Published in final edited form as:
Endocr Relat Cancer. 2010 September ; 17(3): R195–R212. doi:10.1677/ERC-10-0074.

Novel targets for prostate cancer chemoprevention

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Abstract

Among many endocrine-related cancers, prostate cancer (PCa) is the most frequent male malignancy, and it is the second most common cause of cancer-related death in men in the United States. Therefore, this review focuses on summarizing the knowledge of molecular signaling pathways in PCa because, in order to better design new preventive strategies for the fight against PCa, documentation of the knowledge on the pathogenesis of PCa at the molecular level is very important. Cancer cells are known to have alterations in multiple cellular signaling pathways; indeed, the development and the progression of PCa are known to be caused by the deregulation of several selective signaling pathways such as the androgen receptor, Akt, nuclear factor-κB, Wnt, Hedgehog, and Notch. Therefore, strategies targeting these important pathways and their upstream and downstream signaling could be promising for the prevention of PCa progression. In this review, we summarize the current knowledge regarding the alterations in cell signaling pathways during the development and progression of PCa, and document compelling evidence showing that these are the targets of several natural agents against PCa progression and its metastases.

Introduction

Despite significant effort made in the fight against cancers, prostate cancer (PCa) is still the most frequent non-cutaneous male malignancy, and it is the second most common cause of cancer death in the United States with an estimated 192 280 new cases and 27 360 deaths expected in 2009 (Jemal *et al.* 2009). Treatments for PCa include surgery, radiation, chemotherapy, or hormonal ablation therapy. Since PCa is an endocrine-related cancer driven by androgens, androgen deprivation can be used to shrink the cancer significantly even though androgen ablation therapy alone is not the optimal therapy to eradicate PCa; androgen ablation combined with other novel therapies may be more effective. Despite the initial efficacy of androgen-deprivation therapy, most patients with advanced PCa eventually develop resistance to this therapy and progress to castrate-resistant PCa (CRPC) for which there is no curative therapy (Bracarda *et al.* 2005). The emergence of CRPC and its subsequent metastases contributes to overall poor survival and high mortality (Donovan *et al.* 2010). Declining mortality trends for PCa have been observed since the early 1990s, suggesting that early detection using the prostate-specific antigen (PSA) test or digital rectal exam is beneficial. However, it is important to note that prevention should still be the fundamental strategy by which the mortality due to PCa should be reduced.

Recently, a significant proportion of cancers have been believed to be preventable. It is estimated that one-third of all cancers are preventable simply through modification of diet,

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Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

maintenance of optimum body weight, and regular physical activity (American Cancer Society 2009, Amin *et al.* 2009). For the prevention of PCa, chemoprevention could be an important avenue aiming to reduce both the incidence and the mortality through the use of active 'natural agents' to prevent, reverse, or delay the carcinogenic process. So far, some chemopreventive agents have been considered to reduce PCa risks. Several agents including 5-α-reductase inhibitors (finasteride and dutasteride), selenium, vitamins E and D, lycopene, soy isoflavones, green tea polyphenols, 3,3′-diindolylmethane (DIM) and curcumin have demonstrated their various activities in the inhibition of prostate carcinogenesis, with mixed results.

In recent years, significant efforts have been made to understand the biological and molecular mechanisms driving PCa development and progression. It is necessary to reveal the molecular determinants involved in the processes of cancer development and progression of PCa, in order to design or find novel chemopreventive agents that could be useful in targeted prevention and/or treatment strategies against PCa. In this review, we summarize the current knowledge regarding the alterations in cell signaling pathways during the development and progression of PCa, and outline the evidence supporting the development of innovative strategies for targeting selective pathways by novel chemopreventive agents for the prevention of PCa progression.

Cell signaling pathways involved in the development and progression of PCa

Cancer cells are known to have alterations in multiple cellular signaling pathways. In PCa cells, the altered proteins produced as a result of mutations or defects of genes affect the way these cells communicate with each other. The cellular signaling pathways that are known to be important in PCa cells include the androgen receptor (AR), Akt, nuclear factor-κB (NF-κB), Wnt, Hedgehog (Hh) and Notch pathways, among many others (Fig. 1). The alterations in these pathways could occur at different stages of PCa from early to advanced disease.

AR signaling

AR is a ligand-activated transcription factor of the nuclear receptor superfamily that plays a critical role in male physiology and pathology. In prostate epithelial cells, ligand-free AR is sequestered in the cytoplasm and bound to heat shock proteins (HSPs). Binding of androgens to the AR induces a conformational change in the AR, which causes the dissociation of HSPs and phosphorylation of the AR. The conformational change in the AR also allows AR nuclear localization, increased AR phosphorylation in the nuclear compartment, AR homodimer formation, and its interaction with DNA (Heinlein & Chang 2002, 2004). The activated AR then initiates gene transcription by binding to specific androgen response elements in the promoter regions of target genes (Fig. 1), promoting prostate epithelial cell growth (Heinlein & Chang 2002, 2004). Androgens and the AR are involved in all stages of prostate carcinogenesis including initiation, progression, and treatment resistance (Montgomery *et al.* 2001); therefore, AR signaling has been believed to be a critical target for PCa prevention and/or treatment. Moreover, one of the androgen-responsive genes, *PSA*, is a clinically important marker that is routinely used to monitor diagnosis, treatment response, prognosis, and progression in patients with suspected PCa (Kupelian *et al.* 1996, Sato *et al.* 1996). It is known that during the progression of PCa from an androgen-sensitive status to the androgen-independent stage classically known as CRPC, the majority of PCa cells still express AR, suggesting that AR signaling plays a critical role in the development and progression of PCa (Heinlein & Chang 2004). Moreover, phosphorylation of the AR by molecules in other cell signaling pathways could also influence AR transactivation (Lee & Chang 2003). Studies have shown that Akt can phosphorylate the AR at Ser210/213 and Ser790/791, and transactivate the activity of AR independent of androgen signaling (Wen *et al.* 2000). The phosphorylation by Akt also sensitizes the AR to low circulating levels of androgen, such as those present during maximum androgen blockade (Rochette-Egly 2003). This sensitization allows low levels of

androgens to induce phosphorylation at specific sites, which is required for the translocation of the AR to the nucleus. Therefore, Akt is an important activator of the AR, which is required for the androgen-independent survival and growth of PCa cells.

PI3K/Akt/mammalian target of rapamycin signaling

The phosphoinositide-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway plays critical roles in mammalian cell survival signaling and is activated in various cancers including PCa (Liu *et al.* 2009, Morgan *et al.* 2009, Sarker *et al.* 2009, de Souza *et al.* 2009). It has been reported that Akt is activated by phospholipid binding and phosphorylation at Thr308 by PDK1 or at Ser473 by PDK2 (Alessi *et al.* 1996). Activated Akt functions to promote cell survival by inhibiting apoptosis through inactivation of several pro-apoptotic factors including Bad, Forkhead transcription factors, and caspase-9 (Cardone *et al.* 1998, Brunet *et al.* 1999). In addition to promoting cell survival through the inhibition of apoptosis, the Akt pathway regulates cell growth, proliferation, and angiogenesis through the mTOR and PTEN signaling pathways, which facilitates translation of important signaling molecules such as c-Myc, cyclin D, and vascular endothelial growth factor (VEGF). Restoration of functional PTEN activity or inhibition of mTOR activity can block the growth of $PTEN^{-/-}$ PCa xenografts in mice and restore sensitivity to chemotherapy (Neshat *et al.* 2001). It has been estimated that PI3K/Akt/mTOR signaling is up-regulated in 30–50% of PCa cases, often due to the loss of PTEN function (Morgan *et al.* 2009). The alteration of molecules in the PI3K/Akt/mTOR signaling pathway has been found in PCa when comparing malignant prostatic epithelium with normal epithelium. More importantly, the activation of PI3K/Akt/mTOR signaling is associated with increasing tumor stage, grade, and risk of biochemical recurrence; therefore, the Akt pathway is an attractive target for cancer prevention and/or treatment (Sarker *et al.* 2009). It is also important to note that insulin-like growth factor (IGF) is an upstream molecule of Akt signaling, and the up-regulation of IGF, which activates Akt, could promote the development of PCa in animal models (Adhami *et al.* 2004, 2009), suggesting the interrelationship of IGF and Akt signaling in PCa. Studies have also shown that Akt regulates NF-κB signaling via the phosphorylation and activation of molecules in the NF-κB pathway (Fig. 1; Ozes *et al.* 1999, Romashkova & Makarov 1999); therefore, NF-κB signaling is also a critical pathway for the development and progression of PCa, and this pathway is an appropriate target for the management of PCa development and progression.

NF-κB signaling

It is now well accepted that the NF-κB signaling pathway plays important roles in the control of cell growth, apoptosis, inflammation, stress response, and many other physiological processes (Yamamoto & Gaynor 2001, Karin *et al.* 2002, Li & Verma 2002, Lin & Karin 2003, Storz & Toker 2003). There are several important molecules such as NF-κB, inhibitor of κ light polypeptide gene enhancer in B-cells (IκB), and IκB-kinase (IKK) involved in the NF-κB signaling pathway; however, NF-κB is the key protein in the pathway, and has been described as a major culprit and therapeutic target in cancer (Biswas *et al.* 2001, Bharti & Aggarwal 2002, Haefner 2002, Orlowski & Baldwin 2002). The activation of NF-κB has been frequently observed in PCa. The constitutive activation of NF-κB observed in PCa cells is likely to be due to the involvement of other multiple signal transduction pathways including tyrosine kinase, NF-κB inducing kinase (NIK), and IKK activation (Suh *et al.* 2002). Moreover, nuclear translocation and activation of NF-κB has been reported to be significantly greater in PCa patients with lymph node metastasis compared with controls. Such up-regulation of NF-κB activity was observed in the tumor cells as well as in the surrounding lymphocytes (Ismail *et al.* 2004), suggesting that NF-κB plays critical roles in the development and progression of PCa. Indeed, blockade of NF-κB activity in human PCa cells suppressed angiogenesis, invasion, and metastasis in PCa cells (Huang *et al.* 2001). Furthermore, constitutive activation of PI3K/Akt and NF-κB was also observed during PCa progression in an autochthonous

transgenic mouse model (Shukla *et al.* 2005), suggesting that both Akt and NF-κB are potential molecular targets for the prevention and/or therapeutic intervention in PCa.

Wnt signaling

Wnt signaling plays important roles in the embryonic developmental processes including cell proliferation, differentiation, and epithelial–mesenchymal interactions (Angers & Moon 2009). The aberrant activation of the canonical Wnt/β-catenin signaling pathway is one of the most frequent signaling abnormalities known in human cancers. In human cancer, activated Wnt signaling promotes β-catenin accumulation in the nucleus, resulting in the transcriptional activation of specific target genes and the development of cancer (Fig. 1; Behrens 2000, Peifer & Polakis 2000). The inappropriate expression of the Wnt ligand and Wnt-binding proteins and the inappropriate activation of the Wnt signaling pathway have been found in a variety of human cancers including PCa (Taipale & Beachy 2001, Reya & Clevers 2005, Verras & Sun 2006). However, the activation of Wnt signaling may occur in a different manner in PCa than in colorectal cancer or other human malignancies because mutations in adenomatous polyposis coli and other components of the β-catenin destruction complex are rare in PCa cells. Therefore, other regulatory mechanisms could play dominant roles in the activation of β-catenin in PCa. In PCa cells, Wnt-3a was found to stimulate proliferation selectively in AR-positive CWR22Rv1 and LNCaP cells; however, T-cell factor (TCF)-dependent reporter gene transcription was not induced in LNCaP cells, suggesting that the activation of Wnt signaling in AR-positive PCa cells may be through AR-dependent mechanisms rather than classical TCF-dependent mechanisms (Cronauer *et al.* 2005). It was also found that β-catenin enhanced the function of AR and that nuclear translocation of β-catenin takes place in PCa tissue, indicating that Wnt signaling is required for disease progression (Chesire *et al.* 2002). In addition, loss or reduction of E-cadherin and abnormal expression of Wnt ligands, receptors, inhibitors, and other co-regulators could also contribute to the activation of the Wnt signaling pathway in PCa. Therefore, inhibition of aberrant Wnt activity in PCa cells could provide an opportunity for the prevention and/or treatment of PCa (Dihlmann & von Knebel 2005, Barker & Clevers 2006, Verras & Sun 2006).

Hh signaling

Another important signaling pathway involved in cell development and proliferation is the Hh signaling pathway, which is a major regulator of cell differentiation, tissue polarity, and cell proliferation. Hh ligands, Sonic Hh and Indian Hh, stimulate GLI transcription factors, which constitute the final effectors of the Hh signaling pathway (Fig. 1). It has been found that germline mutations that subtly affect Hh pathway activity are associated with developmental disorders (Varjosalo & Taipale 2008). More importantly, somatic mutations that activate the Hh pathway have been linked to a variety of human cancers (Varjosalo & Taipale 2008). Emerging evidence clearly suggests the activation of Hh signaling in various human cancers, including basal cell carcinomas, medulloblastomas, leukemia, gastrointestinal, lung, ovarian, breast, and PCa (Yang *et al.* 2010). Furthermore, because Hh plays a central role in the control of cell proliferation and differentiation of both embryonic stem cells and adult stem cells, the aberrant activation of Hh signaling could lead to the development of cancer and the generation of cancer stem cells (Medina *et al.* 2009). It has been known that epithelial expression of Hh ligand during prostate development exerts autocrine and paracrine signaling activities that regulate growth and differentiation. Increased Hh signaling has been associated with PCa progression and has also been shown to accelerate PCa growth (Vezina & Bushman 2007). Studies have revealed the critical role of Hh signaling in PCa, and demonstrated that autocrine Hh signaling by tumor cells is required for the proliferation, viability, and invasive behavior of PCa (Antón Aparicio *et al.* 2007). Therefore, the development of Hh inhibitors such as those that are currently coming through the drug pipeline hold great promise for the prevention and/or treatment of PCa.

Notch signaling

Hh, Wnt, transforming growth factor-β (TGF-β)/BMP, and Notch signaling pathways all are involved in embryonic development, adult tissue homeostasis, and tumorigenesis. It is known that Notch signaling plays a critical role in the regulation and maintenance of stem cells; therefore, normal functioning of Notch signaling is required for development during early life. Emerging evidence suggests that deregulation of Notch signaling contributes to the development and progression of a number of cancers (Rizzo *et al.* 2008, Zardawi *et al.* 2009). Up-regulation of Notch receptors and their ligands has been observed in cervical, lung, colon, head and neck, renal and pancreatic cancers, and in Hodgkin and large-cell lymphomas (Miele *et al.* 2006). Controversial results have been reported regarding the role of Notch in PCa. Shou *et al.* (2001) reported that the expression of Notch ligands was low or undetectable in PCa cells, and that overexpression of a constitutively active form of Notch-1 inhibited the proliferation of various PCa cells, suggesting that Notch acts as a tumor suppressor. However, we and other investigators have found that Notch ligand Jagged-1 expression was associated with PCa metastasis and recurrence (Santagata *et al.* 2004), and that down-regulation of Notch-1 and Jagged-1 inhibited PCa cell growth, migration, and invasion, while inducing apoptosis via inactivation of Akt, mTOR, NF-κB, MMP-9, and uPA signaling pathways (Bin *et al.* 2009, Wang *et al.* 2010). Therefore, Notch signaling could be an important target for the prevention and/or treatment of PCa; however, more in-depth molecular investigations are needed to address this controversy because the consequences of aberrant Notch signaling could depend on cell context, dose, and timing (Maillard & Pear 2003).

Other signaling pathways

Other signaling pathways that are involved in PCa include epidermal growth factor receptor (EGFR) signaling, VEGF receptor (VEGFR) signaling, IGF receptor (IGFR) signaling, and mitogen-activated protein kinase (MAPK) signaling. The activation of these signaling pathways could stimulate the development of PCa through the activation of PI3K/Akt and NF-κB signaling. It has been found that increased levels of circulating IGF1 and decreased levels of IGF binding protein 3 (IGFBP3) were associated with a higher risk of developing PCa (Renehan *et al.* 2004). Moreover, tumor angiogenesis is an important biological component of PCa metastasis; the contribution of increased angiogenic molecules such as VEGF was investigated in PCa, and found to correlate with advanced clinical stage in PCa (Duque *et al.* 1999, Shariat *et al.* 2004). Therefore, EGFR, VEGFR, IGFR, and MAPK signaling pathways also participate in the development and progression of PCa, suggesting that the inhibitors of these signaling pathways could be important for the prevention of PCa progression and/or treatment.

It is important to note that cellular signaling is a complex signal network with positive or negative feedback loops and is also regulated by compensatory mechanisms (Fig. 1). In PCa cells, deregulations of several signaling pathways often exist; therefore, targeting multiple signaling pathways is needed for the prevention and/or treatment of PCa in the future.

Chemopreventive agents and their targets in PCa prevention

To prevent the development and progression of PCa, the strategy should target the cell signaling pathways that are deregulated in benign and malignant prostate tumors. Thus far, several chemopreventive agents including 5-α-reductase inhibitors (finasteride and dutasteride), selenium, vitamins E and D, lycopene, soy isoflavones, green tea polyphenols and curcumin have shown their various activities in the inhibition of prostate carcinogenesis through the regulation of major cell signaling pathways such as the AR, Akt, NF-κB, Wnt, Hh and Notch. However, the results to date have been mixed as summarized in the subsequent paragraphs.

5-α-reductase inhibitors

It has been well accepted that the activation of AR signaling plays critical roles in the development and progression of PCa. To activate AR signaling, androgens including testosterone and dihydrotestosterone (DHT), a metabolic product of testosterone, bind to the AR and stimulate the activation of the AR. However, DHT has a much higher affinity, leading to different kinetic processes. It is known that both type I and type II 5-α-reductases are responsible for synthesizing DHT from testosterone in prostatic tissue and in peripheral tissues. Therefore, 5-α-reductase inhibitors have been used to inhibit AR activation for the prevention of PCa. It has been found that the use of clinically available 5-α-reductase inhibitors leads to a reduction in prostatic volume of around 30%, and serum PSA levels are reduced by 50–60% in men with benign prostatic enlargement (Marberger 2006); however, the precise role of 5-α-reductase inhibitors for the prevention of PCa development and progression remains to be tested in a large population.

Finasteride is an agent that targets type II 5-α-reductase. This agent was used in the PCa Prevention Trial (PCPT), which tested a hypothesis that treatment with finasteride could lower DHT levels and thereby inhibit the activation of the AR, leading to the prevention of PCa. The PCPT was the first large-scale trial and included 18 882 men with a normal PSA level. Finasteride (5 mg/day) or placebo was given for 7 years. It was found that the prevalence of PCa was reduced by 24.8% in those randomized to finasteride compared with placebo (Thompson *et al.* 2003). However, the prevalence of tumors at Gleason scores 7–10 was higher in the finasteride group than in the placebo group, suggesting that the benefit of reducing the risk of PCa by finasteride must be weighed against the increased risk of development of high-grade PCa (Thompson *et al.* 2003). Recently, several studies have been conducted to re-analyze the data of the PCPT. It was found that sampling density bias alone could explain the excess of high-grade cancers among the finasteride-assigned participants in the PCPT (Cohen *et al.* 2007) and that after adjusting for biopsy sampling density, finasteride significantly reduced PCa risk relative to placebo across multiple Gleason scores in the PCPT, including the most frequently detected intermediate- and high-grade (Gleason scores 6 and 7) PCa (Kaplan *et al.* 2009).

Ongoing trials are addressing the unanswered questions from the PCPT. The second large-scale trial of a 5-α-reductase inhibitor is the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial (Andriole *et al.* 2004*a*, Crawford *et al.* 2010). The REDUCE clinical trial is an international, multi-center, double-blind, placebo-controlled chemoprevention trial. The study will examine the effects of the dual 5-α-reductase inhibitor dutasteride on the natural history of PCa in men at increased risk of this malignancy (Andriole *et al.* 2004*a*). The study will also examine biomarkers and genetic linkage for PCa. Dutasteride is used in the treatment of benign prostatic hyperplasia. It reduces serum PSA levels by ~50% at 6 months and total prostate volume by 25% after 2 years. Dutasteride differs from finasteride in that it inhibits both isoenzymes of 5-α-reductase, type I and type II. Preliminary data suggest a decrease in PCa incidence in dutasteride-treated patients (Andriole *et al.* 2004*b*, Musquera *et al.* 2008); however, we await the final outcome of this trial, which could be promising.

The major target of 5-α-reductase inhibitors is AR signaling through the inhibition of 5-α-reductase (Table 1). Finasteride significantly inhibits the activation of the AR; however, other cell signaling is also involved. It was found that finasteride significantly inhibited the proliferation of LNCaP PCa cells through regulation of the expression of AKR1B1, PTEN, NKX3.1, PMEPA1, PSA, and XRCC2 (Chen *et al.* 2005). In addition, finasteride could also induce apoptosis through the regulation of Akt, caspases, XIAP, and TGF-β signaling (Saez *et al.* 1998,Sawaya *et al.* 2002,Li & Kim 2009). Dutasteride has also been found to effectively inhibit both the viability and proliferation of LNCaP PCa cells, and to induce apoptosis. Dutasteride disrupted genes and cellular pathways that are involved in metabolic, cell cycle,

and apoptotic responses with alterations in TRADD, caspase-7, caspase-8, BIRC1, and other genes (Schmidt *et al.* 2004,2009,Biancolella *et al.* 2007). These mechanistic studies could be useful in explaining the positive or the negative outcome of the ongoing clinical trials using dutasteride.

Vitamin D

Two major forms of vitamin D that are important for humans are vitamin D_2 and D_3. The active form of vitamin D in the body is 1,25-dihydroxyvitamin D, which can be made from either vitamin D_2 or vitamin D_3. Some studies suggest that higher intakes of vitamin D from food and/or supplements and thereby higher levels of vitamin D in the blood are associated with reduced risk of cancer (Garland *et al.* 2006). Several epidemiological studies have suggested that vitamin D could be a preventive agent for PCa. It was found that reduced levels of active vitamin D resulted in a higher PCa incidence and mortality (Garland *et al.* 2006). Native Japanese men, whose diet is rich in vitamin D, have a low incidence of PCa, further supporting the protective role of vitamin D. A study also showed that dietary supplementation with >600 IU of vitamin D reduced the risk of PCa (Ahn *et al.* 2007). However, the results of other studies were conflicting or negative (Whittemore *et al.* 1995, Lee *et al.* 1998), which suggests complexities in vitamin D signaling in PCa. The data from several studies also appeared to show a protective role of sunlight/UVB exposure, which induces vitamin D, against PCa (Gupta *et al.* 2009). Although the results of these studies are conflicting, one should not ignore the fact that vitamin D deficiency is associated with PCa risks. Further molecular understanding of the signaling pathways related to vitamin D is expected to resolve these controversies in the future. The precise mechanisms of vitamin D action on the prevention of PCa are not clear, although it is known that vitamin D regulates the expression of genes such as *CYP24A1*, osteopontin (*Spp1*), *LRP5*, *TRPV6* and *VDR* (Meyer *et al.* 2010, Pike *et al.* 2010; Table 1); however, the significance of the regulation of these genes in relation to vitamin D and PCa remains unclear.

Selenium

Selenium is an essential trace element found in grains, fish, meat, poultry, or eggs. Selenium is currently available in over-the-counter supplements and multi-vitamins. It has been established that selenium is distributed in body tissues and has an antioxidant effect. Epidemiological studies also showed that selenium could be a protective agent against the development of PCa (Klein 2004). A study was conducted to test the level of selenium in serum and prostate of 52 men after selenium supplementation. It was found that selenium supplementation resulted in a significantly higher level of selenium in the prostatic tissue (Gianduzzo *et al.* 2003), suggesting the high bioavailability of selenium. To evaluate the effect of selenium on the prevention of PCa, a large clinical trial has been conducted. It was found that selenium supplementation significantly reduced the overall incidence of PCa with relative risk of 0.51 (95% confidence interval 0.29–0.87; Duffield-Lillico *et al.* 2003). The protective effect of selenium supplementation appeared to be confined to those with a baseline PSA level of <4 ng/ml and low serum levels of selenium (Duffield-Lillico *et al.* 2003). In an animal study, diet with selenium supplementation was given for 7 months and it was found that the extent of DNA damage in prostate cells and peripheral blood lymphocytes, as determined by the alkaline comet assay, was lower, while apoptotic cell death was higher in selenium-supplemented dogs compared with the control dogs (Waters *et al.* 2003), suggesting that selenium is a potent antioxidant. *In vitro* studies have revealed that selenium could inhibit cellular proliferation, induce apoptosis, and modulate genes related to cell growth, apoptosis, and androgen regulation, leading to the suppression of prostatic tumorigenesis (Dong *et al.* 2003, Zhao *et al.* 2004).

The targets of selenium include the AR, estrogen receptor (ER), NF-κB, antioxidant genes and pro-inflammatory molecules (Table 1). It was found that selenium could exert its anticancer property through increasing the expression of a humoral defense gene (*A2M*) and the tumor suppressor-related genes (*IGFBP3* and *HHIP*) while decreasing pro-inflammatory gene expression (*CXC L9* and *HSPB2*) (Zeng & Botnen 2007,Vunta *et al.* 2008). High selenium intake reduced the expression of AR, 24-dehydro-cholesterol reductase (Dhcr24), and ATP-binding cassette sub-family C member 4 (ABCC4; Legg *et al.* 2008,Schmidt *et al.* 2009). Selenium could also inhibit ERα signaling (Shah *et al.* 2005). In addition, treatment with selenium virtually eliminated the binding of NF-κB to target DNA and reduced transcription of NF-κB-regulated genes (Christensen *et al.* 2007); these findings are consistent with the antioxidant effects of selenium. The role of selenium in the prevention of PCa is further discussed below.

Vitamin E

Vitamin E is a lipid-soluble antioxidant found in green leafy vegetables, nuts, seeds, sunflower, and plant oils. Several forms of vitamin E have been identified; however, α-tocopherol is the most active, abundant, and predominant form of vitamin E in human tissues. In addition to the antioxidant effect, as it contains a chromanol moiety, vitamin E could also have antiandrogen activity (Thompson & Wilding 2003). In the 1990s, NIH conducted the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study, which was a placebo-controlled, randomized intervention trial to test the hypothesis of whether β-carotene and α-tocopherol (vitamin E) supplements could prevent lung and other cancers. It was found that the vitamin E group had reduced incidence of PCa compared with the group not receiving vitamin E (number of cases 99 compared with 151) (Albanes *et al.* 1995). Several years later, a prospective nested case–control study to determine the association between serum carotenoids, retinoids, and tocopherols (vitamin E) on both lung and PCa incidence was reported. For PCa, low serum levels of α-tocopherol (vitamin E) were associated with a higher risk of PCa (Goodman *et al.* 2003), suggesting a protective effect of vitamin E against PCa although the results on lung cancer were disappointing.

The mechanism involved in the prevention of PCa by vitamin E is not very clear. It was found that vitamin E mainly modulated two major signal transduction pathways including PI3K/Akt and protein kinase C (Azzi *et al.* 2004), leading to a change in cell proliferation. Several other genes were also regulated by vitamin E partly because of the effects of vitamin E on kinases. These genes include *P450*, glutathione *S*-transferase, *MMP-1*, *MMP-19*, *IL-2*, *IL-4*, cyclin D1, cyclin E, *Bcl-2*, *p27*, *CD95* (APO-1/Fas ligand), 5-α-reductase type I, NF-κ*B* and activator protein 1 (*AP1*), (Azzi *et al.* 2004; Table 1). The antioxidant-responsive element and the TGF-β-responsive element were also regulated by vitamin E (Azzi *et al.* 2004). Recent animal studies have also shown that vitamin E could induce p21 signaling and significantly increase the median lifespan of C57BL/6 mice by 15%, an effect which appeared to be independent of any antioxidant effect of vitamin E (Banks *et al.* 2010); however, the role of vitamin E as a single agent for the prevention of PCa remains to be established.

Since epidemiological and biological studies showed that selenium and vitamin E may prevent PCa, a phase III trial is currently assessing the value of selenium and vitamin E in the prevention of PCa. This trial, known as the Selenium and Vitamin E Cancer Prevention Trial (SELECT), is a randomized, prospective, double-blind study designed to determine whether selenium and vitamin E alone or in combination can reduce the risk of PCa among healthy men. SELECT is the second large-scale study of chemoprevention for PCa, and enrollment began in 2001 with final results anticipated in 2013 (Klein *et al.* 2003). However, the results reported so far are disappointing. As of October of 2008, median overall followup was 5.46 years. A statistically non-significant increased risk of PCa was found in the vitamin E group (P=0.06)

but not in the selenium plus vitamin E group. Selenium or vitamin E alone or in combination at the doses and formulations used did not prevent PCa in this population of relatively healthy men (Lippman *et al.* 2009). A recent animal study also does not support the hypothesis that selenium and vitamin E are potent cancer chemopreventive agents against PCa (McCormick *et al.* 2010), suggesting that more detailed epidemiological and biological studies are needed to investigate the effects of selenium and vitamin E prior to conducting expensive large-scale intervention trials for reducing the risk of PCa.

Soy isoflavone

Isoflavones are a subclass of the more ubiquitous flavonoids and are much more narrowly distributed in soybeans. Genistein, daidzein, and glycitein are three isoflavones found in soybeans and most soy protein products. Several epidemiological studies have shown that soy could have protective effects against prostate and other cancers (Adlercreutz *et al.* 1991, 1993, Hebert *et al.* 1998, Jacobsen *et al.* 1998). A prospective study of 12 395 California Seventh-Day Adventist men who often drank soy milk showed that frequent consumption (more than once a day) of soy milk was associated with a 70% reduction in the risk of PCa (Jacobsen *et al.* 1998), suggesting the possible association between a high intake of soy isoflavones and a reduced risk of PCa. Experimental studies have also revealed that isoflavones, particularly genistein, exert antioxidant effects on human cells. It has been known that genistein protects cells against reactive oxygen species (ROS) by scavenging free radicals and reducing the expression of stress–response-related genes.

Our laboratory has investigated the effects of the isoflavone genistein on several signaling pathways. We have found that isoflavones significantly inhibited the activation of AR, Akt, NF-κB, and Notch signaling (Li & Sarkar 2002*a*,*b*, Wang *et al.* 2006*a*, Li *et al.* 2008, Sarkar *et al.* 2008; Table 1). The isoflavone genistein has also been found to inhibit the molecules in the MAPK pathway. It was reported that genistein blocked the activation of p38 MAPK by TGF-β; p38 MAPK is necessary for TGF-β-mediated induction of MMP-2 and cell invasion in PCa (Huang *et al.* 2005). Therefore, genistein could inhibit cancer cell invasion and metastasis by blocking the activation of p38 MAPK. We have also found that genistein down-regulated the expression of MMP-9, protease M, uPAR, VEGF, neuropilin, TSP, BPGF, LPA, TGF-β2, TSP-1, and PAR-2, which are involved in angiogenesis, tumor cell invasion, and metastasis of PCa cells (Li & Sarkar 2002*b*). Mechanistic studies revealed that isoflavones up-regulate the expression of GSK-3β, enhance GSK-3β binding to β-catenin, and increase the phosphorylation of β-catenin, suggesting that isoflavones could inactivate Wnt signaling to inhibit PCa cell growth (Li *et al.* 2008). Other investigators have also reported that genistein diminished basal and Wnt-1-induced cell proliferation, attenuated Wnt-1 targets such as c-Myc and cyclin D1 expression (Su & Simmen 2009), and that isoflavones inhibit the expression of Wnt-5a (Su *et al.* 2007). Moreover, genistein could reduce *Gli1* mRNA concentrations and down-regulate Gli reporter activity (Slusarz *et al.* 2010). These results suggest an inhibitory effect of isoflavones on Wnt and Hh signaling. In addition, genistein could also inhibit the growth of PCa cells through the induction of neuroendocrine differentiation (Pinski *et al.* 2006), suggesting genistein has effects on multiple signaling pathways.

Lycopene

Tomatoes are rich in lycopene, which is the pigment principally responsible for the deep-red color of tomato and its products. Tomato products including ketchup, tomato juice, and pizza sauce are the richest sources of lycopene in the US diet. The consumption of tomatoes and tomato products containing lycopene is associated with a decreased risk of chronic diseases including cardiovascular diseases and cancers. Lycopene is a potent antioxidant, and it has been established that lycopene is a biologically occurring carotenoid, which exhibits a high physical quenching rate constant with singlet oxygen, suggesting its high activity as an

antioxidant. Giovannucci *et al.* (2002) reported that frequent consumption of tomato products is associated with a lower risk of PCa. Inverse associations between plasma lycopene and PCa have also been reported (Gann *et al.* 1999, Lu *et al.* 2001). Experimental studies have also shown that lycopene inhibits cell growth in breast, prostate, and endometrial cancer cells by regulation of cell cycle-related genes (Nahum *et al.* 2001, Kim *et al.* 2002, Bureyko *et al.* 2009). An in vivo animal study showed that lycopene had anti-tumor effects that could be potentiated by vitamin E, an antioxidant that is also present in tomatoes (Limpens *et al.* 2004), which confirmed the anticancer activity of lycopene. A phase II clinical trial from our group has shown that lycopene supplements reduced tumor size and PSA level in localized PCa (Kucuk *et al.* 2001, 2002), suggesting a promising effect in PCa prevention and/or treatment. Another clinical trial with lycopene intake also showed a small but statistically significant reduction in serum PSA as shown below. In addition, compared with pre-intervention levels, the oxidative DNA damage in both leukocyte and prostate was significantly reduced after intervention (Chen *et al.* 2001), further suggesting an antioxidant effect for lycopene.

The molecular targets of lycopene include NF-κB, AR, Akt, Wnt and MAPK (Table 1). It has been found that lycopene significantly inhibited the DNA-binding activity of NF-κB and the expression of the NF-κB target gene *MMP-9*, leading to inhibition of the invasion of cancer cells (Huang *et al.* 2007). The inhibition of NF-κB DNA-binding activity by lycopene was mediated through the down-regulation of IκB phosphorylation, NF-κB expression, and NF-κB p65 subunit translocation from the cytosol to the nucleus (Huang *et al.* 2007). Another study showed that pretreatment with lycopene markedly inhibited the lipopolysaccharide (LPS)-induced up-regulation of p-ERK, p-p38, p-JNK, and NF-κB (Kim *et al.* 2004), suggesting an inhibitory effect by lycopene on MAPK and NF-κB signaling pathways. Lycopene also showed an inhibitory effect on Akt signaling and cell proliferation (Tang *et al.* 2008). Lycopene treatment suppressed Akt activation, suppressed non-phosphorylated activated β-catenin, increased the phosphorylated form of β-catenin proteins and increased the expression of $p27^{Kip1}$ (Tang *et al.* 2008). Lycopene also induced apoptosis through down-regulation of pAkt, cyclin D1, and pBad (Palozza *et al.* 2005), suggesting an inhibitory effect on Akt signaling. It has been reported that lycopene inhibits IGF1-mediated Akt and AR signaling in rat PCa (Liu *et al.* 2008). Lycopene reduced AR and β-catenin nuclear localization, and inhibited IGF1-stimulated PCa growth, perhaps by attenuating the effects of IGF1 on phosphorylation of Akt and GSK3β. These results suggest the broad effects of lycopene on multiple signaling pathways.

Green tea

Consumption of green tea has been associated with human health including the prevention of cancer and heart disease. Epidemiological observations showed lower incidence of PCa among Asian men with a high dietary intake of green tea, suggesting that green tea might be a preventive agent against PCa (Jian *et al.* 2007). The result from Japan's Public Health Center-based Prospective Study showed that the consumption of green tea was associated with a dose-dependent decrease in the risk of advanced PCa (Kurahashi *et al.* 2008). A clinical trial with oral administration of green tea catechins (GTC) showed that GTC decreased PSA levels and that the effect of PCa prevention by GTC was long lasting (Bettuzzi *et al.* 2006, Brausi *et al.* 2008). Green tea and its constituents have been studied both *in vitro* and *in vivo*. Green tea contains several catechins including epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epigallocatechin-3-gallate (EGCG). EGCG is believed to be the most potent among these catechins for the inhibition of oncogenesis and reduction of oxidative stress (Syed *et al.* 2007, 2008, Khan & Mukhtar 2008, Khan *et al.* 2009, Johnson *et al.* 2010). These results clearly suggest that further clinical trials are needed to appreciate the value of green tea and its active components in PCa prevention and/or treatment.

The inhibitory effects of EGCG on AR signaling have been reported in PCa *in vitro* and *in vivo* (Table 1). EGCG inhibited LNCaP cell growth and the expression of AR at both mRNA and protein levels (Ren *et al.* 2000). Moreover, EGCG showed a significant inhibitory effect on androgen-induced PSA promoter-mediated expression of PSA. It has been reported that EGCG treatment resulted in a significant dose- and time-dependent inhibition of the activation and translocation of NF-κB to the nucleus by suppressing the degradation of IκBα in the cytoplasm (Ahmad *et al.* 2000,Khan & Mukhtar 2008). EGCG has also been shown to inhibit the activation of IKK and the phosphorylation of IκBα (Yang *et al.* 2001,Chen *et al.* 2002). EGCG has been found to inhibit PI3K/Akt activation which, in turn, resulted in the modulation of the Bcl-2 family of proteins, leading to enhanced apoptosis of bladder cancer cells (Qin *et al.* 2007). EGCG also inhibited VEGF-induced angiogenesis *in vitro* through suppression of VE-cadherin phosphorylation and inactivation of Akt, suggesting an inhibitory effect of EGCG on the Akt signaling pathway (Tang *et al.* 2003). The Wnt and Hh signaling pathways have also been found to be inhibited by EGCG in a dose-dependent manner in cancer cells (Kim *et al.* 2006,Slusarz *et al.* 2010). EGCG treatment induced transcription of HBP1, which is a suppressor of Wnt signaling. It has been found that EGCG treatment resulted in a dose-dependent increase of p53 in LNCaP cells which carry the wild-type p53 gene, but not in DU145 cells carrying a mutant p53 (Gupta *et al.* 2000). EGCG also induced stabilization of p53 and caused an up-regulation of its transcriptional activity, thereby causing activation of its downstream targets such as $p21^{WAF1}$ and Bax, resulting in the induction of apoptosis.

Other agents

DIM is the dimeric product of indole-3-carbinol (I3C), which is produced from naturally occurring glucosinolates contained in a wide variety of plants, including members of the family Cruciferae. Under the acidic conditions of the stomach, I3C undergoes extensive and rapid self-condensation reactions to form several derivatives. DIM is believed to be the major derivative and condensation product of I3C. Epidemiological studies indicate that human exposure to indoles through cruciferous vegetable consumption could decrease cancer risk (Higdon *et al.* 2007). DIM has been shown to reduce oxidative stress and stimulate antioxidant response element-driven gene expression, suggesting that indole compounds have an antioxidant function (Benabadji *et al.* 2004, Nho & Jeffery 2004). An animal study showed that DIM is not toxic and has an *in vivo* preventive effect against the development of PCa in a mouse model (Fares *et al.* 2009). Furthermore, several experimental studies have shown that DIM inhibited oncogenesis and cancer cell growth, and induced apoptosis in PCa cells *in vitro* and *in vivo*, suggesting that DIM could serve as a potent agent for the prevention and/or treatment of cancers (Nachshon-Kedmi *et al.* 2004, Garikapaty *et al.* 2006). We and other investigators have also investigated the molecular targets of DIM. It has been found that DIM is a potent inhibitor of the AR (Le *et al.* 2003, Bhuiyan *et al.* 2006), suggesting it has inhibitory effects on PCa cell growth. Moreover, DIM also regulated Akt, Wnt, NF-κB, VEGF, and uPA (Le *et al.* 2003, Garikapaty *et al.* 2006, Kong *et al.* 2007, 2008, Ahmad *et al.* 2009), suggesting multiple molecular targets (Table 1).

Curcumin is another bioactive compound found in *Curcuma longa* (turmeric). Turmeric extract from the rhizomes, commonly called curcuminoids, is mainly composed of curcumin. Curcumin-related research has received considerable attention due to its pronounced anti-inflammatory, anti-oxidative, immunomodulating, anti-atherogenic, and anti-carcinogenic activities (Miquel *et al.* 2002, Banerjee *et al.* 2003). It has been reported that curcumin inhibits IKK, suppresses both constitutive and inducible NF-κB activation, and potentiates TNF-induced apoptosis (Bharti *et al.* 2003). Curcumin showed strong antioxidant and anticancer properties through regulating the expression of genes that require the activation of AP1 and NF-κB (Duvoix *et al.* 2003). We and other investigators have found that curcumin inhibited Notch, Akt, Hh, and Wnt signaling (Wang *et al.* 2006*b*, Ryu *et al.* 2008, Yu *et al.* 2008, Slusarz

et al. 2010). In addition, a number of curcumin analogs have been identified as potential AR antagonists in the presence of the AR and the AR co-activator, ARA70 (Ohtsu *et al.* 2002). Considering the effects of curcumin on NF-κB, Akt, Notch, Wnt, Hh, and AR signaling, curcumin could, in the future, be a non-toxic alternative for PCa prevention and/or treatment; indeed, making improvements in the bioavailability of curcumin and its analogues is an active area of research.

Many other botanical compounds have been proposed for the prevention of cancer. It was found that apigenin, baicalein, quercetin, and resveratrol with IC_{50} values ranging from <1 to 25 μM could inhibit *Gli1* mRNA concentrations by up to 95%, suggesting an inhibitory effect on Hh signaling (Slusarz *et al.* 2010). These compounds also reduced or delayed PCa *in vivo* in TRAMP mice, consistent with *in vitro* data showing that these compounds inhibited the growth of human and mouse PCa cell lines, suggesting a potential role in the prevention of PCa (Slusarz *et al.* 2010); further in-depth investigation in pre-clinical models and human clinical trials is warranted.

Conclusions and perspectives

In conclusion, PCa cells are known to have alterations in multiple cellular signaling pathways, among which the AR, Akt, NF-κB, Wnt, Hh, and Notch pathways appear more important than others. The alterations in these pathways could occur at different stages of PCa. Therefore, novel strategies targeting these important pathways could be promising for the prevention of PCa and its metastases. So far, the preventive effects of 5-α-reductase inhibitors show more promising results for the prevention of PCa; however, it is important to note that natural agents such as soy isoflavones, lycopene, EGCG, DIM, and curcumin which target multiple pathways could be useful for the prevention of tumor progression and/or treatment, which further suggests that agents harvested from the bounties of nature could be useful either alone or in combination with targeted or non-targeted conventional preventive or therapeutic agents for the prevention and/or treatment of PCa. Further in-depth mechanistic *in vitro* studies and animal model *in vivo* studies together with intelligently designed clinical trials are needed to fully appreciate the value of natural products for the prevention and/or treatment of human PCa.

Acknowledgments

We also thank Puschelberg and Guido foundations for their generous contribution in support of our research.

Funding

The authors' work cited in this review article was funded by grants from the National Cancer Institute, NIH (5R01CA083695, 2R01CA108535, 5R01CA131151, 3R01CA131151-02S109, and 1R01CA132794 awarded to F H Sarkar), and a sub-contract award to F H Sarkar from the University of Texas MD Anderson Cancer Center through SPORE grant (5P20-CA101936 and 3P20CA101936-05S109) on pancreatic cancer was awarded to James Abbruzzese.

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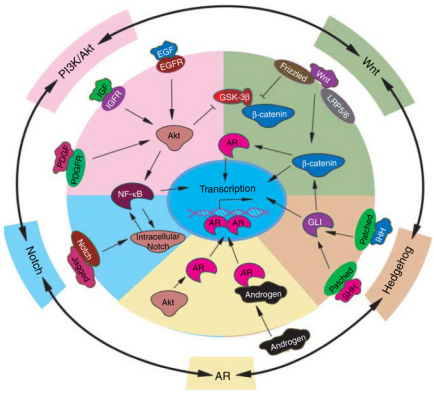

Figure 1.

Major cell signaling pathways altered during the development and progression of prostate cancer. The dysfunctions of AR, Akt, NF-κB, Wnt, Hedgehog, and Notch signaling could result in the uncontrolled transcription and proliferation of prostatic epithelial cells, leading to the formation of prostate cancer. The crosstalk between AR, Akt, NF-κB, Wnt, Hedgehog, and Notch signaling plays critical roles in prostatic carcinogenesis. Therefore, targeting these signaling pathways is important strategy for the prevention of prostate cancer.

Table 1

Chemopreventive agents and their targets in the prevention of prostate cancer

Agent	Target signaling or altered molecules	References
Finasteride	AR, AKR1B1, PTEN, NKX3.1, PMEPA1, PSA, XRCC2, Akt, caspases, XIAP, TGF-β, etc.	Saez *et al.* (1998), Sawaya *et al.* (2002), Chen *et al.* (2005), Li & Kim (2009)
Dutasteride	AR, TRADD, caspase-7, caspase-8, BIRC1, Wnt, VEGF, etc.	Schmidt *et al.* (2004, 2009), Biancolella *et al.* (2007)
Vitamin D	CYP24A1, osteopontin (Spp1), LRP5, TRPV6, VDR, etc.	Meyer *et al.* (2010), Pike *et al.* (2010)
Selenium	AR, ER, NF-κB, A2M, IGFBP3, HHIP, CXC L9, HSPB2, Dhcr24, Abcc4, etc.	Shah *et al.* (2005), Christensen *et al.* (2007), Zeng & Botnen (2007), Legg *et al.* (2008), Schmidt *et al.* (2009)
Vitamin E	Akt, protein kinase C, NF-κB, AP1, P450, glutathione *S*-transferase, MMP-1, MMP-19, IL-2, IL-4, cyclin D1, cyclin E, Bcl-2, p27, CD95, TGF-β, etc.	Azzi *et al.* (2004), Banks *et al.* (2010)
Soy isoflavone	AR, Akt, NF-κB, Wnt, Notch, VEGF, p21, Bcl-2, Bax, Src, cyclin B, p27, MMP-9, protease M, uPAR, VEGF, neuropilin, TSP, BPGF, LPA, TGF-β2, TSP-1, PAR-2, Gli1, etc.	Li & Sarkar (2002*a*, *b*), Wang *et al.* (2006*a*), Li *et al.* (2008), Sarkar *et al.* (2008)
Lycopene	NF-κB, AR, Akt, Wnt, MAPK, p-ERK, p-p38, p-JNK, p27, Bax, β-catenin, cyclin D1, etc.	Kim *et al.* (2004), Palozza *et al.* (2005), Huang *et al.* (2007), Liu *et al.* (2008), Tang *et al.* (2008)
Green tea	AR, PSA, NF-κB, PI3K/Akt, VE-cadherin, Wnt, HBP1, p53, $p21^{WAF1}$, Bax, Gli1, etc.	Ahmad *et al.* (2000), Gupta *et al.* (2000), Ren *et al.* (2000), Tang *et al.* (2003), Kim *et al.* (2006), Qin *et al.* (2007), Khan & Mukhtar (2008)
DIM	AR, Akt, Wnt, NF-κB, VEGF, uPA, etc.	Le *et al.* (2003), Li *et al.* (2003, 2007), Kong *et al.* (2007, 2008), Ahmad *et al.* (2009)
Curcumin	NF-κB, Akt, Notch, Wnt, Hedgehog, AR, etc.	Ohtsu *et al.* (2002), Bharti *et al.* (2003), Duvoix *et al.* (2003), Ryu *et al.* (2008), Yu *et al.* (2008)