Oncology Research, Vol. 22, pp. 129–137
Printed in the USA.

0965-0407/15 $90.00 + .00
DOI: http://dx.doi.org/10.3727/096504015X14267282610894
E-ISSN 1555-3906
www.cognizantcommunication.com

Review

Role of Vitamin D Metabolism and Activity on Carcinogenesis

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The vitamin D endocrine system regulates a broad variety of independent biological processes, and its deficiency is associated with rickets, bone diseases, diabetes, cardiovascular diseases, and tuberculosis. Cellular and molecular studies have also shown that it is implicated in the suppression of cancer cell invasion, angiogenesis, and metastasis. Sunlight exposure and consequent increased circulating levels of vitamin D are associated with reduced occurrence and a reduced mortality in different histological types of cancer, including those resident in the skin, prostate, breast, colon, ovary, kidney, and bladder. The vitamin D receptor (VDR) as a steroid hormone superfamily of nuclear receptors is highly expressed in epithelial cells at risk for carcinogenesis, providing a direct molecular link by which vitamin D status impacts on carcinogenesis. Because VDR expression is retained in many human tumors, vitamin D status may be an important modulator of cancer progression in persons living with cancer. The aim of this review is to highlight the relationship between vitamin D, VDR, and cancer, summarizing several mechanisms proposed to explain the potential protective effect of vitamin D against the development and progression of cancer.

Key words: Vitamin D; Vitamin D receptor (VDR); Carcinogenesis; Cancer

INTRODUCTION

Laboratory and epidemiological data published over the past several years have contributed to the hypothesis that vitamin D metabolites inhibit cancer development at various tissue sites. In 1937, Peller and Stephenson hypothesized that sunlight exposure reduces the risk of cancer (1), and Apperly demonstrated an association between latitude and cancer mortality in 1941 (2). Four decades later, Garland et al. hypothesized that poor vitamin D status accounts for an elevated risk of colon, breast, and ovarian cancers at higher latitudes in the US (3,4). Schwartz and colleagues hypothesized a similar relationship for prostate cancer (5,6). More recently, Grant demonstrated an inverse correlation between regional type B ultraviolet (UV-B) radiation levels and mortality rates of many cancers, particularly digestive organ cancers, and found that in males approximately 80% of the cancers attributable to low regional solar UV-B were digestive system cancers (7). Mizoue also found an inverse correlation between averaged annual solar radiation levels and mortality from digestive system cancers (i.e., esophagus, stomach, colon, rectum, pancreas, gallbladder, and bile ducts) but not other cancer types in Japan (8).

THE VITAMIN D SYSTEM

The vitamin D system includes a group of lipid-soluble steroids and their respective metabolites. There are two major forms of vitamin D in nature: ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3). Vitamin D_2 is photochemically synthesized in plants or is acquired by a diet of fortified milk products, while vitamin D_3 is produced in the skin of animals and humans in response to sunlight too, in particular to UV-B radiations of appropriate wavelength: 270–300 nm. In most countries in Europe and in the US, the requirement of vitamin D is given by 90% of the 7-dehydrocholesterol cholesterol synthesis in the skin from solar irradiation, and only about 10% is taken up by the diet (9). The classical synthetic pathway involves 25- and 1-α-hydroxylation of vitamin D_2 and D_3 in the liver and kidney, respectively. First, hydroxylation occurs in the liver, and it is led to generate 25(OH) D_3. 25(OH)D_3 enters the systemic circulation, and it has a

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half-life of 12–19 days. Second, hydroxylation occurs in the kidneys, and it constitutes the most biologically active hormonal form of vitamin D: $1,25(OH)_2D_3$ (calcitriol) (Fig. 1). The serum levels of $25(OH)D_3$ are a reflection of overall vitamin D status in the body. There are two principal enzymes involved in the formation of circulating $1,25(OH)_2D_3$ from dietary absorbed or skin synthesized vitamin D: the hepatic microsomal or mitochondrial vitamin D 25-hydroxylase (CYP27A1) and the renal mitochondrial enzyme 1α-hydroxylase (CYP27B1) for vitamin D and $25(OH)D_3$, respectively (10). These hydroxylases belong to a class of proteins known as cytochrome P450

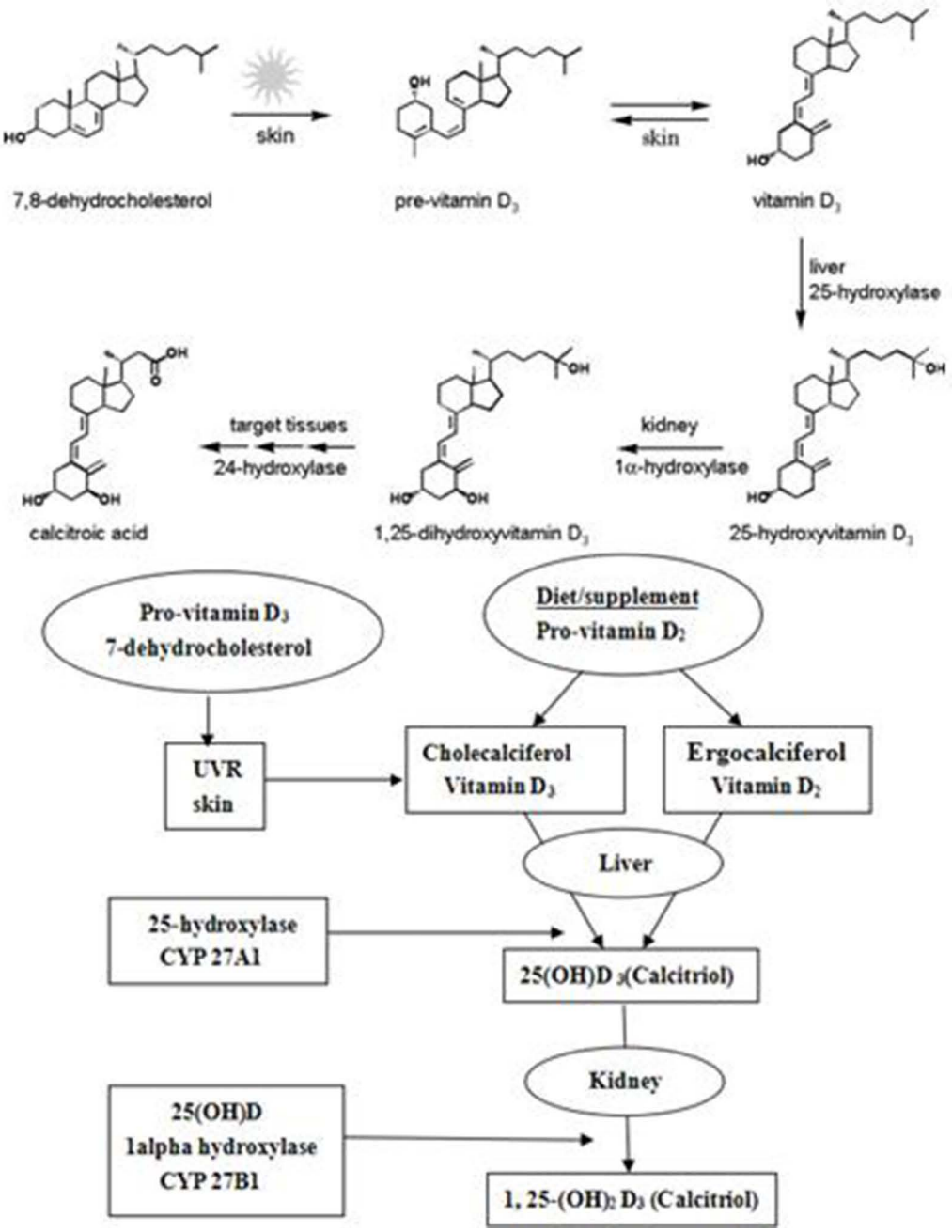

Figure 1. Vitamin D and its metabolites. The vitamin D requirement is from the exposure of skin to sunlight, while a minor portion may be obtained from dietary sources. Upon exposure to ultraviolet B, 7-dehydrocholecalciferol in the skin is photolyzed to form a 9,10-seco-sterol pro-vitamin D_3. Vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol) made in the skin or ingested in the diet can be stored in and then released from fat cells. The synthetic pathway involves 25- and1-α-hydroxylation of vitamin D_2 and D_3, in the liver and kidney, respectively. First hydroxylation occurs within the liver and lead to the formation of $25(OH)D_3$ or calcidiol; second hydroxylation occurs within the kidneys and constitutes the most biologically active hormonal form of vitamin D: $1,25(OH)_2D_3$ or calcitriol.

mixed function monooxidases. In recent years, extrarenal activity of $25(OH)D_3$-1α-hydroxylase (CYP27B1) has been reported in various cell types including macrophages, keratinocytes, prostates, and colon cancer cells (11,12). It was shown that $1,25(OH)_2D_3$ is produced locally in several tissues. It has been demonstrated that potential vitamin D target tissues (e.g., colon, prostate, breast, lung, pancreas) can synthesize and degrade calcitriol. Local production and degradation of calcitriol have been suggested to represent key factors in several types of human cancer (13–15).

THE VITAMIN D RECEPTOR

The vitamin D receptor (VDR) belongs to the superfamily of transacting transcriptional regulatory factors, which includes the steroid and thyroid hormone receptors as well as the retinoid-X receptors and retinoic acid receptors (16). It is an endocrine member of the nuclear receptor superfamily (17) because it is the only nuclear protein that binds the nuclear hormone $1,25(OH)_2D_3$ with high affinity. The human VDR protein is a 427-amino acid peptide that has a DNA-binding domain, a ligand-binding domain, and activating domains. The VDR protein contains two zinc finger motifs that bind to the DNA, while the ligand-binding domain, located at the carboxy l terminus, changes conformation when $1,25(OH)_2D_3$ binds, allowing interaction with transcription factors. Activated VDR forms a heterodimer with the retinoic acid X receptor, which translocates to the nucleus (18,19) and binds to the vitamin D response element in the promoter region of target genes (20). VDR protein is encoded by a large gene (>100 kb) located on chromosome 12q12-14. The VDR gene encompasses two promoter regions, eight protein-coding exons, and six untranslated exons (21). It has an extensive promoter region capable of generating multiple tissue-specific transcripts. It has been demonstrated that VDR requires heterodimerization with auxiliary proteins for effective DNA interaction.

ROLES OF VITAMIN D AND VITAMIN D RECEPTOR ON CARCINOGENESIS

Several levels of evidence support the relationships among vitamin D, VDR, and cancer: (a) solar UV-B irradiance and vitamin D reduce the risk of incidence and death for many types of cancer, (b) a low intake of vitamin D is associated with a increased risk of cancer; (c) high circulating levels of vitamin D are associated with reduced risk of developing cancer; (d) the aggressiveness of a cancer is lower in summer when the production of vitamin D is higher; (e) polymorphisms of VDR genes affect the risk of developing cancer. These relationships are supported by in vitro studies and epidemiologic studies. A lot of in vitro studies have demonstrated that exposure of tumor cells to high concentrations of vitamin D compounds inhibits their proliferation and induce differentiation. Numerous epidemiologic studies have shown the association between factors expected to reduce vitamin D levels (e.g., geography and latitude, history of sun exposure, lifestyle) and the increased rates of cancer, highlighting the protective effects of sunlight and high levels of vitamin D on various types of tumors (2–4,6–9) (Fig. 2).

Colorectal Cancer (CRC)

The ability of $1,25(OH)_2D_3$ to induce differentiation in colon cancer cells was recognized more than 20 years ago (22), and there is substantial evidence supporting an inverse association between circulating $25(OH)D_3$ and CRC risk; meta-analyses and systematic reviews have observed a 50% lower risk of CRC comparing extreme quintiles of $25(OH)D_3$ (23,24). Several mechanisms have been hypothesized to underlie this association, some of which may be shared by pathways associated with the putative functional consequences of CRC susceptibility SNPs proximal to VDR DNA binding sites. In addition, vitamin D signaling occurs through binding of the active form $1,25(OH)_2D_3$ to VDR along specific genomic sequences known as VDREs, which act to activate or repress gene transcription. Several prospective epidemiologic studies, including from this cohort (1), have consistently found an inverse association between higher prediagnostic $25(OH)D_3$ levels and CRC risk. Similar to the results for CRC incidence, higher vitamin D levels have been suggested to be inversely associated with CRC-specific and overall mortality among persons diagnosed with CRC in a small number of studies (25–27). Findings from the Nurses' Health Study and the Health Professionals Follow-up Study have shown an association between either higher prediagnostic $25(OH)D_3$ levels or higher predicted postdiagnosis $25(OH)D_3$ scores and improvement in CRC-specific and overall survival (28). However, one study (29) was limited by its relatively small sample size and the other (30) by its use of predicted, not actual, postdiagnosis vitamin D levels. Another study from Japan has suggested that higher $25(OH)D_3$ levels at surgery are associated with a better survival (31), but it is also limited by small sample size.

Breast Cancer

In 1990, Garland et al. first reported an inverse association between total average annual sunlight energy that strikes the ground and age-adjusted breast cancer mortality in the US (4). Several case-control studies have focused on the association between breast cancer risk and circulating levels of $25(OH)D_3$. Results have consistently revealed an inverse association between $25(OH)D_3$ and breast cancer (32–34). Other studies have examined the effects of vitamin D on mammary carcinogenesis in vitro and in animal models, and the data support a protective role for vitamin D in breast cancer development (35,36). In addition, mice

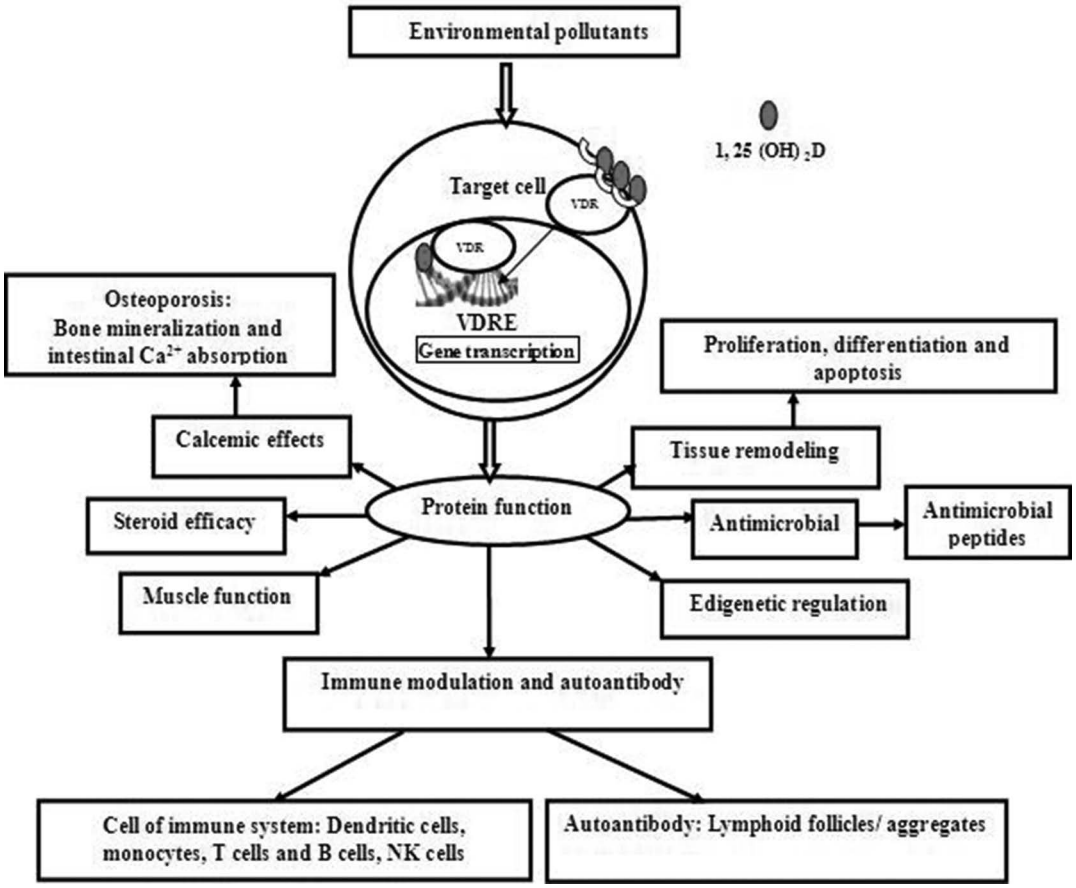

Figure 2. The role of vitamin D/VDR in environmental agent-mediated deregulation. Environmental agents, such as cigarette smoke, particulate matter (less than 10 μm, PM10), ultrafine particles, inhaled oxidants, ozone, and aldehydes activate vitamin D receptor (VDR) and affect different downstream cellular and molecular targets as a result of vitamin D-mediated deregulation. Calcitriol is bound to VDR and vitamin D response elements (VDRE). In conjunction with several transcription factors, this complex led to the transcription of vitamin D-responsive genes. The major cellular and molecular functions affected due to vitamin D/VDR deregulation include calcemic effects, antimicrobial, tissue remodeling, immune modulation and autoantibody production, muscle function, steroid efficacy, epigenetic regulation, immune response, inflammation, and cellular proliferation, differentiation, and apoptosis.

rendered vitamin D deficient exhibit enhanced cancer development (37), as do VDR knockout mice (38). Several mechanisms underlying the inhibitory effects of vitamin D on the growth of breast cancer cells have been proposed. Six case-control studies have examined the relationship between vitamin D intake and breast cancer risk. The largest was an Italian study that included 2,569 cases and 2,588 controls in which a 78-item food frequency questionnaire was used to collect information on dietary sources of vitamin D. Women with the highest vitamin D intake (>190 IU) had a 34% lower risk for breast cancer than those with the lowest vitamin D intake (<60 IU) (39). The odds ratios (ORs) were 0.80 [95% confidence interval (CI) 0.64–0.99] and 0.78 (95% CI 0.66–0.92) among pre- or perimenopausal and postmenopausal women, respectively (40). The strengths of the study are the large dataset and the use of a reproducible and valid food frequency questionnaire (41). The study results were adjusted for many known risk factors for breast cancer. Limitations of the study include the absence of information on sun exposure or serum levels of vitamin D and the use of hospital-based controls. Two other case-control studies also reported a relatively lower breast cancer incidence with greater vitamin D intake (42). A similar finding was reported in the Women's Health Study cohort that included 10,578 premenopausal women and 20,909 postmenopausal women (43). Higher intake of vitamin D was associated with a lower risk for breast cancer in premenopausal women (OR 0.65; 95% CI 0.42–1.00) but not in postmenopausal women (OR 1.30; 95% CI 0.97–1.13) (44). Other studies that included predominantly postmenopausal women either showed a trend toward a lower breast cancer risk with higher vitamin D intake (45,46) or did not show a protective effect of higher vitamin D intake for breast cancer.

Lung Cancer

In vitro and in vivo studies have demonstrated the antiproliferative effects of $1,25(OH)_2D_3$ in lung cancer. Higashimoto et al. reported that $1,25(OH)_2D_3$ inhibited the growth of lung cancer cell lines (47). This effect was mediated by VDR and affected cell cycle regulation in squamous cell carcinoma (SCC) (48). $1,25(OH)_2D_3$ has also been shown to inhibit lung tumor growth and lung metastases in mouse models (49). Owing to the high number of blood vessels in the lungs, circulating tumor cells easily metastasize there and have proven to be difficult to treat with chemotherapy. Nakagawa et al. demonstrated using Lewis lung carcinoma cells: green fluorescent protein (GFP) construct in a murine model that $1,25(OH)_2D_3$ strongly inhibited metastatic growth in the lung of VDR null mice (50). In parallel in vitro experiments using Lewis lung carcinoma cells, it was noted that VEGF mRNA, an indicator of angiogenesis, was suppressed following treatment with $1,25(OH)_2D_3$ at 24 h. The data suggests that $1,25(OH)_2D_3$ directly reduces tumor metastatic growth in lung cancer cells (51). Several studies reported normal tracheobronchial cells have high levels of 1α-hydroxylase (CYP27B1) enzyme that leads to increased local production of $1,25(OH)_2D_3$ and low levels of CYP24A1 that leads to increased breakdown. This is in contrast to lung cancer cells that show higher CYP24A1 expression and low to absent CYP27B1. Reciprocal changes that involve an increase in CYP27B1 mRNA and a decrease in CYP24A1 mRNA may play a pivotal role in maintaining the local tissue level of $1,25(OH)_2D_3$ to be antiproliferative to lung cancer cells (51–53). VDR expression is ubiquitous, and there are data to suggest that higher nuclear VDR expression in lung cancer correlates with improved survival (52). This may relate to increased genomic effects mediated by nuclear VDR on cell cycle-related genes that lead to apoptosis, but this is yet to be confirmed in lung cancer. There are also data to suggest that VDR expression is higher in well-differentiated SCC compared with normal or dysplastic bronchial epithelium (53). This finding is intriguing and worthy of further study to elucidate the relationship between the differentiation status of lung cancer and vitamin D. Chen et al. show a high-level expression of CYP24A1 in subsets of lung cancers and demonstrate an inverse relationship between high CYP24A1 expression and antiproliferative activity of vitamin D (54). Earlier reports regarding increased expression of CYP24A1 in lung adenocarcinoma (55) found that the tumors that had a higher CYP24A1 expression were more poorly differentiated, as well as associated with poor survival. In a parallel in vitro experiment, it was demonstrated that lung cancer cell lines with high CYP24A1 expression had a poorer response to the antiproliferative effects of $1,25(OH)_2D_3$ compared with those with lower levels of CYP24A1 mRNA. Ramnath et al. confirmed that CYP24A1 expression was indeed highly expressed in lung cancer compared with nontumorigenic normal bronchial epithelium (56). Analysis of non-small-cell lung carcinoma (NSCLC) cell cultures revealed time-dependent loss of $1,25(OH)_2D_3$ coincident with the appearance of CYP24A1-generated metabolites. Specific inhibition of CYP24A1 slowed the loss of $1,25(OH)_2D_3$ and increased the $1,25(OH)_2D_3$ half-life. These data suggest that increased CYP24A1 expression in lung tumors restricts $1,25(OH)_2D_3$ antitumor activity.

Prostate Cancer

There is striking geographical variation, such that regional intensity of exposure to solar ultraviolet radiation (UVR) is inversely associated with prostate cancer incidence and mortality in fair-skinned populations (57). Furthermore, inverse associations of cumulative UVR exposure, adult sunbathing, childhood sunburn, and regular holidays in sunny climates with prostate cancer risk have been observed at the individual level (58,59). The effects of UVR on prostate cancer may be mediated by circulating vitamin D levels, the main environmental source of which is sun exposure, which stimulates vitamin D synthesis in the deeper layers of the epidermis. A study based on the Health Professionals Follow-up Study (HPFS) and the Physicians Health Study (PHS) showed that patients with $25(OH)D_3$ levels <40.5 nmol/L were more likely to die from prostate cancer (HR 1.59, 95% CI 1.06–2.39) compared with levels >95.9 nmol/L (60). From both cohorts, prediagnostic serum samples were used. The association was largely explained by the association between low $25(OH)D_3$ levels and cancer of advanced stage and higher Gleason score. The association tended to be stronger when restricting the analyses to patients with samples collected within 5 years of the cancer diagnosis. Similar results were observed in a Norwegian study of prostate cancer patients, based on serum samples collected ±3 months from the date of the cancer diagnosis (61). The risk of cancer death in patients with $25(OH)D_3$ levels >80 nmol/L was 0.16 (95% CI 0.05–0.43) relative to patients with levels <50 nmol/L. A risk reduction was also seen in patients with $25(OH)D_3$ levels 50–79 nmol/L (RR 0.33, 95% CI 0.14–0.77). Mice with prostate epithelial cell-specific deletion of VDR (PEC VDRKO) were generated to study the direct effects of VDR on epithelial cell turnover during castration and in response to testosterone repletion. PEC VDRKO mice exhibit lower rates of apoptosis in response to castration and higher rates of proliferation in response to testosterone administration than control mice. These data show that low vitamin D status and VDR deletion alter cell turnover and hormonal responsiveness in normal prostate tissue changes that likely contribute to an increased susceptibility of VDR null mice to PIN and tumorigenesis.

Skin Carcinogenesis

UV induces various types of DNA damage either photochemically or by UV activation of endogenous photoreceptors that create genotoxic free radicals that modify the DNA molecular structure. The most frequently occurring photolesion in sun-exposed human skin is the cyclobutane pyrimidine dimer (CPD) (62,63) particularly thymine dimers, which are induced primarily by UV-B, and also by UV-A to a lesser extent (64,65). CPDs are produced by the dislocation of double bonds in two adjacent pyrimidines by UV absorption, resulting in a cyclobutane ring conformation linking the two nucleobases as a dimer (66,67). Many studies have shown that $1,25(OH)_2D_3$ reduces thymine dimers in irradiated skin cells in vitro (68) and also in vivo in mouse (69) and human skin (70). Thymine dimers are also reduced in irradiated skin cells in the presence of the low calcemic rapid acting cis-locked nongenomic analogs, $1,25(OH)_2$-lumisterol$_3$(JN) and $1,25(OH)_2$-7-dehydrocholesterol (JM) in vitro (71) and in mouse skin (69) and also by the transcriptionally active hybrid 1-hydroxymethyl-16-ene-24,24-difluoro-25-hydroxy-26,27-bis-homovitamin D_3. Evidence that the vitamin D photoprotective effect on reductions in thymine dimer DNA damage is via the rapid nongenomic pathway is demonstrated with various vitamin D-like compounds. As noted above, studies by our group have shown that the transcriptionally nonactive $1,25(OH)_2$-lumisterol$_3$ protects against UV-induced thymine dimers. Of relevance to the mechanism of action of vitamin D compounds in photoprotection, the coincubation of skin cells with $1,25(OH)_2D_3$ and 25-dehydro-1α-hydroxyvitamin D_3-26, 23S-lactone (TEI-9647), an antagonist of the genomic action of $1,25(OH)_2D_3$, did not alter the protective effects of $1,25(OH)_2D_3$ on thymine dimers. In contrast, coincubation with 1β, 25-dihydroxyvitamin D_3 (HL), an antagonist of the nongenomic pathway, abolished the photoprotective effect of $1,25(OH)_2D_3$ (72,73).

Other Tumors

The pathway of vitamin D seems to be involved in the development of endocrine and neuroendocrine tumors too. Studies by Grant as well as by Freedman et al. on cancer mortality rates in the US and Europe, using latitude or DNA-weighted solar UV-B exposure as surrogate endpoints for photoproduction of vitamin D_3 in the skin, found a highly significant association with the incidence of esophagus, stomach, pancreas, bladder, ovary, and uterus, as well as non-Hodgkin lymphoma (3,6,74–75).

THE EFFECT OF VITAMIN D AND CALCIUM ON CARCINOGENESIS

Studies on tissue-specific expression of the CYP27B1-encoded 25-hydroxyvitamin D-1α-hydroxylase and of the extracellular calcium-sensing receptor (CaR) have led to an understanding of how locally produced $1,25(OH)_2D_3$ and extracellular calcium act jointly as key regulators of cellular proliferation, differentiation, and function. Thus, impairment of antimitogenic, proapoptotic, and prodifferentiating signaling from the $1,25(OH)_2D_3$-activated VDR and from the CaR in vitamin D and calcium insufficiency has been implicated in the pathogenesis of the aforementioned types of cancer. $1,25(OH)_2D_3$ and calcium interact in modulating cell growth in different ways: (a) signaling pathways from the VDR and the CaR converge on the same downstream elements, for example, of the canonical Wnt pathway; (b) high extracellular calcium modulates extrarenal vitamin D metabolism in favor of higher local steady-state concentrations of $1,25(OH)_2D_3$; (c) $1,25(OH)_2D_3$ may upregulate expression of the CaR and thus augment CaR-mediated antiproliferative responses to high extracellular calcium. Grau et al. studied the effect of vitamin D and calcium supplementation on recurrence of colorectal adenomas, who found that calcium supplementation was effective only in patients with normal $25(OH)D_3$ values (76). Conversely, high $25(OH)D_3$ levels were associated with a reduced risk of adenoma recurrence only among subjects receiving calcium supplements. Synergistic actions of calcium and vitamin D are probably the reason why high intake of low-fat dairy products is associated with a reduced risk of breast cancer in premenopausal women. Finally, results from studies in animal models of human autoimmune diseases indicated that calcium supplementation was necessary to optimize the therapeutic effect of vitamin D. Therefore, vitamin D, its analogs, and calcium should be further evaluated in clinical trials in patients with early cancer. In the case of established cancer, it is reasonable to consider that combination therapy will be required and that vitamin D, calcium, or an analog added to other effective therapies will likely increase the benefit of the standard therapy and perhaps reduce some of the side effects.

CONCLUSIONS AND FUTURE PERSPECTIVES

This review highlights the relationship between vitamin D, VDR, calcium, and cancer, summarizing several mechanisms proposed to explain the potential protective effect of vitamin D against the development and progression of cancer. It suggests vitamin D, its analogs, and calcium should be further evaluated in clinical trials in patients with early cancer.

ACKNOWLEDGMENTS: This research was supported by the National Natural Science Foundation of China (Project No. 31260268), the cooperation project with the United Gene High-Tech Group and Doctor Startup Project.

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