Protein Kinase C as a Molecular Target for Cancer Prevention by Selenocompounds

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Abstract: Selenium is a very effective cancer-preventive agent, suppressing tumor promotion and early stages of tumor progression. However, the mechanisms by which selenium exerts these cancer-preventive actions are not known. Protein kinase C (PKC) is a receptor for certain tumor promoters and also plays a crucial role in events related to tumor progression. Therefore, it is not only a potential target for the cancer-preventive activity of selenium, but also it has the structural basis for interaction with selenium. Redox-active selenocompounds can inactivate PKC, particularly the Ca²⁺-dependent isozymes, by reacting with the critical cysteine-rich regions present within the catalytic domain while, in some cases, also reacting with the cysteine residues present within the zinc-fingers of the regulatory domain. The selenoprotein thioredoxin reductase (TR), acting through thioredoxin, reverses the inactivation of PKC induced by selenometabolites. Furthermore, TR, through a direct interaction involving its selenol sulfur center with the zinc-thiolates of PKC, can reverse the redox modification of this kinase induced by selenometabolites. Thus the selenometabolite-induced toxicity is reversed by a selenoprotein, and therefore an interrelationship exists between these two mechanisms of selenium actions. Moreover, this also explains how a resistance to selenium develops in advanced tumor cells probably due to an overexpression of functional TR. Selenium-induced inactivation of PKC may, at least in part, be responsible for the selenium-induced inhibition of tumor promotion, cell growth, invasion, and metastasis, as well as for the induction of apoptosis.

Introduction

Epidemiological data suggest that cancer mortality is inversely correlated with selenium consumption (1,2). Experimental studies in animals indicate that selenium supplementation at levels (1–3 ppm) above the dietary requirement (0.1 ppm) can prevent tumorigenesis at various sites, including breast and skin (3–12). Cancer prevention clinical trials carried out by Dr. Larry Clark and his associates suggested that supplemental selenium may reduce the incidence and mortality of prostate, lung, and colorectal cancers, but not skin or breast cancer (13–15). This landmark achievement is not only a tribute to Dr. Larry Clark, but it also gives hope to cancer prevention researchers that prevention or delay of human cancer will eventually be possible through chemoprevention.

Many important issues remained to be answered to achieve cancer prevention in humans by selenium supplementation. Despite the well-demonstrated ability of selenium to inhibit breast cancer in animal studies (7–10), it is not clear whether selenium can decrease breast cancer in humans (13). Therefore, it is imperative to know why selenium prevents cancers in some cases while it fails to do so in other cases. Furthermore, it is important to understand whether a particular stage(s) in carcinogenesis is well suited for the cancer-preventive activity of selenium. Thus it is important to identify the molecular targets and mechanisms by which selenium prevents cancer. This will help us understand which types of cancers are best prevented by selenium and identify those individuals who would most benefit from selenium supplementation.

Selenium Inhibits Initiation and Postinitiation Stages in Carcinogenesis

To be most effective, chemopreventive agents should inhibit several stages in multistage carcinogenesis (16–18). Selenium, which can inhibit various stages in carcinogenesis, is thus well suited for prevention of carcinogenesis in humans. Selenium exerts its chemopreventive effects at the initiation phase of tumorigenesis by inhibiting carcinogen binding to DNA (19). In addition, selenium inhibits tumor promotion, progression, and angiogenesis (20–26). Selenium also stimulates the immune system (27). Experimental studies reveal that selenium is very effective at the post-initiation stages in carcinogenesis (10,28). The decades of tumor preneoplasia and/or early neoplasia, comprising tumor promotion or the early stages of tumor progression in
the development of cancer in organs such as the prostate in humans, make these stages ideal for chemoprevention by selenium (29–31). However, the mechanisms by which selenium inhibits tumor promotion or progression are not known.

Selenium was shown to inhibit cell transformation in vitro at concentrations lower than that needed for the inhibition of growth of malignant cells (20–23). Furthermore, there is limited evidence to support the theory that dietary selenium can prevent the growth of transplanted tumors in animals (32–34). Recent in vitro studies have shown that various selenocompounds, especially at higher doses, induce apoptosis of tumor cells in culture (35–39). These growth-inhibiting and apoptosis-inducing mechanisms may be important in the promotion phase of carcinogenesis, where there is a clonal expansion of preneoplastic cells that escape death.

**Selenium Actions as Selenoproteins and Selenometabolites**

The original suggestion that selenium acts as a redox catalyst is an important clue to understand the actions of selenium present in trace amounts in the biological systems (40). It is believed that selenium can exert its cancer-preventive actions by two different mechanisms: one involves the actions of selenoproteins, and the other involves direct actions of selenometabolites. Both mechanisms have been found to have limitations; nevertheless, it is important to understand whether these two distinct mechanisms are interrelated and complementary.

**Selenoproteins**

At a nutritional level (0.1 ppm), selenium is essential to glutathione peroxidase (GPx), which protects cells from \( \text{H}_2\text{O}_2 \) and organic peroxides (41,42). Because peroxides can induce tumor promotion, there is a possibility that GPx may have a role in inhibiting tumor promotion. However, the requirement of selenium for cancer prevention (1–3 ppm), well above levels required for optimal expression of GPx activity, suggests involvement of complementary mechanisms for chemoprevention (8). Recently, selenocysteine was identified as the penultimate COOH-terminal residue in thioredoxin reductase (TR) (43–45). Unlike other selenoproteins previously characterized, TR activity is not saturated with nutritionally adequate dietary selenium, but a twofold increase in TR activity by increasing dietary selenium to cancer-preventive doses has been reported (46–49). Compared with normal tissues, tumors have increased expression of TR and thioredoxin, which are believed to protect cells from cell death (50). However, there are also suggestions that, under certain conditions, TR and thioredoxin can induce cell death, but the mechanism of this opposite action is unknown (51,52). Given the importance of oxidative stress in tumor promotion, the antioxidant functions of GPx and TR are very relevant to the cancer-preventive actions of selenium. Nevertheless, their precise role is not clear.

**Selenometabolites**

Selenocompounds such as selenite, selenodiglutathione, selenomethionine, and Se-methylselenocysteine ultimately generate selenide (8), which is incorporated into the selenoproteins by a specialized mechanism (41,42). When selenide is generated in greater amounts, it also reacts with oxygen to produce superoxide and, ultimately, \( \text{H}_2\text{O}_2 \), which results in toxicity (53–55). This oxidative injury caused by selenide redox cycling is believed to be responsible for the toxic or cancer-preventive actions of selenium (53). Furthermore, selenide is methylated to methylselenol, dimethylselenide, and trimethylselenonium (4). Trimethylselenonium is excreted through urine, whereas dimethylselenide is exhaled (8). Although this methylation pathway was originally thought to be a detoxification pathway, previous elegant studies suggested a role for methylselenol and dimethylselenide in mediating the anticarcinogenic actions of selenium (8).

Although selenomethionine inhibits tumor cell growth or induces apoptosis in vitro at high (40–130 µM) concentrations (63,64), it is present in plasma and tissues primarily in proteins, incorporated in place of methionine (65,66). Thus, at cancer-preventive doses, while excess selenium is excreted, most (>90%) selenium in the circulation is present as selenoproteins, and only a limited amount (<5%) is present as selenometabolites (67). Therefore, although these in vitro cellular actions of selenometabolites may be relevant to cancer prevention, it is important to determine whether these actions occur in vivo at bioavailable concentrations of selenium, as well as how they are related to the actions of selenoproteins. Therefore, a true molecular target for cancer-preventive actions of selenium may clarify the interrelationship between the actions of selenoproteins and selenometabolites.

**Protein Kinase C as a Target for Tumor Promoters and Antitumor Promoters**

Protein kinase C (PKC), a family of isozymes, is activated not only by lipid second messengers (68–70), but also by tumor promoters such as phorbol esters and oxidants (71–75). PKC regulates tumor promotion and cell growth by inducing activation of transcriptional factors, such as activa-
tor protein-1 (AP-1) and nuclear factor-κB (NF-κB), and by increasing the expression of key enzymes, such as ornithine decarboxylase, inducible nitric oxide synthase, and cyclooxygenase-2 (76–80).

PKC has unique structural aspects that render it susceptible to activation by oxidant tumor promoters, such as H$_2$O$_2$, periodate, and tobacco-related tumor promoters (71–73). Selective oxidative modification of the regulatory domain results in Ca$^{2+}$/lipid-independent activation, while selective oxidative modification of the kinase domain results in inactivation (81,82). The regulatory domain contains 12 cysteine residues that coordinate the binding of 4 zinc atoms; the zinc-thiolate structure is required for binding of phorbol ester and diacylglycerol (83,84). This positively charged zinc-thiolate is more susceptible to tumor-promoting oxidants (81,82). Thus phorbol esters activate the enzyme by binding to the structure supported by zinc-fingers, while oxidants directly induce a similar effect by reacting with zinc-thiolates and induce a collapse of the zinc-fingers (Fig. 1). In both cases, changes occurring in the regulatory domain relieve its autoinhibitory effect, caused by the interaction of its pseudo-substrate, autoinhibitory region of PKC that prevents binding of protein substrate to catalytic domain.

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Some cancer-preventive agents, such as polyphenolics (curcumin, 4-hydroxytamoxifen, and ellagic acid) in their oxidized state, can inactivate PKC by oxidizing the vicinal thiols present within the catalytic domain (88–90). Therefore, PKC, by having different oxidation-susceptible regions in the regulatory and catalytic domains, can respond to oxidant tumor promoters and chemopreventive agents to elicit opposite cellular responses. In addition to scavenging free radicals, antioxidants also interrupt signaling mechanisms triggered by oxidants (91,92). Although tumor promoters have their own receptors, it is not known whether chemopreventive agents also have their own receptors to induce their cellular actions. However, if they act on the same cellular target(s) as the tumor promoters, they can efficiently block cell signaling induced by tumor promoters.

### Inactivation of PKC by Redox-Active Selenometabolites

#### Selenite

Several studies have explored the effects of selenium on PKC (93,94). At lower concentrations, selenite decreased PKC activity [concentration resulting in half-maximal inhibition (IC$_{50}$) = 0.5 µM] and induced a modification of four cysteine residues, resulting in the formation of two disulfides (93). However, at higher concentrations, it decreased phorbol ester binding and induced a modification of seven to eight cysteine residues, resulting in the formation of three to four disulfides. The isozymes α, β, and γ exhibited higher sensitivity to selenite than the ζ and δ isozymes. A cluster of at least four cysteine residues is needed for the rapid reaction of selenite with protein sulfhydryls (95). The four conserved cysteine residues present within the catalytic domain of α, β, and γ isozymes, although separated in the sequence, may be clustered in the tertiary structure, providing high specificity for selenite reaction with these PKC isozymes (93). However, PKC-ζ, which has only two of four of these conserved cysteines, reacted weakly with selenite; PKC-ε, which has only three conserved cysteine residues, was intermediate in exhibiting the sensitivity to selenite-induced inhibition (Fig. 2).

In intact cells, PKC modification by selenite was not interfered by glutathione, probably because of the shielding of the cysteine-rich region of the enzyme by a weak hydropho-

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**Figure 1.** Multidomain structure of protein kinase C (PKC). Oxidation-susceptible sites within regulatory and catalytic domains are shown. Unique structural aspects of PKC enable it to serve as receptor for tumor promoters and antitumor-promoting agents. C1, cysteine-rich constant region in various isozymes of PKC; C1A, first 2 zinc-fingers in C1 domain; C1B, second 2 zinc-fingers in C1 domain; C2, Ca$^{2+}$-binding domain; C3, ATP-binding region in catalytic domain; C4, protein substrate-binding region in catalytic domain; V3, proteolysis-sensitive variable region in various isozymes; pseudosubstrate, autoinhibitory region of PKC that prevents binding of protein substrate to catalytic domain.

**Figure 2.** Differential sensitivity of various PKC isozymes to selenite. Rat brain PKC-α and -β were isolated by Ca$^{2+}$-dependent hydrophobic chromatography (71). PKC-δ and -ε were purified from rat brain; PKC-ζ was purified from rat kidney. Desalted PKC isozymes free from thiol agents were preincubated with indicated concentrations of selenite in wells of a multwell plate for 5 min. Then PKC activity was determined using PKC-ε pseudosubstrate peptide.
bic association with the membrane (23). Because of the presence of cofactors in the membrane, PKC was more sensitive to selenium than in the purified form and was inactivated by low concentrations of selenite (IC$_{50}$ = 0.05 µM). Selenite did not affect protein kinase A, phosphorylase kinase, and protein phosphatase 2A, suggesting that there is specificity in the reaction of selenium with PKC (93).

**Selenoamino Acids**

Selenocystine and selenodiglutathione readily inactivated the kinase activity, but not the phorbol ester binding to PKC. An inactivation of PKC in cells treated with S-methylselenocysteine was previously reported (94). Certain selenocompounds, such as selenomethionine and methylselenocysteine, are not redox active by themselves and may require their metabolism to methylselenol (4). The redox-active selenocompounds, such as selenite, are also metabolized to methylselenol (8). This selenium metabolite has been suggested to react with cysteine residues in proteins (8). A sulfur-selenium adduct is also expected to induce a vicinal thiol oxidation.

**Synthetic Selenocompounds**

Synthetic organoselenium compounds, such as 1,4-phenylenebis(methylene)selenocyanate, have been reported to inhibit tumorigenesis in vivo (96) and the activities of thymidine kinase, protein kinase A, and PKC in vitro (97,98). This compound was shown to elevate GPx levels in the tissues, suggesting that selenium from this compound may be entering the assimilatory pathway (96). Ebselen (PZ51), another synthetic selenocompound with a GPx-mimetic activity, did not show any cancer-preventive activity when it was supplemented at 10 ppm in the diet (99). Previous studies showed that selenium present in ebselen was not incorporated into selenoproteins, suggesting the importance of selenium metabolism for its chemopreventive activity (100). Ebselen has also been shown to inhibit PKC activity in the test tube with an IC$_{50}$ of 1 µM (101). However, in vitro studies have shown that ebselen has antitumor-promoting activity by inhibiting phorbol ester-induced cellular events (102). Given the fact that ebselen is poorly absorbed from the digestive tract (103), there is a possibility that the limited amount (10 ppm) of ebselen, used in the previous studies in animals, may not be sufficient to induce cancer-preventive activity (99). Nevertheless, whether ebselen, which inhibits PKC but cannot donate selenium to selenoprotein synthesis, acts as a cancer-preventive agent, if supplemented at higher doses (>10 ppm), remains to be determined.

**PKC Interrelationship Between Selenometabolites and Selenoproteins**

It is important to consider that the selenoprotein TR can directly or indirectly reverse the inactivation of PKC induced by redox-active selenometabolites. Although the reactions of selenometabolites with PKC can induce antitumor-promoting actions, the reversal of these reactions by TR can prevent the toxic actions of selenometabolites in normal cells. In contrast, during peroxide-induced tumor promotion, because of the depletion of reducing equivalents (NADPH), TR may not function as a reductase, and thus a compromise in its action could allow the toxic action of selenometabolites, leading to the inactivation of PKC. This may provide selectivity in the action of selenometabolites to precancer cells vs. normal cells. It is also possible that in some advanced tumor cells, which are resistant to selenium, an induction of TR, along with the cellular ability to generate sufficient amounts of reducing equivalents, can give them resistance to selenium toxicity. Recent studies revealed that the PKC pathway is involved in induction of the selenoproteins TR and GPx (105–107).

**Selenoproteins as a Defense for Selenium Toxicity**

Previous studies have shown that selenide reacts with oxygen and induces the generation of H$_2$O$_2$ (53–55). Again, the enzyme that protects cells from this toxicity is a selenoprotein, GPx. Therefore, selenoproteins serve as a safeguard against the toxicity induced by selenometabolites (108) and also protect cells from global oxidative stress. These bi-
directional effects of selenium provide a testable hypothesis to address how a selective toxicity can be achieved in precancer cells while the safety of normal tissues is maintained and how a resistance to the preventive actions of selenium is possibly developed in advanced cancer cells. Selenium actions at the low but nutritionally adequate dose are considered to be primarily mediated by selenoproteins, while toxicity to the host at higher doses of selenium is primarily mediated by selenometabolites. However, at the cancer-preventive medium, but safer, doses of selenium, its level in the body is more than that needed for the synthesis of selenoproteins. Thus, to attain selective cytotoxicity to precancer cells, there is a need for a greater retention of selenometabolites, an increase in their cytotoxic actions, or a decrease in the functions of protective selenoproteins in precancer cells compared with that in normal tissues.

**PKC as a Potential Site for Selenium Interaction With Zinc and Vitamin E**

Nutritional studies suggest that selenium actions are influenced by zinc and vitamin E. Zinc, by reacting with selenide, forms zinc selenide and removes excess selenium (109). Moreover, zinc, by inducing metallothionein, which can react with redox-active selenocompounds, can prevent the toxicity of selenium (110,111). Vitamin E prevents lipid peroxidation induced by diets containing high-unsaturated fat as well as that induced by selenite (108). Furthermore, selenium and vitamin E can synergistically produce anticarcinogenic actions in animals (112,113). Consistent with selenium actions that are known to be influenced by zinc and vitamin E, PKC is also regulated by these antioxidants (114,115). PKC is a zinc metalloprotein, and its activity is regulated by intracellular zinc homeostasis (114). Moreover, PKC is inhibited by vitamin E (115). These unique features, in addition to cysteine-rich regions, make PKC a more relevant target for cancer-preventive activity of selenium than other proteins that have only cysteine-rich regions.

**Significance of PKC Inhibition to Cancer-Preventive Actions of Selenium**

Given the facts that PKC serves as the receptor for tumor promoters and plays a crucial role in the events related to tumor promotion/progression, it may be an appropriate target for redox-active selenocompounds. The inactivation of PKC by redox modification induced by selenocompounds has functional significance in the chemopreventive actions of selenium in the various stages of carcinogenesis.

**Inhibition of Tumor Promotion**

Selenium has been shown to inhibit tumor promotion (20–23). Previous studies showed that an inhibition or downregulation of PKC abolished the phorbol ester-induced induction of ornithine decarboxylase (79). Because overexpression of ornithine decarboxylase is associated with tumorigenesis (116), selenocompounds, by blocking the induction of ornithine decarboxylase and other genes via interruption of PKC function, may elicit in part their cancer-preventive action (23). Selenium-induced inhibition of PKC may also play a role in the selenium-mediated inhibition of AP-1 and NF-kB transactivation in intact cells. However, selenium is known to directly regulate AP-1 and NF-kB by oxidizing critical cysteine residues present in their DNA-binding domains (117,118). Because PKC is an important enzyme in the induction of inducible nitric oxide synthase, cyclooxygenase-2, and other enzymes involved in tumor promotion (76–80), inhibition of PKC by selenium may have a significant role in preventing the induction of these enzymes.

**Inhibition of Cell Growth**

Inhibition of cell proliferation is considered to be an important mechanism by which selenium inhibits carcinogenesis (56–59). Methylselenocysteine is an effective chemopreventive agent against mammary cell growth in vivo and in vitro (94). This selenocompound was shown to decrease PKC activity (94). These studies suggested PKC as an upstream target for methylselenocysteine that may trigger downstream events such as the decrease in cdk2 kinase activity and DNA synthesis, elevation of gadd gene expression, and finally apoptosis (94).

**Induction of Apoptosis**

A variety of cancer-preventive agents are believed to elicit anticarcinogenic effects, at least in part, by inducing apoptosis to remove precancerous or cancer cells that are genetically altered through mutations in oncogenes or tumor suppressor genes (119). Inhibition and/or inactivation of PKC induced by various selenocompounds may have a role in inducing apoptosis. Moreover, various commonly used PKC inhibitors, such as calphostin C, hypericin, chelerythrine, and staurosporine, induce apoptosis, which further suggests that the inactivation or inhibition of PKC triggers apoptosis (120,121).

Inhibition of PKC by its inhibitors induces apoptosis via the generation of ceramide (122,123). Furthermore, selenium-induced inactivation of PKC in prostatic carcinoma cells also leads to an elevation of ceramide and induction of apoptosis (124). PKC was shown to act as a negative modulator for sphingomyelinase and inhibit its activity (123). Therefore, an inhibition of PKC activity leads to activation of sphingomyelinase and increased generation of ceramide (123). Ceramide can increase the mitochondrial generation of reactive oxygen species and increase mitochondrial transition permeability (125). Although this can be prevented by Bcl-2, its antiapoptotic function is suppressed by a lack of phosphorylations mediated by PKC-α and mito-
gen-activated protein kinases (126). Then the ceramide-induced changes in mitochondria lead to the release of cytochrome c into the cytosol, where it induces the activation of caspase-3, a key protease involved in inducing apoptotic events (127). Caspase-3 activates PKC-δ by a limited proteolysis (128). Furthermore, ceramide activates PKC-ζ and c-Jun NH2-terminal kinase, which further help in executing apoptosis. PKC isozymes, particularly PKC-α and -β, are better suited for inactivation by selenocompounds to trigger early events in apoptosis, and PKC-ζ and -δ are less susceptible for this inactivation and may facilitate the later events in apoptosis. Thus differential susceptibility of PKC isozymes to selenium is well suited for inducing apoptosis-related events.

Inhibition of Invasion and Metastasis

PKC plays an important role in regulating events related to tumor progression, such as invasion, metastasis, and tumor cell adhesion to endothelium and extracellular matrix components (129–132). Experimental tumor promoters, such as phorbol esters, and tobacco-related tumor promoters increase invasion and haemogenous metastasis (73,129,130). Therefore, the selenium-induced inactivation of PKC may have significance in blocking these progression-related events. Selenium has been shown to decrease tumor cell invasion and attachment to matrix components in vitro (24,133). Furthermore, selenium supplementation in the diet has been shown to decrease hematogenous metastasis (25,134).

Conclusions and Perspectives

Given the importance of dietary selenium in cancer prevention, it is important to identify the molecular targets and mechanisms by which selenium prevents cancer and exerts toxicity to the host. PKC serves as a receptor for tumor promoters, including oxidants and lipid hydroperoxides, and is activated by these agents. Redox-active selenometabolites act on the same cellular target on which the tumor promoters act, but they induce inactivation of this kinase. This may bring an efficient counteractive mechanism to block signal transduction induced by the tumor promoter at the first step. TR, a selenoprotein, can reverse this antitumor-promoting action of selenium. This suggests an interesting interrelationship between the actions of selenometabolites and selenoproteins in regulating PKC. Furthermore, PKC acts as a sensor for the induction of selenoproteins and as a site for selenium interaction with zinc and vitamin E. Selenium-induced inactivation of PKC may have significance in the cancer-preventive actions of selenium, such as inhibition of tumor promotion, cell growth, invasion, and metastasis, and in the induction of apoptosis. Therefore, in many ways, PKC is a relevant molecular target for selenium to block tumor promotion and/or early stages of tumor progression.

If PKC is acting as a target for selenium, it is important to understand why this inactivation of PKC occurs only in precancer or cancer cells, and not in normal cells, to cause toxicity to the host. It is especially important that PKC is ubiquitously distributed and plays a crucial role in many normal cellular processes. Furthermore, the concentrations of selenium that are required to achieve inhibition of various cellular processes or PKC in vitro are often higher, and only a limited concentration of selenium exists in the plasma and tissues as selenometabolites. Thus whether certain redox-cycling mechanisms can amplify the action of the selenometabolites giving specificity to precancer or cancer cells remains to be determined. Whether lipophilic and nonvolatile selenometabolites produced from some synthetic selenocompounds, such as 1,4-phenylenebis(methylene)selencyanate, can be better retained in the membrane (98) and, thereby, can more efficiently inactivate the membrane-associated form of PKC than the natural selenocompounds, which generate the volatile metabolites, such as methylselenol or dimethylselenide, requires further study.

Acknowledgments and Notes

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