Molecular targets of selenium in prostate cancer prevention (Review)

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Abstract. Prostate cancer is one of the leading causes of cancer-related deaths among males. Although use of the micronutrient selenium in prostate cancer clinical trials is limited, the outcomes indicate that selenium is a promising treatment. Furthermore, selenium inhibits prostate cancer through multiple mechanisms, and it is beneficial in controlling the development of this disease. This review highlights the latest epidemiological and biomolecular research on selenium in prostate cancer, as well as its prospects for future clinical use.

Contents

1. Introduction

Cancer is a devastating disease and currently is the cause of more than 7 million deaths worldwide each year. Cancer is the uncontrolled growth and spread of cells, and it can affect almost any tissue in the body (1). Among all cancers, prostate cancer is the fifth most common (2), and the second most common cancer in men worldwide (2-4).

The worldwide geographical distribution of prostate cancer varies. Rates are lower in Asian countries and much higher in North America, Australia and Europe. In 2002, the incidence per 100,000 individuals in China was 75- and 50-fold lower than the incidence in North America and Australia, respectively (2). In American men, prostate cancer is the most common cancer, with an estimated 218,890 new cases and 27,050 deaths in 2007 (5).

This distribution may be correlated with racial differences, which is believed to play a role in prostate cancer development (6,7). The highest prevalence of prostate cancer is in the African-American population, whereas there is a much lower risk in Asian populations (8). However, recent publications have reported that in Asian countries, prostate cancer incidence has rapidly increased in the last three decades (9,10).

Due to this high incidence, the identification of a compound that may inhibit cancer development is becoming an important objective for scientists. Currently, hundreds of chemicals have been and are being evaluated for their anticancer activity. Among them, selenium has been reported to be successful in epidemiological, *in vitro* and *in vivo* experiments, including experiments with prostate cancer. In this review, we discuss the recent developments in selenium research as both an alternative and combination treatment option in the management of prostate cancer.

2. Epidemiology

The promising effects of selenium against prostate cancer were triggered by the findings of Clark and co-workers in 1996, who reported a strong inverse association between selenium and prostate cancer after the supplementation of free-living people with selenized brewer's yeast for a mean of 4.5 years. They reported a 63% reduced risk in prostate cancer among subjects taking selenium supplements (11). This result was supported by a later study in 2005 that found that selenium supplementation combined with vitamin E induced proteomic changes that were associated with a prostate cancer-free status (12). In 2006, Sabichi and co-workers conducted a randomized, controlled, short-term trial of selenomethionine supplementation and reported that selenium taken as an oral supplement accumulates preferentially in the prostate gland which may contribute to its anticancer effects (13).

Blood and toenail selenium status has also been associated with prostate cancer incidence. Several studies have reported an inverse correlation between blood selenium levels and prostate cancer and have suggested that selenium may reduce the risk of prostate cancer (14-16). Similar reports have been published based on measurements of toenail selenium (17,18), a well-accepted biomarker of long-term selenium status (19,20).

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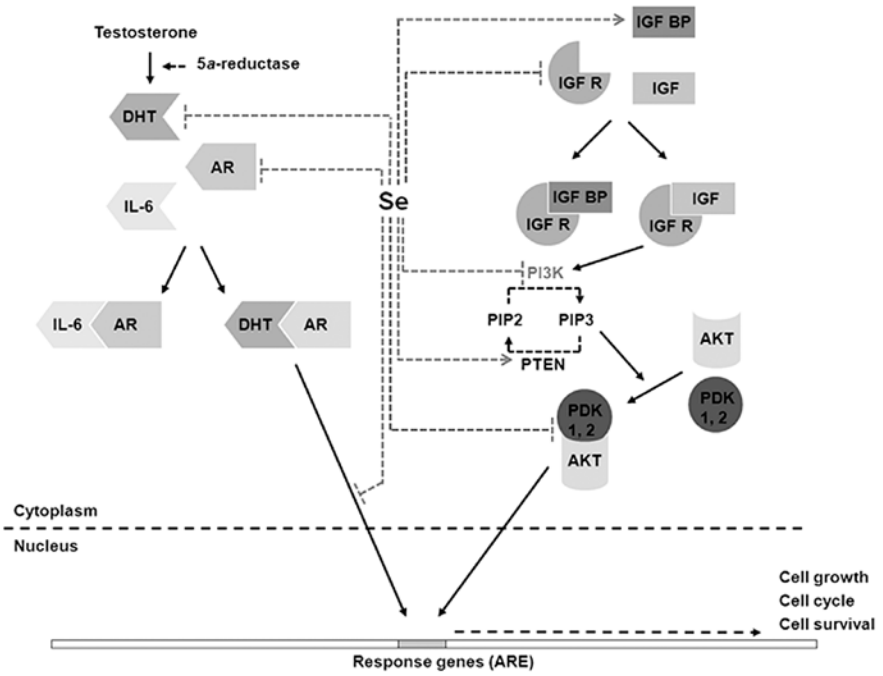

Figure 1. Reported mechanisms of how selenium (Se) inhibits the androgen receptor and PI3K/Akt signaling.

Aside from these results, however, conflicting results have also been reported. Studies in the UK and the US suggested that there was no strong association between nail and serum selenium and prostate cancer risk (21-23). A recent SELECT study (selenium and vitamin E cancer prevention), the largest cancer chemoprevention trial ever conducted, is a long-awaited randomized placebo-controlled trial study that involved 35,533 men in North America; the study showed that selenium or vitamin E alone or in combination did not lower prostate cancer incidence (24). In this study, selenium was supplemented in the form of selenomethionine, which is the major selenium compound in selenized yeast, the material used in Clark's study (11). Notably, the result was predicted by Drake (25) based on a lack of the enzyme required to convert selenomethionine to its active form, methylselenol, in humans. Moreover, a later analytical study reported that the selenomethionine distribution in the supplement used in Clark's study accounted for only 27% of the total selenium (26). Thus, it is possible that the effect of selenium in Clark's supplementation study was not caused by selenomethionine, but rather by other selenium compounds or the combination of selenium-containing compounds in the yeast (26,27). Therefore, the negative results of the SELECT study do not discredit any preventive properties of selenium against prostate cancer. Indeed, from three meta-analysis studies on articles that examined the association between selenium and prostate cancer, all suggested that selenium intake may reduce the risk of prostate cancer (4,28,29).

3. The mechanism of selenium in prostate cancer

Signaling pathways

Androgen receptor signaling. Androgen receptor (AR) signaling is one of the key factors in prostate cancer development and progression. AR is a transcription factor of the nuclear receptor family (30) that mediates androgen by activating the androgen response element (ARE) (31).

Testosterone becomes an active androgen after conversion into dihydrotestosterone (DHT) by the enzyme 5α-reductase (32). Active androgen then binds with AR, leading to its nuclear translocation and interactions with AREs to activate androgen-responsive gene transcription (31,32). Aside from active androgen, AR signaling was also found to be induced by interleukin (IL)-6 and oncostatin M in *in vitro* experiments (33,34).

Several selenium compounds are known to disrupt AR signaling in prostate cancer cells. In *in vitro* experiments using human prostate cancer cells, methylseleninic acid (MSeA), a methylselenol precursor, was reported to reduce androgen signaling at multiple stages by increasing AR protein degradation at both the mRNA and protein levels and by reducing AR nuclear translocation (35-37). Furthermore, MSeA also reduced AR-mediated gene expression, including prostate-specific antigen (PSA) expression (35-39). Another methylselenol precursor, selenomethionine (SeMet), was found to decrease AR activity in the LNCaP human prostate cancer cell line (40). Additionally, Se-methylselenocysteine (Se-MSC) significantly inhibited LNCaP tumor growth in LNCaP-induced mice by decreasing AR expression in tumor tissues and serum PSA levels (41).

Selenite, an inorganic form of selenium, has also been reported to disrupt AR signaling. Husbeck and co-workers (39) found that selenite inhibited AR signaling by decreasing AR expression and activity through a redox mechanism. Moreover, unlike MSeA, selenite also inhibited IL-6-mediated AR signaling in the LNCaP human prostate cancer cell line (42). Taken together, as summarized in Fig. 1, these reports describe a potential role of selenium in the disruption of AR signaling in prostate cancer.

Insulin-like growth factor signaling. Insulin-like growth factor (IGF) signaling involves IGF ligands (IGF-I and IGF-II), IGF receptors (IGF-IR and IGF-IIR) and IGF binding protein (IGFBP) (43). IGFBP-3 is the binding protein that regulates IGF (44). Once released from IGFBP-3, IGF activates the IGF receptor to induce downstream signaling cascades, thereby controlling cell proliferation and cell survival (43). The ability of the IGF receptor to induce downstream signaling cascades comes from IGF-IR. Upon binding with IGF-I, IGF-IR induces downstream signaling via Ras/Raf/mitogen-activated protein kinase (MAPK) and/or phosphatidylinositol 3-kinase (PI3K)/Akt (43-46). However, IGF-IIR bound with IGF-II still lacks tyrosine kinase activity and does not transduce signals (47), so its precise function in tumorigenesis and tumor growth is still unclear (48). IGF-I is a mitogenic ligand that is overexpressed in prostate cancer and is associated with prostate cancer risk (49,50); therefore, down-regulation of IGF-IR signaling may be a promising target for the chemoprevention of prostate cancer.

Schlicht and co-workers (51) identified 154 genes that showed similar levels of differential expression upon SeMet treatment in the human PC-3 and rat PAII prostate cancer cell lines. Their analysis and data mining showed that IGFBP-3 was up-regulated by SeMet in both cell lines. Moreover, SeMet and MSeA have also been reported to down-regulate IGF-IR gene expression in LNCaP cells (52). Although further research is still needed, their findings suggest that restoration of IGFBP-3 by selenium may inhibit prostate tumorigenesis by disrupting the IGF-IR signaling pathway.

Toll-like receptor signaling. Toll-like receptors (TLR) have gained interest in recent years since being identified as one of the important mediators of inflammation. Furthermore, they are able to recognize many microbial pathogens with various adaptor proteins and activate different transcription factors. Activation of TLR-dependent signaling leads to activation of the immune response, as well as the expression and release of various cytokines and associated molecules (53). Recent studies have shown that sequence variations in the TLR4 gene and TLR6-TLR1-TLR10 gene cluster are associated with prostate cancer risk (54-56). However, the functional role of TLR variants in the growth and development of prostate cancer remains to be established (57).

There are limited reports on the ability of selenium compounds to affect the TLR signaling pathway, especially in prostate cancer. However, MSeA has been reported to up-regulate TLR2 gene expression in PC-3 cells (58). TLR2 is known as the death receptor in apoptosis (59). Up-regulation of TLR2 stimulates apoptosis through adaptor molecules via a pathway that involves caspase-8 (59). This report may lead to additional details on the role of selenium and TLR signaling in prostate cancer chemoprevention.

Phosphatidylinositol 3-kinase (PI3K)/Akt signaling. Up-regulation of PI3K/Akt is important for the growth of many types of cancers, including prostate cancer. PI3K converts phosphatidylinositol-4,5-biphosphate (PIP2) to phosphatidylinositol-3,4,5-triphosphate (PIP3), which recruits phosphoinositide-dependent kinase 1 (PDK1) and Akt to the cell membrane. This recruitment partially activates Akt by phosphorylation at Thr308 by PDK1. Full activation of Akt occurs after a second phosphorylation by another kinase at Ser473. It is still unclear which kinase is responsible for Ser473 phosphorylation; however, several kinases have been reported to play an important role in this event, including integrin-linked kinase (ILK), MAPKAP kinase and rictor-mTOR kinase. Through its downstream actions, Akt activation mediates cancer cell proliferation, motility, survival and angiogenesis. Phosphatase and tensin homologue (PTEN) is known to negatively regulate PI3K/Akt signaling by blocking the conversion of PIP2 to PIP3. However, in cancer cells, PTEN is either absent or nonfunctional, resulting in a high level of PIP3 and hyperactivation of Akt (60).

As reported by Wu and coworkers (61), in PC-3 cells, MSeA is capable of reducing the activity of PI3K by 30%, which leads to a decrease in Akt and PDK1 membrane localization. Furthermore, MSeA inhibits Akt phosphorylation at both Thr308 and Ser473 (61) and up-regulates PTEN gene expression in PC-3 cells (58). In DU-145 cells, Berggren and co-workers found increased PTEN activity and decreased Akt phosphorylation at Ser473 after the cells were treated with selenite (62). Inhibition of Akt phosphorylation at Ser473 in DU-145 cells was also reported after the cells were treated with MSeA (63,64) and SeMet (64).

We recently reported that the addition of selenium to broccoli sprouts, which generates Se-MSC as the major selenium compound, induces the down-regulation of phosphorylated Akt and downstream phosphorylated mTOR in LNCaP cells (65). As expected, this down-regulation was not noted in LNCaP cells treated with normal broccoli sprout extract that contained only sulforaphane as the active anticancer agent. In recent years, the PI3K/Akt signaling pathway has been shown to play a major role in cancer development and survival. Thus, as shown for selenium in Fig. 1, the PI3K/Akt pathway may be a fruitful target for cancer therapy.

Cell cycle pathway

Cyclins, cyclin-dependent kinases (CDKs) and CDK inhibitors (CKIs). Interactions between cyclins, CDKs and CKIs are known to play critical roles in the cell cycle. Among the CDKs, CDK2, CDK4, CDK6 and CDK1 are the most frequent kinases that are deregulated in prostate cancer (57). CDKs can be activated by association with cyclin, by phosphorylation of its T-loop threonine by CDK-activating kinase and by dephosphorylation of threonine 14/tyrosine 15 by cdc25 phosphatase (66).

CDK activation by specific cyclins regulates different phases of cell cycle progression and finally induces uncontrolled cell proliferation and survival (67). For example, association of CDK4 and CDK 6 with D-type cyclin accelerates the early and mid-G1-phase progression (68,69), and CDK2 interacting with cyclin E promotes the late G1 and G1-S transition (70-72). CDK2 interacting with cyclin A is responsible for S-phase and early G2 phase progression (73-75), and CDK1 interacting with cyclin B promotes the G2-M transition (76,77).

However, these cyclin-CDK complexes are negatively regulated and controlled through associations with CKIs (67,78). There are two families of CKIs; the first family is the cip/kip family. This family includes p21/cip1, p27/kip1 and p57/kip2 (66). p21/cip1 is known as the universal inhibitor of CDKs because of its ability to be involved in all phases of the

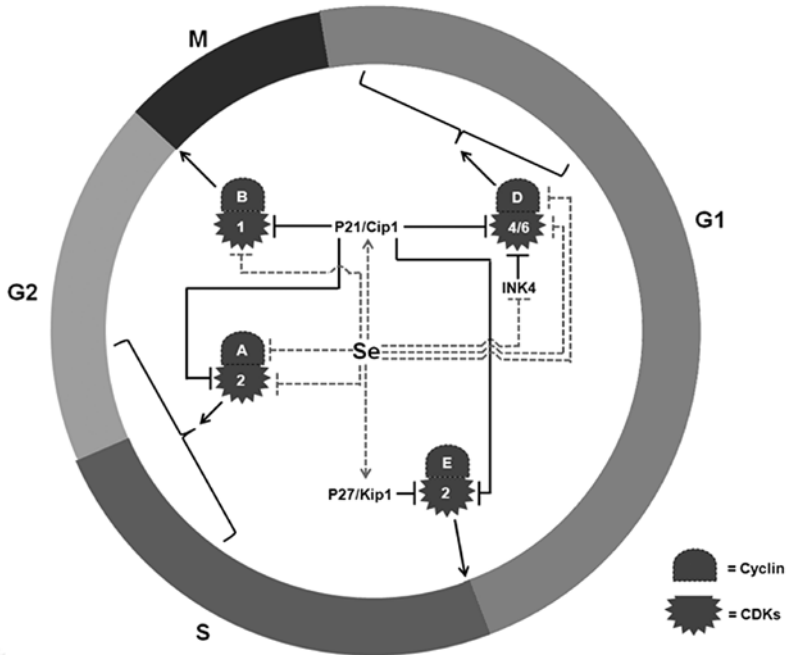

Figure 2. Mechanisms of selenium inhibit prostate cancer cell cycle by altering cyclins, CDKs and CKIs.

cell cycle (79). p27/kip1 is involved in cell cycle regulation during the G1-S transition (80), whereas the specific role of p57/kip2 in cell cycle progression is still poorly understood.

The second family of CKIs is the INK4 family, which includes p15 (INK4b), p16 (INK4a), p18 (INK4c) and p19 (INK4d) (66). This family specifically inhibits CDK4 and CDK6 activity (81,82), thereby inducing G1 arrest in the cell cycle by competing with the cyclin D and CDK4/CDK6 association (66,82). The modulation of cyclin-CDK-CKI association, as shown for selenium in Fig. 2, is promising in prostate cancer treatment.

Chronic treatment with selenite was reported to induce p21 and p27 protein expression followed by G2/M phase arrest in LNCaP cells (83), whereas in DU-145 cells, 24 h of exposure to selenite decreased cyclin D protein expression (63). SeMet has also been shown to induce G2/M cell cycle arrest by tyrosine phosphorylation of CDK1 in LNCaP, PC-3 and DU-145 cells (84). Moreover, SeMet also down-regulates cyclin D (85) and induces p21 and p27 protein expression in LNCaP cells (86,87).

Studies using MSeA reported a decrease in cdc25 and increases in p19, p21 and p57, followed by G1 phase arrest in LNCaP cells (36). In PC-3 cells, MSeA also decreased cyclin A, CDK1, CDK2 and CDK4, and increased p19 and p21 gene expression (58). However, in DU-145 cells, MSeA down-regulated cyclin D expression and up-regulated p27 and p21 expression levels (63).

Retinoblastoma-E2F. Another important cell cycle regulator is retinoblastoma (Rb). Rb is a known tumor suppressor that functions by inhibiting the E2F-mediated gene transcription that is required for cell cycle progression (88). Hypophosphorylated Rb is recognized as an active Rb because of its ability to sequester E2F family transcription factors. However, phosphorylation of Rb by CDKs (CDK 4/6-cyclin D or CDK 2-cyclin E) inactivates Rb, thereby releasing E2Fs. Free E2Fs then heterodimerize with their DNA-binding partners leading to transcriptional activation of growth-promoting genes (88-91).

There are three Rb proteins (Rb/p110, Rb1/p107 and Rb2/p130) and six E2F families (E2F1-6) that heterodimerize with two DNA-binding partners (DP1 and DP2) to form 12 different DNA-binding transcriptional regulators that are needed for entry from the G0 to S phase (90,92,93). Upon entering the S phase, Rb is kept inactivated by CDK/cyclin throughout the remainder of the cell cycle (94,95) until mitosis, when Rb activity is reset by phosphatase activity (93). High levels of E2F have been observed in cancerous cells (96); therefore, targeting the modulation of Rb and E2F expression may inhibit cancer cell growth by inhibiting S phase entry (97).

In vitro experiments using MSeA have been shown to modulate Rb-E2F expression by increasing Rb1 gene expression in PC-3 cells (58). MSeA has also been reported to decrease E2F1 gene expression, followed by G2/M phase arrest in LNCaP cells (36,52). These findings suggest that the modulation of Rb-E2F expression is one of the potential targets of selenium in its inhibition of prostate cancer growth (Fig. 3).

Apoptotic targets

Nuclear factor-κ B (NF-κB) pathway. NF-κB is a family of transcription factors consisting of NF-κB1 (p50/p105), NF-κB2 (p52/p100), RelA (p65), RelB and c-Rel (98). In its inactivated form, NF-κB is sequestered by inhibitory-κB (IκB) in the cytoplasm. However, when IκB is phosphorylated at specific serine sites by IκB kinases (IKKs), NF-κB is free and active. Free NF-κB translocates to the nucleus and binds to the κB sites of a wide spectrum of genes that are involved in cell proliferation, tumor angiogenesis and metastasis (99-101). NF-κB is reportedly active in androgen-independent prostate cancer; thus, NF-κB activation could be a potential target in controlling prostate cancer growth and malignancy.

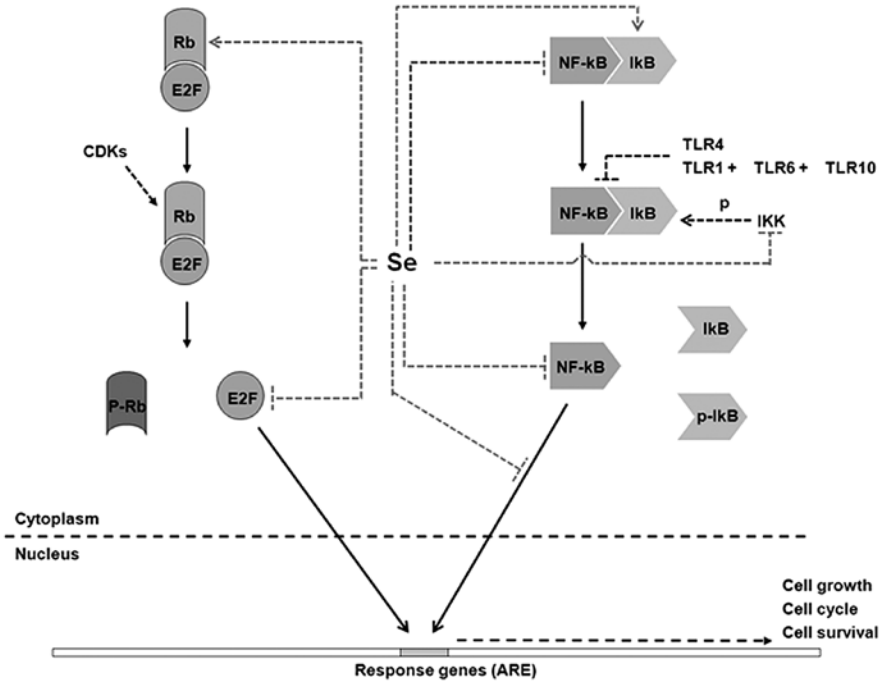

Figure 3. Reported mechanisms of retinoblastoma and NF-κB signaling inhibition by selenium in prostate cancer.

Selenite and MSeA have been reported to inhibit the IKK activity in DU-145 cells, thereby inhibiting the activation of NF-κB-mediated transcription (102). Using an oligonucleotide array, Dong and co-workers reported that treatment of PC-3 cells with MSeA was able to decrease NF-κB1 gene expression (58). In LNCaP cells, MSeA is able to prevent the binding of NF-κB to its DNA response element, resulting in a reduction in the transcription rates of NF-κB-regulated genes (103). Furthermore, Zhao and Brooks found an up-regulation of IκB and down-regulation of NF-κB2 gene expression in LNCaP cells treated with SeMet (52). Taken together, these results showed that selenium compounds may target the NF-κB activation pathway in prostate cancer growth and malignancy (Fig. 3).

Bcl-2 family proteins. Bcl-2 family proteins are known to play important roles in apoptosis. Based on structural and functional features, they can be divided into three subfamilies: an anti-apoptotic protein subfamily that contains the 1-4 homology domains (Bcl-2, Bcl-XL, Bcl-w, Mcl-1, Bfl1 and Bcl-B), a multi-domain pro-apoptotic protein subfamily that contains the 1-3 homology domains (Bax, Bak and Bok) and a BH3-only pro-apoptotic protein subfamily that contains only the BH3 domain (Bim, Bad and Bid) (104).

During mitochondrial apoptosis, cytochrome-c is released from the mitochondria to the cytosol upon stimulation from death stimuli. Cytochrome-c then associates with Apaf-1 and pro-caspase-9 to form the apoptosome, which induces apoptosis through the activation of caspase-3 and PARP cleavage (104,105). Bcl-2 family proteins regulate this mitochondrial apoptosis by controlling the permeabilization of the mitochondrial membrane. The balance between Bcl-2 family proteins is the key factor determining cell survival or apoptosis. Upon death stimulation, pro-apoptotic bax/bak proteins are activated and mediate pores in the outer mitochondrial membrane that facilitate the release of cytochrome-c, which leads to apoptosis. However, it has been reported that in cancerous cells, the balance of Bcl-2 family proteins is disrupted, and anti-apoptotic Bcl-2 is overexpressed. Overexpression of the anti-apoptotic Bcl-2 protein will block the activation of pro-apoptotic proteins; hence, the cells become resistant to apoptotic death (104-106).

Inorganic selenite has been reported to decrease Bcl-2 expression and increase Bax protein expression in prostate cancer cells lines (LNCaP, DU-145 and LAPC-4) and primary prostate epithelial cell cultures of cancerous subjects. This phenomenon leads to a decrease in the Bcl-2:Bax ratio, a release of cytochrome-c and the activation of mitochondrial apoptosis (107-111). Furthermore, two methylselenol precursors, MSeA and SeMet, have also been found to decrease the ratio of these pro-apoptotic and anti-apoptotic protein expression levels. MSeA decreased Bcl-2 anti-apoptotic protein levels and increased the Bax, Bak and Bid pro-apoptotic proteins of LNCaP, DU-145 and PC-3 cells (112), while SeMet increased the Bax pro-apoptotic protein levels in LNCaP cells (87). These findings may suggest that the Bcl-2 protein families play key roles in selenium-induced mitochondrial apoptosis.

Inhibitor of apoptosis protein (IAP). IAP proteins consist of nine family members: X-linked IAP, cIAP1, cIAP2, melanoma IAP, IAP-like protein 2, neuronal apoptosis inhibitor protein, livin, appolon and survivin (113,114). They play important roles in the regulation of cell cycle progression and inhibition of apoptosis (115). Survivin, the smallest (16.5 kDa) member of the family, is overexpressed in many types of cancer, including prostate cancer (116). Survivin prevents apoptosis by directly binding to caspase-3 and caspase-7 and blocking their activation (117). Thus, survivin expression is associated with cancer cell malignancy and survival. The activity of survivin can be inhibited by Smac/DIABLO (118), which is released from the

mitochondria together with cytochrome-c. Due to its rare expression in normal tissues (except embryonic tissues) and overexpression in cancerous tissues, survivin is a promising target for cancer therapy.

To our knowledge, research on the effect of selenium on survivin expression in prostate cancer is still limited to MSeA. MSeA was reported to repress survivin gene expression in PC-3 cells in an oligonucleotide array experiment (58). Later, Chun and co-workers confirmed that MSeA down-regulated survivin protein expression in PC-3 and C4-2 cells by preventing the binding of Sp1 transcription factor to the promoter of survivin (119). Moreover, in combination with tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), a cytotoxic agent that preferentially induces apoptosis, MSeA also induces the translocation of Smac/DIABLO from the mitochondria to the cytosol of DU-145 cells, thereby enhancing the efficacy of TRAIL (120). These results show that the down-regulation of survivin expression is one of the selenium-mediated anticancer mechanisms.

Angiogenesis targets

Angiogenesis has been proven to play an important role in cancer growth. Although it is strictly regulated by physiological conditions, it has been reported that unregulated angiogenesis occurs under pathological conditions, including cancer (121). Angiogenesis supplies cancerous cells with nutrients and oxygen, removes their waste products and facilitates cancer cell metastasis (122,123). Therefore, the growth of a cancer cell should be inhibited if it is located more than 100 μm from a blood vessel (124).

Angiogenesis begins when cancerous cells synthesize and secrete pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and IL-8, among others (125). Secreted proangiogenic factors will activate nearby endothelial cells by binding to specific receptors on the cell surface (121). Upon activation, multiple signaling pathways are activated in endothelial cells that lead to the production of matrix metalloproteinases (MMPs), a special class of degradative enzymes that break down the extracellular matrix support material that fills the spaces between cells (126). Breakdown of this extracellular matrix allows for the migration and growth of endothelial cells (126,127).

Although there are several reports addressing the ability of selenium to decrease cancer cell angiogenesis, research on prostate cancer angiogenesis properties is still limited to MSeA. MSeA treatment of DU-145 cells decreased both cellular and secreted VEGF concentrations in a dose-dependent manner (128). Furthermore, in PC-3 cells, MSeA exposure decreased VEGF and bFGF gene expression (58). Because angiogenesis plays a key role in cancer development, selenium-based anti-angiogenic therapy may become an attractive method of preventing cancer cell growth and metastasis.

4. Conclusions and future challenges

Prostate cancer has become one of the most common cancers and is one of the leading causes of cancer-related deaths, particularly in developed countries (5). The existence of an agent with multiple anticancer mechanisms, such as selenium, will be beneficial in controlling the development of this disease. Furthermore, selenium concentrations have been reported to be associated with prostate cancer incidence, leading to the idea of selenium supplementation for prostate cancer prevention. As previously mentioned, recent epidemiological studies that have reported the failure of selenium to lower prostate cancer incidence do not directly discredit the potential of selenium in prostate cancer prevention and therapy because of the type of selenium compound used in those studies.

Although selenium anticancer trials are some of the most successful, its chemical form is critical to its biological activity (1). Methylselenol is believed to be the critical metabolite in selenium chemoprevention (129-131). Since methylselenol is highly reactive, methylselenol precursors such as SeMet and Se-MSC are important both in *in vitro* and *in vivo* experiments (41,52,87). SeMet and Se-MSC conversion to methylselenol, however, requires enzymatic conversion by the enzyme β-lyase, which is 800 times less prevalent in human tissues than in mouse tissues (132). This may explain why the results of SeMet and Se-MSC anticancer studies in humans were not as impressive as *in vivo* experiments. Although researchers have now turned to other Se compounds such as MSeA, which do not need enzymatic conversion to methylselenol, or selenite, which does not need to be converted to methylselenol for its anticancer properties (25), more substantial research on selenium compound metabolism in human tissues is necessary. Only then will the results of the *in vitro*, *in vivo* and human trials be consistent. Understanding the biochemical transformation of each selenium compound in the human body is a critical step in the use of selenium as an option in prostate cancer management.

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