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The Role of Vitamin D in the Prevention and Treatment of Prostate Cancer

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1. Introduction

Prostate cancer is the most common non-cutaneous cancer in American men and the second most deadly (Jemal et al., 2010). One in six American men will get prostate cancer in his lifetime, and the risk increases with age. Prostate cancer progresses over the course of decades, so there is ample opportunity for prevention earlier in life. Epidemiological and laboratory studies point to vitamin D_3 as a promising chemopreventative agent for prostate cancer. Vitamin D_3 metabolites and analogs have been shown to induce cell cycle arrest, differentiation, and senescence in normal prostate cells and prostate cancer cells. Ongoing studies are interrogating the mechanistic effects behind vitamin D_3 actions in the prostate. Additionally, clinical trials aim to investigate the potential chemopreventative and therapeutic effects of vitamin D_3 metabolites and analogs, both alone and in combination with taxol-based chemotherapeutic agents. Herein we will summarize the epidemiological, laboratory, and clinical studies with vitamin D_3 and the prostate and discuss how the current data supports a role for vitamin D_3 in the prevention and treatment of prostate cancer.

2. Prostate cancer treatment and prevention

If prostate cancer is thought to be localized to the prostate and is classified as low-grade, "watchful waiting" is an option, since some prostate tumors do not become life-threatening. Otherwise, a prostatectomy or external beam radiation is the first line of therapy (or in some cases, brachytherapy). Both prostatectomy and radiation therapy can damage the nerves that rest along the prostate, so side effects include impotence and incontinence that may or may not reverse over time. If the cancer is thought to have spread beyond the prostate, then a more systematic therapeutic approach is needed.

Since androgens are required for growth of both normal prostate cells and most prostate cancer cells, androgen ablation therapy is standard in the forms of surgical or chemical castration. Castration has significant side effects, but it reduces tumor burden and metastatses and it can help ease pain from metastatic outgrowths. However, androgen deprivation therapy inherently selects for prostate cancer cells that can grow in the absence of androgens, which often leads to tumor recurrence in 18 to 24 months in the form of castration-resistant prostate cancer (Feldman & Feldman, 2001). The median survival time

for patients with castration-resistant prostate cancer is only 12-18 months. There is no standard successful treatment for castration-resistant prostate cancer, but therapies include docetaxel or pacilaxel-based chemotherapy, which are palliative at best. The impacts on quality of life and the success rates of current treatment options for prostate cancer (especially for castration-resistant prostate cancer) highlight the need for improved therapeutic approaches and the importance of chemoprevention, especially in men who are at higher risks for prostate cancer.

The American Cancer Society states that some cases of prostate cancer may be prevented by maintaining a healthy lifestyle and by hormonal control. Men who take Finasteride, a 5-alpha reductase inhibitor, which is a treatment for benign prostatic hyperplasia (BPH) and male-pattern baldness, have a lower incidence of prostate cancer, but this drug is not widely used for its chemopreventative properties (Hamilton et al., 2010). Dietary sources of chemoprevention are promising, but clinical studies are lacking due to the time and funds required to carry them out (Thompson et al., 2005). One of the most promising dietary chemopreventative agents for prostate cancer is vitamin D_3, which we will discuss in detail below.

3. Prostate cancer risk factors

The major risk factors for prostate cancer include age, race, family history, and geographic location. Prostate cancer develops over the course of decades, so its incidence and detection rates increase with age. Men of African-American descent are almost twice as likely to get prostate cancer as Caucasian men, and the prostate cancer mortality rate is more than twice as high for African-American men (Jemal, et al., 2010). Conversely, Asian men have among the lowest prostate cancer incidence and mortality rates in the world. Interestingly, prostate cancer risk increases in Asian men who relocate to the United States, which emphasizes the contributions of diet and lifestyle to prostate cancer risk (Severson et al., 1989; Luo et al., 2004). Prostate cancer can also have a strong heritable component. The estimated lifetime risk for prostate cancer increases with the number of family members diagnosed, with up to a 45% increase for men with three or more relatives with prostate cancer (Bratt, 2002). The heritable component of prostate cancer is attributed to a number of heritable genetic and epigenetic aberrations, reviewed elsewhere (Nelson et al., 2003).

3.1 Prostate cancer risk factors and vitamin D_3

Of the major risk factors for prostate cancer, age, race, and geographic location are closely tied to vitamin D_3 status. Older men get less sun exposure and have a thinner epidermis (in which UV light synthesizes vitamin D_3) than younger men, which are two reasons why older men have lower serum vitamin D_3 levels (MacLaughlin & Holick, 1985; Lips, 2001). Studies have shown inverse correlations between prostate cancer incidence and geographical regions with less exposure to UV radiation (Hanchette & Schwartz, 1992). Prostate cancer risk and mortality rates are at least twice as high in African-American men than in Caucasian men, and one reason for this may be the high levels of melanin in the skin that blocks UV-induced synthesis of vitamin D_3 (Matsuoka et al., 1991). Japanese men have very low risks for prostate cancer and have among the highest serum vitamin D_3 levels in the world due to the traditional vitamin D_3-rich diet (Nakamura et al., 2000).

These and other epidemiological studies support a role for vitamin D_3 in prostate cancer prevention.

4. Vitamin D_3 metabolism

Vitamin D was discovered in 1920 and characterized as a vitamin that is necessary for skeletal development and calcium homeostasis (Mellanby, 1921). Its chemical structure later revealed that vitamin D is not a vitamin, but a seco-steroid hormone belonging to the steroid hormone family that can be synthesized in the body or obtained from the diet (Brockmann, 1936; Lawson et al., 1971). Vitamin D_3 can be synthesized upon exposure to sunlight or obtained from dietary sources such as oily fish, eggs, and fortified milk. Upon exposure to UV radiation, 7-dehydrocholesterol in the skin is converted to vitamin D_3, also known as cholecalciferol (Figure 1). Vitamin D_3 is the natural form of vitamin D obtained from the diet (DeLuca, 2004). Vitamin D_3 travels to the liver where vitamin D_3 25-hydroxylase (25-OHase, encoded by the cytochrome P450 enzyme CYP27A1) hydroxylates it to become 25-hydroxyvitamin D_3 ($25OHD_3$) (Blunt et al., 1968). $25OHD_3$ then enters the kidney where 25 hydroxyvitamin D_3 1α-hydroxylase (1α-OHase, encoded by CYP27B1) hydroxylates it at the 1α position, generating the hormonally active form 1,25 dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) (Fraser & Kodicek, 1970). $1,25(OH)_2D_3$ then travels to target tissues to carry out its effects such as regulating mineral homeostasis. Tissues other than the kidney express endogenous 1α-OHase such as the bone, liver, placenta, macrophages, skin, breast, colon, and prostate, so $25OHD_3$ can be activated directly in these tissues (Schwartz et al., 1998; Zehnder et al., 2001).

Once activated, $1,25(OH)_2D_3$ (also known as calcitriol) can bind the vitamin D receptor (VDR) within the cytosol (Figure 2). Upon binding, conformational changes occur that expose the retinoid X receptor (RXR) dimerization domains and the nuclear localization domains, allowing the VDR and the RXR to heterodimerize and enter the nucleus (Yasmin et al., 2005). Nuclear receptor co-activators such as DRIP/Mediator and SRC/p160 associate with the $1,25(OH)_2D_3$ -VDR-RXR complex and regulate its transcriptional activity (Rachez & Freedman, 2000; MacDonald et al., 2001). The conformational change also causes the release of co-repressors such as nuclear co-repressors (NCoRs) and the silencing mediator for retinoid and thyroid hormone receptors (SMRT) histone deacetylase complex, allowing histones to be released and the $1,25(OH)_2D_3$ -VDR-RXR complex to bind the vitamin D response element (VDRE) in the promoters of target genes (Tagami et al., 1998). RNA polymerase II (RNA Pol II) is recruited to the transcriptional machinery complex and transcribes $1,25(OH)_2D_3$ target genes.

Plasma $1,25(OH)_2D_3$ levels are tightly regulated by a negative feedback loop because high levels of $1,25(OH)_2D_3$ can be toxic. One of the universal $1,25(OH)_2D_3$ -VDR-RXR target genes is CYP24A1, which encodes 24-hydroxylase (24-OHase). 24-OHase hydroxylates $1,25(OH)_2D_3$ at the 24 position, which targets it for further oxidation to C23 carboxylic acid which is catabolized to calcitroic acid and excreted from the body (Figure 1) (Prosser & Jones, 2004). Normal serum circulation levels of $25OHD_3$ are 30-50 ng/mL, while normal serum levels of $1,25(OH)_2D_3$ are only ~30 pg/mL (Shepard et al., 1979; Horst & Littledike, 1982). $1,25(OH)_2D_3$ circulates bound to the vitamin D binding protein (DBP) from which it disassociates before entering the cell (Arnaud & Constans, 1993). Responses to vitamin D_3 intake differ among individuals and among tissue-types due to variables including CYP24A1 levels, kidney function, and genetic and epigenetic differences in vitamin D_3 metabolic proteins.

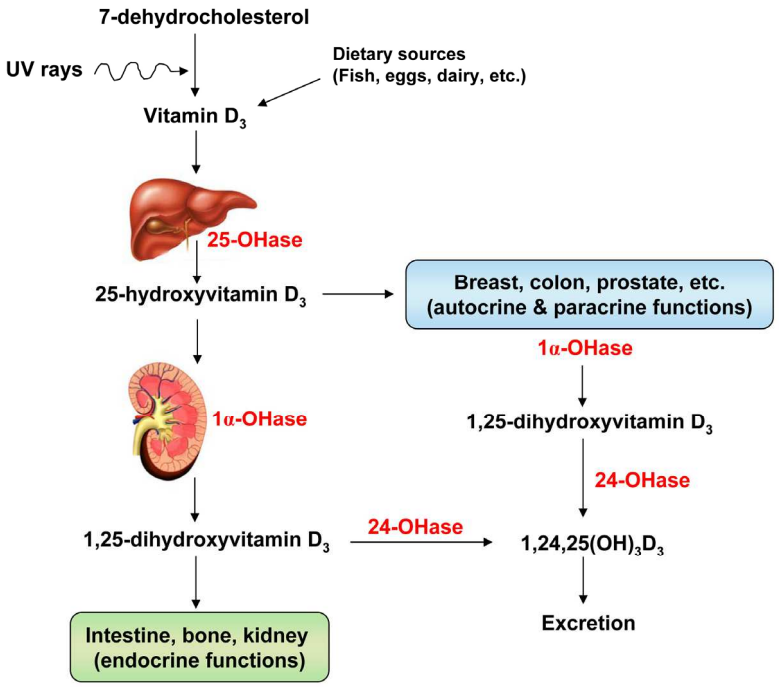

Fig. 1. Vitamin D_3 metabolism.

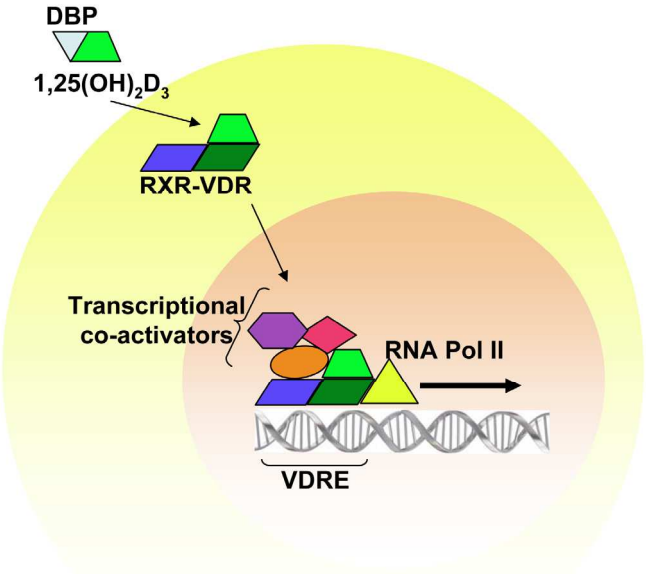

Fig. 2. Intracellular trafficking of $1,25(OH)_2D_3$.

5. Vitamin D_3 epidemiology

There is an established association between increased prostate cancer risk and mortality and low serum $25OHD_3$ levels (Ahonen et al., 2000; Tretli et al., 2009), as well as an association between prostate cancer risk and genetic polymorphisms of the VDR (Ingles et al., 1997). However, other studies report no association or even a positive association between serum $25OHD_3$ and prostate cancer risk (Nomura et al., 1998; Park et al., 2010). The inconsistencies among reports warrant improved investigation and evaluation methods (reviewed in (Trottier et al., 2010)). One reason for the inconsistencies could be the apparent impact on prostate cancer risk of vitamin D_3 exposure over the course of a lifetime as opposed to the impact of serum levels of $25OHD_3$ over a defined time period (John et al., 2004; John et al., 2007); studies have shown that childhood sunburn frequency and UV exposure correlates with lower prostate cancer risks (Luscombe et al., 2001; Bodiwala et al., 2003). Another reason could be that, since prostate cancer develops over the course of decades, some patients' cancer cells may have lost the ability to activate $25OHD_3$ to $1,25(OH)_2D_3$ (Guileyardo et al., 1980; J. Y. Hsu et al., 2001; Chen et al., 2003). Studies with follow-up periods greater than 10 years are better for evaluating the implications of vitamin D_3 status in prostate cancer development (Ahonen, et al., 2000; Li et al., 2007). Additionally, intermittent high doses (>100,000 IU) of vitamin D_3 may be metabolized differently from lower daily doses (Rosen, 2011). There is no standardization for vitamin D_3, $25OHD_3$ or $1,25(OH)_2D_3$ administration, which has hampered clinical studies. Overall, the epidemiological studies encourage more laboratory and clinical investigations into a therapeutic role for vitamin D_3 and its metabolites in the prevention and treatment of prostate cancer.

6. *In vitro* and *in vivo* studies

As mentioned above, prostate cells express endogenous 1α-OHase and can synthesize $1,25(OH)_2D_3$ from $25(OH)D_3$, which suggests an important role for $1,25(OH)_2D_3$ in prostate biology (Schwartz, et al., 1998). We and others have shown that $25OHD_3$ inhibits prostate epithelial cell growth and induces p21 and p27 (common downstream targets of $1,25(OH)_2D_3$) to the same extents as does $1,25(OH)_2D_3$ (Barreto et al., 2000). This supports the application of $25OHD_3$ as a therapeutic that targets prostate tissue. Interestingly, 1α-OHase activity is lost and 24-OHase expression is elevated in prostate cancer cells compared to normal prostate cells, which supports a correlation between decreased $1,25(OH)_2D_3$ levels and prostate cancer (Miller et al., 1995; Whitlatch et al., 2002).

One of the ways that $1,25(OH)_2D_3$ is thought to maintain prostate homeostasis is by keeping cell growth in check. $1,25(OH)_2D_3$-induced apoptosis is rarely observed. LNCaP cells treated with $1,25(OH)_2D_3$ undergo cell cycle arrest at G1 as a result of increased p21 and p27 levels and decreased CDK2 activity followed by dephosphorylation of retinoblastoma (pRB) and subsequent suppression of E2F transcriptional activity (Figure 3) (Zhuang & Burnstein, 1998; Yang & Burnstein, 2003). Two of the most common downstream targets of $1,25(OH)_2D_3$ are CDKN1A (which encodes p21) and CDKN1B (which encodes p27). $25OHD_3$, $1,25(OH)_2D_3$, and its analogs have been shown to elevate p21 and p27 expression in several tissue types in conjunction with cell growth inhibition (Kawa et al., 1997; Barreto, et al., 2000; Colston & Hansen, 2002). CDKN1A contains a VDRE, so its transcription can be directly regulated by $1,25(OH)_2D_3$. $1,25(OH)_2D_3$ can also elevate p21 indirectly through direct transcriptional

induction of insulin-like growth factor binding protein-3 (IGFBP-3), an upstream mediator of p21 transcription (Boyle et al., 2001; Peng et al., 2004; Peng et al., 2008). CDKN1B does not contain a VDRE, so p27 is regulated indirectly by $1,25(OH)_2D_3$. CDK2 activates SKP2-mediated degradation of p27, so $1,25(OH)_2D_3$-mediated induction of p27 is likely due to inhibition of CDK2 and p27 protein stabilization (Yang & Burnstein, 2003).

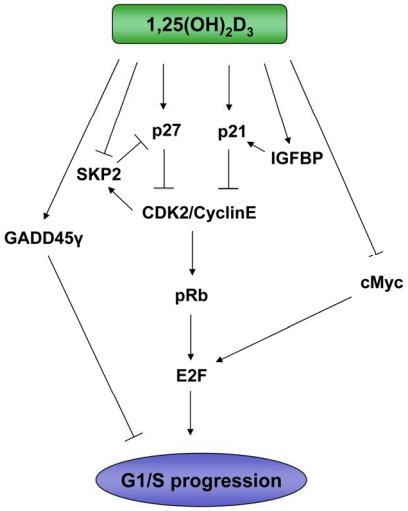

Fig. 3. $1,25(OH)_2D_3$ signaling leading to G1 cell cycle arrest in prostate cancer cells.

More recently, $1,25(OH)_2D_3$ has been shown to inhibit E2F and/or induce G1 arrest independently from pRB (Figure 3). In the C4-2 prostate cancer cell line, $1,25(OH)_2D_3$ inhibited cMYC which subsequently suppressed E2F activity and cell cycle progression regardless of pRB status (Washington et al., 2011). We have reported that $1,25(OH)_2D_3$ induces cell cycle arrest independently from pRB in prostate progenitor/stem cells (Maund et al., 2011). Flores and Burnstein recently reported that the cell cycle inhibitory protein GADD45γ mediates $1,25(OH)_2D_3$-induced accumulation of LNCaP cells in G1 (Flores & Burnstein, 2010). Cell cycle arrest in G1 is a common downstream effect of $1,25(OH)_2D_3$ treatment, and additional mechanisms of cell cycle regulation by $1,25(OH)_2D_3$ are still being uncovered.

$1,25(OH)_2D_3$ can induce differentiation of several cell types including prostate stem cells, prostate epithelial cells and prostate cancer cells (Miller et al., 1992; Tokar & Webber, 2005; Maund, et al., 2011). Differentiated prostate cells do not normally divide, so $1,25(OH)_2D_3$ may slow or halt any aberrant cell division. $1,25(OH)_2D_3$-induced differentiation of the LNCaP prostate cancer cell line is evidenced by increased levels of prostate-specific antigen (PSA), kallikrein 2, E-cadherin, and androgen receptor (AR) (Esquenet et al., 1996; Campbell et al., 1997; Zhao et al., 1997; Darson et al., 1999; Zhao et al., 1999; Tokar & Webber, 2005).

AR signaling plays critical roles in prostate development, function, and pathogenesis. We reported that prostate progenitor/stem cells are AR-negative but, upon treatment with $1,25(OH)_2D_3$, they become AR-positive (Barclay et al., 2008; Maund, et al., 2011). AR is not a direct transcriptional target of $1,25(OH)_2D_3$ because it does not contain a VDRE, but we did

observe increased AR mRNA in response to $1,25(OH)_2D_3$; its mechanism of upregulation is unclear (Zhao, et al., 1999). Since AR signaling can contribute to prostate tumor growth, the induction of AR by $1,25(OH)_2D_3$ may not be considered an anti-tumor effect. However, the induction of AR by $1,25(OH)_2D_3$ signifies a transition from a less-differentiated prostate cell toward a more-differentiated prostate cell that is either less likely to become cancerous or, if already transformed, more responsive to therapeutic intervention such as castration. These hypotheses have yet to be tested *in vivo*. In LNCaP cells, growth inhibition by $1,25(OH)_2D_3$ has been shown to be dependent on AR (Miller, et al., 1992; Zhao, et al., 1997; Zhao et al., 2000). AR-mediated induction of IGFBP-3 has been implicated in this process (Peng, et al., 2008). The exact mechanism(s) of $1,25(OH)_2D_3$-induced differentiation is unknown, though differentiation is often preceded by an enrichment of cells in the G1 phase of the cell cycle (Studzinski & Harrison, 1999). Upregulation of p21 and p27 are implicated in differentiation of LNCaP and PC3 cells, and p27 is involved in senescence in a mouse model of prostate cancer (Campbell, et al., 1997; Majumder et al., 2008). This suggests that accumulation of prostate cells in G1 may precede $1,25(OH)_2D_3$-induced differentiation and/or senescence, but the mechanisms remain unknown.

Our group recently reported that $1,25(OH)_2D_3$ can induce senescence of prostate cancer cells *in vitro* (Axanova et al., 2010). Senescence is defined as a terminally-arrested state in which cells are metabolically active but cannot resume cell cycle progression (Muller, 2009), so induction of senescence is an additional form of $1,25(OH)_2D_3$-mediated growth suppression. Senescence has been observed in cases of PIN that do not progress to prostate cancer (Majumder, et al., 2008), so it is possible that additional senescence induced by $1,25(OH)_2D_3$ may impede prostate cancer progression. This has yet to be tested *in vivo*.

Another way that $1,25(OH)_2D_3$ may impede prostate cancer progression and metastasis is through inhibition of cellular invasion and migration. *In vitro* studies have shown that $1,25(OH)_2D_3$ decreases expression of alpha-6 and beta-4 integrins to inhibit the invasive capacities of prostate cancer cell lines (Sung & Feldman, 2000). $1,25(OH)_2D_3$ is known to induce E-cadherin in prostate cancer cells (Campbell, et al., 1997), and E-cadherin was recently reported to mediate $1,25(OH)_2D_3$-induced cellular adhesion that mitigates the metastatic capabilities of prostate cancer cells (J. W. Hsu et al., 2011). $1,25(OH)_2D_3$ has also been shown to regulate a range of matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs), also thought to mediate the effects of $1,25(OH)_2D_3$ on invasion of prostate cancer cells (Bao et al., 2006).

In vivo studies with $1,25(OH)_2D_3$ have been carried out primarily in xenograft models of prostate cancer as well as in the Dunning rat model of prostate cancer and, more recently, the $Nkx3.1^{+/-}$-$PTEN^{+/-}$ mouse model (Getzenberg et al., 1997; Lokeshwar et al., 1999; Banach-Petrosky et al., 2006; Trump et al., 2006). In the rat Dunning model, $1,25(OH)_2D_3$ and $1,25(OH)_2D_3$ analogs decreased tumor volumes and lung metastases, but the animals developed hypercalcemia. Use of $1,25(OH)_2D_3$ analogs alone, however, were sufficient to reduce PC3 and LNCaP xenograft volumes without inducing hypercalcemia (Schwartz et al., 1995; Blutt et al., 2000). $Nkx3.1^{+/-}$-$PTEN^{+/-}$ mutant mice develop high-grade PIN with the capacity for progression to advanced metastatic and androgen-independent prostate cancer (Kim et al., 2002; Abate-Shen et al., 2003). Sustained intravenous delivery of 46 ng/kg/day of $1,25(OH)_2D_3$ or vehicle control were administered to $Nkx3.1^{+/-}$-$PTEN^{+/-}$ pre-cancerous and cancerous cohorts of mice for 4 months (Banach-Petrosky, et al., 2006). Interestingly, $1,25(OH)_2D_3$ suppressed PIN formation in the pre-cancerous cohort, but it did not affect prostate cancer progression in the cancerous cohort. Furthermore, increased levels of the

VDR were observed in the pre-cancerous cohort after $1,25(OH)_2D_3$ administration, while there was only a modest increase in VDR in the cancerous cohort, which could account for the ineffectiveness of $1,25(OH)_2D_3$ on tumor progression in the cancerous cohort. These results suggest that prostate cancer cells may have aberrations in the vitamin D_3 response pathway. Therefore, vitamin D_3 may be more effective as a chemopreventative agent than as a chemotherapeutic.

6.1 Prostate stem cells and vitamin D_3

Accumulating evidence supports the presence of adult prostate-specific stem cells, which undergo self-renewal into an identical prostate stem cell and multi-lineage differentiation into the multiple epithelial cell types of the prostate (Burger et al., 2005; Barclay, et al., 2008; Goldstein et al., 2010). They serve to maintain prostate tissue homeostasis and to stimulate tissue regeneration after injury. There are many similarities between the signalling pathways found to regulate stem cell processes and those that regulate cancer progression, which has led to the cancer stem cell hypothesis (Reya et al., 2001; Maund & Cramer, 2009; Mimeault & Batra, 2010). The prostate cancer stem cell hypothesis proposes that a transformed prostate stem cell can give rise to a heterogeneous prostate tumor, and that the tumor cannot be ablated unless the cancer stem cells are eliminated.

The aim of chemoprevention is to impede tumor development at the earliest point in its progression. According to the cancer stem cell hypothesis, the target cell population for prostate cancer prevention would be the prostate stem/progenitor cells (Maund & Cramer, 2010). Stem cells intrinsically have an extended replicative capacity. Agents that limit this capacity and promote differentiation are promising chemopreventative agents. We have recently reported that $1,25(OH)_2D_3$ is growth-inhibitory in adult prostate stem/progenitor cells (Maund, et al., 2011). $1,25(OH)_2D_3$ can induce G1 and G2 cell cycle arrest, stimulate differentiation toward a luminal epithelial cell type, and trigger senescence in this cell population, supporting a relevant role for vitamin D_3 in prostate chemoprevention (particularly in light of the cancer stem cell hypothesis). We found that the cytokine interleukin-1 alpha is highly upregulated by $1,25(OH)_2D_3$ and is a novel mediator of $1,25(OH)_2D_3$-induced growth inhibition of prostate stem/progenitor cells. In addition, microarray data revealed that $1,25(OH)_2D_3$ can impact gene expression and signalling pathways involved in stem cell self-renewal and multilineage differentiation including Hedgehog, Wnt, and TGFβ signaling (Maund, et al., 2011). $1,25(OH)_2D_3$ regulates components of these pathways in other cell types as well (Sarkar et al., 2010; Tang et al., 2011). This work is just beginning to reveal the cellular and genomic impacts of $1,25(OH)_2D_3$ in the stem cell population. Furthermore, $1,25(OH)_2D_3$ has been shown to exert anti-proliferative and pro-differentiating effects on hematopoietic and skin progenitor cells (Liu et al., 1996; Lehmann et al., 2010). The identification of tissue-specific stem cells and their potential contributions to cancer initiation and progression is changing the way we approach cancer prevention and treatment. A major aim is to identify compounds that effectively target the stem cell population, and $1,25(OH)_2D_3$ is a promising candidate for further investigation.

7. Clinical studies

Most clinical trials involving $1,25(OH)_2D_3$ and $1,25(OH)_2D_3$ analogs are carried out in combination with chemotherapeutic agents, particularly the taxanes, and are tested in patients with castration-resistant prostate cancer. $1,25(OH)_2D_3$ analogs such as EB1089 and

22-oxacalcitriol (OCT) are VDR ligands designed to recapitulate the anti-proliferative effects of $1,25(OH)_2D_3$ while minimizing the effects on calcium homeostasis that often lead to hypercalcemia (Steddon et al., 2001). To date, no $1,25(OH)_2D_3$ analog has fared significantly better than $1,25(OH)_2D_3$ alone. There are still many studies missing that are necessary for designing accurate clinical trials with $1,25(OH)_2D_3$ and $1,25(OH)_2D_3$ analogs including determination of the maximum-tolerated and optimal doses, definitions of phase II single-agent and combination doses, and randomized phase II trials that compare $1,25(OH)_2D_3$ alone versus $1,25(OH)_2D_3$ in combination with a single chemotherapeutic agent. These issues must be resolved in order to generate accurate phase II and phase III clinical trial data (Trump et al., 2010).

A high-dose formulation of $1,25(OH)_2D_3$ called DN-101 was tested for safety and efficacy in the ASCENT I (Androgen-independent prostate cancer Study of Calcitriol Enhancement of Taxotere) phase II trial in combination with docetaxel (Brawer, 2007). DN-101 administration was associated with improved survival but it did not impact PSA response (Beer et al., 2007). A large phase III trial (ASCENT II) was terminated in 2007 due to greater death rates in the experimental arm (docetaxel, prednisone, and DN-101) than the control arm (docetaxel, prednisone, and placebo). However, ASCENT II was not accurately designed to test the efficacy of DN-101 versus the placebo (Trump, et al., 2010). The docetaxel administration schedule and the DN-101 dosages were not consistent with those previously established. Since the optimal dose and maximum-tolerated dose for oral $1,25(OH)_2D_3$ remain undefined, the DN-101 doses used in the ASCENT trials were based on convenience: a weekly oral dose of 0.5 μg/kg. In pre-clinical trials, however, intravenous administration of >1 μg/kg $1,25(OH)_2D_3$ was required for anti-tumor effects (Trump, et al., 2010). Although the results from the ASCENT II trial were ambiguous, they highlighted several questions that need to be resolved before designing new $1,25(OH)_2D_3$ clinical trials.

Vitamin D_3 oral supplementation doses are still being defined; they vary depending on the desired endpoint and on individual vitamin D_3 metabolic capacity (Bischoff-Ferrari, 2009). Individuals with serum $25OHD_3$ levels less than 30 ng/mL are considered to be vitamin D_3 deficient. A recent retrospective analysis measured the impact of 8,000 IU/day vitamin D_3 supplementation on $25OHD_3$ levels in 2198 cancer patients (Vashi et al., 2010). They found that patients with baseline $25OHD_3$ levels between 20 and 32 ng/mL responded to supplementation better than those with baseline levels <20 ng/mL. Additionally, patients with prostate cancer were the most responsive to vitamin D_3 supplementation, in terms of the number of individuals whose $25OHD_3$ levels were >32 ng/mL after 8 weeks of supplementation. This finding supports further clinical investigations of vitamin D_3 in prostate cancer prevention and treatment. This study reported that 8,000 IU/day for 8 weeks was a safe and effective regimen for prostate and lung cancer patients, and they suggested that supplementation levels should be higher in colorectal and pancreatic cancer patients (Vashi, et al., 2010). Further studies are required to define maximum-tolerated and optimal doses for patients with different types of cancers.

The range of serum $25OHD_3$ associated with cancer prevention is 60-80 ng/mL (CF Garland et al., 2009). A recent community-based study of voluntary vitamin D_3 supplementation sought to define the doses necessary to reach serum $25OHD_3$ levels in this range (C. F. Garland et al., 2011). They reported that total vitamin D_3 intake from 9,400 to 17,400 IU/day would be necessary to achieve serum $25OHD_3$ levels of 30-50 ng/mL in this population. Additionally, they reported no toxicity from up to 40,000 IU/day. They proposed that most individuals should supplement their vitamin D_3 intake by 4,000-8,000 IU/day in order to

reach serum $25OHD_3$ levels associated with cancer prevention. This study will help shape additional clinical trials for vitamin D_3-based chemoprevention, and in the meantime it will help inform the public about the importance of sufficient vitamin D_3 supplementation. However, there is much controversy over the recommended vitamin D_3 supplementation doses. In 2010 the Institute of Medicine recommended a daily dose of 600 IU vitamin D_3, with a tolerable upper limit of 4,000 IU/day. However, the long-term benefits of vitamin D_3 doses in this range are unknown, and others (such as C.F. Garland et al., 2011 and Vashi et al., 2010) argue that 600 IU is insufficient for significant clinical benefits and that the tolerable upper limit exceeds 4,000 IU/day. It is becoming clear that the optimal daily vitamin D_3 dose is dependent on 1) the individual's baseline serum $25OHD_3$ level, 2) the individual's vitamin D_3 metabolic capacity, and 3) the individual's health status and lifestyle (diabetic, prostate cancer vs. colorectal cancer patient, etc.). For these reasons and for the lack of definititve clinical studies there is controversy surrounding universal recommended vitamin D_3 doses. Future work should focus on resolving this continuing controversy.

8. Conclusion

Further understanding of the mechanisms of action behind $1,25(OH)_2D_3$ signaling in the prostate and a deeper understanding of prostate stem cell biology will help potentiate the chemopreventative effects of vitamin D_3 and promote its concomitant use in primary and adjuvant prostate cancer therapies. Prostate cancer is a slow-growing disease that develops over the course of decades and typically affects men late in life. Treatment decisions are based on tumor severity and rate of PSA change, and some prostate tumors do not even progress to stages necessary for therapeutic intervention. The aim of prostate cancer chemoprevention is to delay tumor onset and progression. Chemopreventative strategies that delay prostate tumor onset or progression by even five years will drastically decrease the incidence of clinically-relevant prostate cancer and will reduce the need for prostate cancer treatment. Current findings that $1,25(OH)_2D_3$, the metabolically active form of naturally-derived and FDA-approved vitamin D_3, is effective in regulating prostate progenitor/stem cell growth and differentiation supports the use of vitamin D_3 as a safe and effective chemopreventative agent for prostate cancer. Thorough studies assessing the efficacy of vitamin D_3 or its analogs in the clinical therapeutic setting are still needed.

9. References

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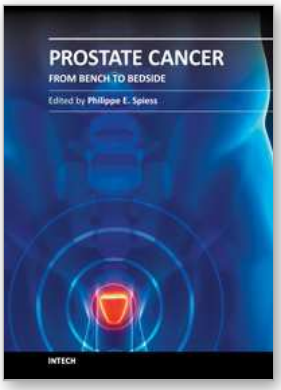

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The present textbook highlights many of the exciting discoveries made in the diagnosis and treatment of prostate cancer over the past decade. International thought leaders have contributed to this effort providing a comprehensive and state-of-the art review of the signaling pathways and genetic alterations essential in prostate cancer. This work provides an essential resource for healthcare professionals and scientists dedicated to this field. This textbook is dedicated to the efforts and advances made by our scientific community, realizing we have much to learn in striving to some day in the not too distant future cure this disease particularly among those with an aggressive tumor biology.

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