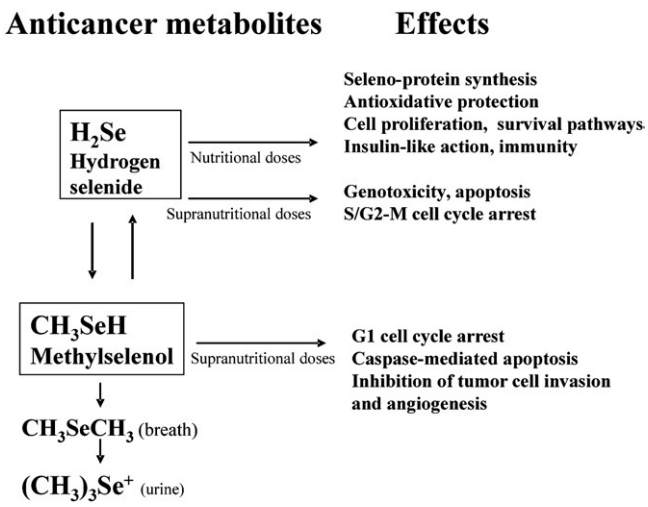

Fig. 2. Proposed cellular effects of hydrogen selenide and methylselenol.

low doses, Se function is an essential component of SeCys in several specific selenoproteins and promote cell proliferation, a fact of particular importance to the immune response. At higher doses, but still nontoxic, Se can reduce cancer risk. This effect involves the stimulation of tumor cell cycle arrest and apoptosis and the inhibition of tumor cell migration and invasion (Fig. 2).

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