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Molecular Actions of Vitamin D Contributing to Cancer Prevention

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Abstract

The population-based relationship between low vitamin D status and increased cancer risk is now generally accepted. While these relationships are between serum 25 hydroxyvitamin D and cancer, cell-based studies show that the metabolite 1,25 dihydroxyvitamin D is biologically active and influences cell biology relevant to cancer through vitamin D receptor gene-mediated transcription. This review examines this paradox and also discusses the cell and gene targets influenced by 1,25 dihydroxyvitamin D that may account for the anti-cancer actions of vitamin D. A review of the literature shows that while vitamin D-induced growth arrest and apoptosis of tumor cells or their non-neoplastic progenitors are plausible mechanisms, other gene targets related to DNA repair and immunomodulation, and other cell targets such as the stromal cells and cells of the immune system, may be regulated by 1,25 dihydroxyvitamin D and contribute to vitamin D mediated cancer prevention.

Keywords

1,25 dihydroxyvitamin D; 25 hydroxyvitamin D; proliferation; apoptosis; transcription; vitamin D receptor

1. Introduction

Although vitamin D function is most closely associated with the control of calcium and bone metabolism (1) it is proposed to have a variety of other biological roles, including anti-cancer effects. This line of research was initiated nearly 30 years ago when Garland and Garland first proposed that the North-South geographic gradient in cancer rates (high in North, low in South) first observed by Apperly (2) was due to the UV light-induced production of vitamin D in the skin (3). This hypothesis was later extended to the protection of prostate cancer by vitamin D (4). In a recent commentary to celebrate the 25th anniversary of the Garland and Garland paper, Giovannucci (5) outlined that various levels of support that exist from population-based studies to support the vitamin D-cancer chemoprevention hypothesis: i.e. high vitamin D intake is associated with reduced colon cancer risk, high pre-diagnostic serum levels of 25 hydroxyvitamin D (25OH D) relate to low cancer risk, fatality for cancer of the colon, prostate, and breast is 30% lower in fall and summer when skin vitamin D production is high, composite score predictors of 25OH D levels show that low vitamin D status is associated with increased risk of a variety of cancers, and polymorphisms in the genes encoding proteins involved in the vitamin D signaling pathway relate to altered cancer risk. These lines of evidence suggest that

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vitamin D or its metabolites have a direct inhibitory action on the development and progression of various cancers. However, the mechanistic foundation for these relationships are still being determined. In this review I summarize our current thinking on the mechanisms used by vitamin D metabolites to influence the development of cancer.

2. Vitamin D metabolism and cellular actions of 1,25 dihydroxyvitamin D (1,25(OH)₂ D)

2.1 Vitamin D metabolism and the production of the active hormone, 1,25 dihydroxyvitamin D (1,25(OH)₂ D)

Vitamin D has been termed the “sunshine vitamin” because it can be produced from 7-dehydrocholesterol when skin is exposed to UV B light. However, regardless of whether vitamin D comes from the skin or the diet, vitamin D is transported in the circulation by the Vitamin D Binding Protein (DBP) (6). Once delivered to the liver, vitamin D is hydroxylated on its side chain to form 25 hydroxyvitamin D (25OH D), a stable metabolite of the vitamin D whose serum levels are used to assess of vitamin D status. The production of the hormonally active form of vitamin D, 1,25(OH)₂ D, was traditionally thought to be accomplished exclusively within the kidney, but new evidence suggests there is extra-renal production of this hormone that may have relevance to cancer prevention (see below). Renal 1,25(OH)₂ D production is mediated through the 1 alpha hydroxylase (CYP27b1); the renal expression of the gene for this enzyme is activated by PTH and suppressed by 1,25(OH)₂ D (7). Once produced in the kidney, 1,25(OH)₂ D is released into the serum and acts as an endocrine hormone on the intestine, bone, and kidney to control calcium metabolism. Although there is controversy regarding the role renal 1,25(OH)₂ D production in cancer prevention, this is the metabolite responsible for the anticancer actions of vitamin D at the cellular level.

2.2 Question: What are the target cells of 1,25(OH)₂ D action in cancer prevention?

Cancer is a complex and heterogeneous disease that is characterized by the accumulation of mutations in genes that control cellular processes such as cell proliferation, differentiation, apoptosis, cell migration, and DNA repair. This model of sequential acquired mutation is best characterized for the cancer of the distal colon where mutations in four specific genes accumulate as the colon cancer moves through the stages of initiation, promotion, and progression, i.e. APC loss of function, k-ras activation, SMAD loss of function, and p53 loss of function (8). However, such a well described course of events does not define cancers of the proximal colon where mutations in genes encoding mismatch repair enzymes are more common (9). In other cancers the molecular etiology is even less clear. As a result, researchers interested in cancer preventions should appreciate that what one learns in one cancer may not apply to another. In addition, since the cancer cell changes dramatically from the initiation steps through to the development of tumor or the metastasis of tumor cells to other tissues, there may also be stage-specific differences in the impact of an agent on cancer cells (see below).

With this in mind, the traditional thinking has been that the target cells for the anti-cancer action of vitamin D are tumor cells and the normal cell types within tissues that transform into tumor cells. The best-studied non-calcium regulatory effects of 1,25(OH)₂ D is the growth arrest of proliferating epithelial cells from the skin, breast, colon, and prostate. This phenomenon was first reported by Colston et al., who showed a dose-dependent decrease in growth rate of melanoma cells treated with 1,25(OH)₂ D (10). Growth inhibitory properties of 1,25(OH)₂ D were subsequently reported for tumor-derived cells from the colon (11), breast (12) and prostate (13). Others have reported that 1,25(OH)₂ D influences apoptosis, however this effect is not uniformly observed. For example while MCF-7 breast cancer cells (14) and a variety of colon

cancer cell lines (15) become apoptotic after $1,25(\text{OH})_2 \text{D}$ treatment, the prostate cancer cell line LNCaP does not (16) even though $1,25(\text{OH})_2 \text{D}$ treatment causes LNCaP cell growth arrest.

Although most cell-based vitamin D research has focused on the impact of $1,25(\text{OH})_2 \text{D}$ on either tumor cells or their non-neoplastic progenitors, there is also evidence that other cells that exist in the tissue or tumor microenvironment are targets of vitamin D action. For example, in the prostate the communication between epithelial cells and the stromal cells surrounding them is critical for the progression of cancer in that organ (17). Lou et al. (18) have reported that $1,25(\text{OH})_2 \text{D}$ can suppress the growth of prostate stromal cell lines but is not yet clear if it can alter stromal-epithelial cell communication. Recent data shows that inflammation is a critical part of carcinogenesis in the colon, liver, and stomach (19) and it has been proposed to be a part of the etiology of prostate cancer (20). In this light, the immune system becomes an important cell target for limiting cancer. Using data from a variety of disease states, $1,25(\text{OH})_2 \text{D}$ has been shown to modulate the number or activity of many types of immune cells (21). In general, $1,25(\text{OH})_2 \text{D}$ promotes immunotolerance and immunosuppression. It does so by altering dendritic cell differentiation and the function of tolerogenic dendritic cells (22), suppressing $\text{NF}\kappa\text{B}$ signaling necessary for T helper cell activation (23), and increasing the activity of regulatory T cells necessary for immunosuppression (24). These actions would be expected to protect tissues from pro-inflammatory stresses that promote cancer but the interaction between vitamin D, inflammation, and cancer has not been tested.

2.3 Molecular mechanism of $1,25(\text{OH})_2 \text{D}$ signaling

2.3.1 Transcriptional activation through the vitamin D receptor (VDR)—It is well established that the primary molecular action of $1,25(\text{OH})_2 \text{D}$ is to initiate gene transcription by binding to the vitamin D receptor (VDR), a member of the steroid hormone receptor superfamily of ligand-activated transcription factors (25). The VDR is therefore essential for $1,25(\text{OH})_2 \text{D}$ -mediated events. For example, $1,25(\text{OH})_2 \text{D}$ -induced growth arrest is lost in mouse epidermal keratinocytes (26) and SaOS-2 osteosarcoma cells (27) lacking VDR. Similarly, antisense inhibition of VDR abolished $1,25(\text{OH})_2 \text{D}$ -induced growth arrest in ALVA-31 prostate cancer cells (28), while over expression of VDR enhanced $1,25(\text{OH})_2 \text{D}$ induced growth arrest in several prostate cancer cell lines, e.g. DU-145, PC-3 cells (29), and JCA-1 cells (30).

The VDR can be found in both the cytoplasm and nucleus of vitamin D target cells. Binding of $1,25(\text{OH})_2 \text{D}$ to the VDR promotes association of VDR with the retinoid X receptor (RXR). This heterodimerization is required for migration of the RXR-VDR-ligand complex from the cytoplasm to the nucleus (31-34). Once in the nucleus, the $1,25(\text{OH})_2 \text{D}$ -VDR-RXR complex regulates gene transcription by interacting with specific vitamin D response elements (VDRE) in the promoters of vitamin D-responsive genes (25). To overcome the constraints imposed on transcription by higher order chromatin structure, the VDR-RXR dimer recruits protein complexes with histone acetyl transferase (HAT) activity (e.g. CBP/p300, SRC1 (35;36)) as well as ATP-dependent remodeling activity (e.g. the BAF57 subunit of SWI/SNF directly interacts with SRC1 and steroid hormone receptors (37)). After chromosomal unwinding, the VDR-RXR dimer recruits the mediator complex to the promoter and utilizes it to recruit and activate the basal transcription unit containing RNA polymerase II (38). For those interested in more details regarding the molecular activation of VDR and its role in gene transcription, the subject was recently reviewed by Pike et al. (39).

2.3.2 Rapid, membrane initiated actions of $1,25(\text{OH})_2 \text{D}$ —There is growing evidence that $1,25(\text{OH})_2 \text{D}$ also has rapid actions that are not mediated through transcriptional events involving the VDR (40). In this model $1,25(\text{OH})_2 \text{D}$ binds to either a unique cell surface vitamin D binding protein (i.e. the Membrane Association Rapid Response Steroid binding protein or

MARRS) or a membrane associated pool of the traditional VDR (41). This leads to the activation of various kinases and the modulation of cell biology through phosphorylation of proteins. Unfortunately, there is very little to link this rapid signaling mechanism to the anticancer actions of $1,25(\text{OH})_2 \text{D}$. To address this question, Wu and Zanello (27) recently evaluated the role of rapid signaling on the growth regulatory ability of $1,25(\text{OH})_2 \text{D}$ in the osteosarcoma cell line SaOS-2. They found that while both sustained (3 days) and transient (15 min) $1,25(\text{OH})_2 \text{D}$ treatment activated JNK and ERK1/2 MAPK signaling in a non-genomic, VDR-dependent manner, only sustained exposure to hormone led to upregulation of cell cycle regulatory proteins like p21 and subsequent genomic control of the cell cycle. While this can be interpreted as support for a VDR-mediated transcriptional role, Wu et al. found that blocking MAPK signaling with MEK1 inhibitors abrogated $1,25(\text{OH})_2 \text{D}$ -mediated antiproliferative effects. However, this study did not present data to show that MEK inhibition was unique to vitamin D mediated growth arrest (i.e. there was no data showing the impact of MEK inhibitors on cell growth arrest in the absence of $1,25(\text{OH})_2 \text{D}$).

3. Question: How does the protection provided by high serum 25OH D levels translate to molecular regulation by $1,25(\text{OH})_2 \text{D}$ in target tissues?

While cell studies show that $1,25(\text{OH})_2 \text{D}$ binds to the VDR 1000-times more avidly than 25OH D and that it is the most biologically active metabolite of vitamin D, population studies show that 25OH D, not $1,25(\text{OH})_2 \text{D}$, is the serum vitamin D metabolite that best associates with cancer risk. The current hypothesis to explain this paradox is that there is local production of $1,25(\text{OH})_2 \text{D}$ mediated by extra-renal expression of the enzyme CYP27B1. In addition to the activity found in the kidney, low levels of CYP27B1 protein and message have been observed in many tissues, including cells of the skin, lymph nodes, colon, pancreas, adrenal medulla, brain, placenta (42), prostate epithelial cells (43) and MCF-7 breast cancer cells (44). The hypothesis that higher serum 25OH D drives local production of $1,25(\text{OH})_2 \text{D}$ is consistent with studies showing that the CYP27B1 is substrate starved (the enzyme operates well below its K_m (45)) and with studies in humans showing an inverse relationship between colonocyte proliferation and serum 25OH D (46). However, the weakness of this hypothesis is that no direct evidence currently exists to prove that meaningful local production occurs in vivo.

4. Question: What are the $1,25(\text{OH})_2 \text{D}$ -regulated gene targets relevant to cancer prevention?

4.1 Evidence for vitamin D-mediated regulation of genes controlling cell proliferation

Because of the strong antiproliferative effects that $1,25(\text{OH})_2 \text{D}$ has on cells, many investigators have looked for direct effects of the hormone on the expression of genes that control cell cycle. The strong first evidence to support this idea was the demonstration that $1,25(\text{OH})_2 \text{D}$ directly drives transcription of the gene encoding the cyclin-dependent kinase inhibitor p21 in the myelomonocytic cell line U937 (47). In this cell, growth arrest by $1,25(\text{OH})_2 \text{D}$ leads to differentiation towards a macrophage-like phenotype. A number of other cell-based studies are consistent with the hypothesis of vitamin D-mediated cell cycle inhibition. However, most of these studies show that cyclin-dependent kinase inhibitors like p21 or p27 increase, and cell cycle regulatory proteins like cyclins decrease, coincident with $1,25(\text{OH})_2 \text{D}$ -induced growth arrest (48-51). Thus, a cause and effect relationship has not been established between $1,25(\text{OH})_2 \text{D}$ treatment and most of cell cycle proteins. Consistent with an essential role for p21 in $1,25(\text{OH})_2 \text{D}$ -induced cell growth arrest, two groups have shown that this process is inhibited by antisense RNA or siRNA against p21 (49;52). However, Navarez et al. (53) found that $1,25(\text{OH})_2 \text{D}$ has a minimal effect on p21 mRNA levels in MCF-7 cells that growth arrest. In addition, while Zhuang et al. (16) found that p21 is involved in $1,25(\text{OH})_2 \text{D}$ -mediated LNCaP cell growth arrest, they observed that $1,25(\text{OH})_2 \text{D}$ increased p21 protein but not mRNA. This

suggests the effect is not mediated by a VDR-mediated transcription activation of the p21 gene promoter.

Another way that $1,25(\text{OH})_2 \text{D}$ could influence the growth rate of cells is by interfering with the action of growth factors that normally stimulate proliferation. This paradigm appears to be in place to limit the action of insulin-like growth factors (IGF). Colston et al. (54) first noted that IGF1-stimulated cell growth could be inhibited by vitamin D analogs in MCF-7 breast cancer cells and that this was associated with increased release of IGF binding protein 3 (IGFBP3) into the medium. IGFBP3 is known to bind IGF1 and IGF2 and limit their ability to interact with cell surface receptors, thus limiting their biological action (pro-proliferative, anti-apoptotic). This may be particularly important in prostate cancer where IGF1 has been shown to play a significant role (55). Huyunh et al. (56) found that $1,25(\text{OH})_2 \text{D}$ and vitamin D analog-induced IGFBP3 accumulation was associated with interference of IGF2-action in prostate cancer cells and the association of IGFBP synthesis with the antiproliferative actions of $1,25(\text{OH})_2 \text{D}$ was later confirmed in cultured primary prostate epithelial cells (57). Nickerson and Huyunh (58) later showed that 14 d treatment with the vitamin D analog EB1089 could reduce prostate size and that it increased the expression of many IGFBP isoforms including IGFBP3. The increase in IGFBP3 following $1,25(\text{OH})_2 \text{D}$ treatment is likely to be direct (59); a putative VDRE was identified and characterized (EMSA, ChIP) in the IGFBP3 gene promoter.

Recently, an alternate hypothesis has emerged to account for vitamin D-mediated growth arrest. This mechanism involves disruption of beta catenin transcriptional activity that is the downstream mediator of the pro-proliferative effects of Wnt signaling. Normally beta catenin is held in the cytoplasm of cells by the protein APC. Release of beta catenin from APC permits its translocation to the nucleus where it then partners with TCF4 to stimulate the transcription of genes whose protein products control cell cycle (e.g. c-myc, cyclin D1, PPAR δ (60)). Palmer et al. (61) found that $1,25(\text{OH})_2 \text{D}$ -treatment induced the translocation of beta catenin away from the nucleus to the membrane resulting in reduced expression of c-myc and other genes regulated by the beta catenin/TCF transcriptional complex in SW480 colon cancer cells. C-myc is a transcription factor whose activity promotes cell growth; its expression had previously been found to be suppressed by $1,25(\text{OH})_2 \text{D}$ -treatment in a number of cell types. Shah et al. later showed that the AF-2 domain of the VDR can interact directly with the C-terminal end of beta catenin and that this interaction is unrelated to the traditional transcriptional effects of VDR (62). The VDR-beta catenin interaction also may account for the inhibitory effects that $1,25(\text{OH})_2 \text{D}$ treatment has on the expression of dickkopf-4, a Wnt regulator that enhances cell migration and whose expression is increased in human colon cancer (63). In addition, $1,25(\text{OH})_2 \text{D}$ treatment can also enhance expression of the Wnt antagonist dickkopf-1, although this effect is thought to be indirect and mediated through the $1,25(\text{OH})_2 \text{D}$ -mediated induction of E-cadherin (64). The ability of $1,25(\text{OH})_2 \text{D}$ to interfere with beta catenin action through a VDR-mediated mechanism suggests that vitamin D may be an effective counter-measure to the loss of APC function that occurs in the early stage of colon cancer.

4.2 Microarrays are a useful tool to define novel $1,25(\text{OH})_2 \text{D}$ -regulated genes

The use of DNA microarrays permits researchers to identify the full scope of transcript-level changes that occur in response to a treatment. Unfortunately, the application of transcriptomics to the study of $1,25(\text{OH})_2 \text{D}$ action has been relatively limited to date and the full power of the technology has been applied in only a few cases. Gene expression profiles for the effects of $1,25(\text{OH})_2 \text{D}$ treatment have been generated in a variety of non-classical vitamin D-target cells, e.g. squamous cell carcinoma, colon cancer, breast cancer, and prostate epithelial cells. These studies have used a variety of platforms that sometime contain a limited number of transcript probes and rarely have a significant transcript target overlap with other platforms. This lack of

consistency makes it very hard to compare the results of one experiment to the next. However, even with this caveat, the few studies available have been very informative and suggest new mechanisms by which vitamin D could provide protection from cancer.

Of the 14 published microarrays on vitamin D treated cancer cells, the most complete genomic profiling has been reported in squamous cell carcinoma (SCC) cell lines (65-67). In studies using small cDNA filter arrays Akutsu et al (65) found that treatment of SSC cells with 100 nM of the 1,25(OH)₂ D analog EB 1089 up-regulated gadd45 α , a p53 target gene that is involved in DNA repair, as well as components of various signal transduction pathways (e.g. amphiregulin, AP-4, STAT3, and fra-1) and cell adhesion proteins like integrin α 7B. Later studies by Lin et al. (66) extended this observation with an early generation Affymetrix array and a significance cut-off of 2.5 fold. Cluster analysis of this data showed that the vitamin D-induced transcript-level responses were more diverse than previously thought. EB1089 treatment changed the levels of transcripts involved in oxidative stress, signaling peptides, extracellular matrix, and immunoregulation. Finally, a more recent study by Wang et al. (67) using a more extensive Affymetrix array and a formal statistical analysis found 1400 differentially expressed transcripts – many of which contained putative vitamin D response elements (67). The ability of VDR to bind to promoter/enhancer regions of several of these putative vitamin D target genes were confirmed by ChIP assay.

In prostate cancer there is another interesting story developing from arrays studies. Although only a small number of differentially expressed transcripts have been reported for 1,25(OH)₂ D-treated prostate cells using microarrays, these include genes encoding proteins that modulate prostaglandin synthesis (cox-2), metabolism (15-prostaglandin dehydrogenase), and action (the prostaglandin receptors EP2 and FP) and suggest that vitamin D suppresses the pro-inflammatory prostaglandin signaling pathway (68;69). Collectively, these microarray-based discovery projects reveal that the biological impact of 1,25(OH)₂ D extends beyond the simple modulation of cell cycle (see Figure 1 for summary). However, functional studies following-up on these findings to determine the role that the new target genes may have on cancer development still need to be conducted.

5. Question: Is 1,25(OH)₂ D action uniform across all stages of cancer (from normal tissue to metastatic tumors?)

Although we generally focus on the impact that vitamin D has on the development of cancer, in terms of prevention, it is just as important to understand the impact that cancer has on vitamin D action. For example, Matusiak et al. (70) found that VDR protein level declines as a function of colon tumor dedifferentiation. This suggests that the development of colon cancer may lead to lower responses to 1,25(OH)₂ D. This is consistent with evidence that activated Ras, a common mutation in many cancers including colon cancer, can impair vitamin D transcriptional activity. For example, H-Ras transformation has also been shown to reduce VDR levels in HC-11 mammary cells (71). In addition, H-Ras transformed keratinocytes (72) have reduced VDR transcriptional activity due phosphorylation of the VDR heterodimeric partner RXR α at serine 260.

Another way that cancer can influence the effects of 1,25(OH)₂ D are by influencing its metabolism. Several groups have shown that CYP27b1 activity, and the ability to produce 1,25(OH)₂ D locally, is lost as cancer develops. Hsu (43) found that CYP27b1 was present in normal prostate epithelial cells but that its activity was reduced in cells isolated from subjects with benign prostatic hypertrophy and nearly absent in cells from subjects with prostate cancer. As a result, while normal cells could respond to treatment with 25OHD by growth arresting, cancer cells with low CYP27b1 expression could not. This observation was confirmed by Chen et al. (73) who also showed that transgenic expression of CYP27b1 restores the growth inhibitory

response to 25OH D in LNCaP cells that normally have low CYP27b1 activity. CYP27B1 expression is also absent in metastases from colon tumors in humans (74). However, cancer-associated reductions in CYP27b1 levels are not uniformly observed for all cancers. Friedrich et al. (44) found that CYP27b1 was present in normal breast tissue but actually higher in malignant breast tissue.

Some have also hypothesized that the enzyme responsible for the degradation of vitamin D metabolites, the 25 hydroxyvitamin D-24 hydroxylase (CYP24), is influenced by cancer. In 2000, CYP24 was identified as a putative oncogene because the CYP24 gene was identified as amplified in breast tumors (75). Consistent with this, Anderson et al. (76) reported that CYP24 mRNA expression was increased in colorectal cancer as compared to adjacent normal tissue. Matusiak and Benya (77) subsequently found that CYP24 protein was present in the nuclei of normal tissue, increased in aberrant crypt foci and polyps, and finally shifted to the cytoplasm in tumors and metastatic colon cancer. This suggests that increased 1,25(OH)₂ D metabolism may be a feature of advanced cancer.

The overall impact of these changes to vitamin D metabolism and signaling would affect cancer prevention in two ways. First, the protection provided by high vitamin D status will depend upon the level of CYP27b1 in the developing tumor; if CYP27b1 activity is lost, so will the protection due to high vitamin D status. Second, when CYP24 activity is elevated and/or VDR level or signaling is reduced, higher cellular levels of 1,25(OH)₂ D will be needed to influence the biology of cancer cell. It is unclear whether this is possible through local production of the hormone and increases in serum 1,25(OH)₂ D levels are likely to have a negative impact on calcium metabolism. Hypercalcemia associated with 1,25(OH)₂ D-treatment has been a major motivation to produce vitamin D analogs that separate the calcemic and non-calcemic effects of 1,25(OH)₂ D but even vitamin D analog effectiveness will be limited if a cancer leads to reduced VDR expression. Figure 2 summarizes the putative effects of cancer on vitamin D signaling.

6. Conclusions

The last 30 years have been a remarkable period of expanding our understanding regarding the non-calcium regulatory roles of vitamin D and vitamin D metabolites. There is now strong evidence that higher vitamin D status is a protective factor against a variety of cancers. However, there are several mechanistic issues that have not yet been resolved in this area. First, the paradox needs to be resolved that higher serum 25OH D is associated reduced cancer risk, yet 1,25(OH)₂ D is the active metabolite regulating biology through the VDR. The barrier here is in vivo evidence demonstrating that the low-level expression of CYP27b1 in tissues leads to meaningful local production of 1,25(OH)₂ D, and that this mediates the protection from cancer provided by high vitamin D status. Second, we need to expand our thinking when it comes to the cell and gene targets for vitamin D mediated cancer protection. For example, rather than focusing on tumor cells or their non-transformed progenitors, we should consider the entire tissue microenvironment. Several lines of evidence suggest that immunoregulatory actions of vitamin D metabolites is worth investigation for cancer prevention. Finally, we need to resolve whether our assumption that vitamin D will offer protection at in every cancer and at every stage in the development of a cancer is accurate. There is growing, but not complete, evidence that there are unfavorable shifts in vitamin D metabolism and signaling through the VDR as certain cancers progress. We need to better understand the impact that various oncogenic mutations have on vitamin D action and we need to use this information to drive the translation of vitamin D research into meaningful public health messages.

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Figure 1.

A summary of the molecular targets affected by 1,25(OH)₂ D. Cell-based studies and microarray analysis suggest that 1,25(OH)₂ D action can influence many cellular systems directly through transcriptional events mediated through the vitamin D receptor (VDR)-retinoid X receptor (RXR) heterodimer or indirectly by using the VDR to interfere with beta catenin signaling.

Figure 2.

The relationship between vitamin D metabolism, vitamin D action, and cancer. (A) Transcriptional activation of genes through the vitamin D receptor (VDR) is dependent upon both the production of the active metabolite, $1,25(\text{OH})_2 \text{D}$, through the enzyme CYP27b1, and its degradation by the enzyme CYP24. (B) A schematic demonstrating how the process of cancer may influence vitamin D action.