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Extraskeletal actions of vitamin D

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Abstract

The vitamin D receptor (VDR) is found in nearly all, if not all, cells in the body. The enzyme that produces the active metabolite of vitamin D and ligand for VDR, namely CYP27B1, likewise is widely expressed in many cells of the body. These observations indicate that the role of vitamin D is not limited to regulation of bone and mineral homeostasis, as important as that is. Rather, the study of its extraskeletal actions has become the major driving force behind the significant increase in research articles on vitamin D published over the past several decades. A great deal of information has accumulated from cell culture studies, *in vivo* animal studies, and clinical association studies that confirms that extraskeletal effects of vitamin D are truly widespread and substantial. However, randomized, placebo controlled clinical trials, when done, have by and large not produced the benefits anticipated by the *in vitro* cell culture and *in vivo* animal studies. In this review, I will examine the role of vitamin D signaling in a number of extraskeletal tissues, and assess the success of translating these findings into treatments of human diseases affecting those extracellular tissues.

Keywords

vitamin D; CYP27B1; cancer; cardiovascular; skin; immune system

Introduction

The original paradigm for vitamin D signaling involved its production in the skin from 7-dehydrocholesterol under the influence of ultraviolet light with spectrum 280–320 (UVB), its removal from the skin carried by the vitamin D binding protein (DBP) to the liver where it was subsequently hydroxylated in the 25 position of the side chain to 25 hydroxyvitamin D (25OHD) by CYP2R1 and CYP27A1 among other 25 hydroxylases, which provided the substrate for the renal 1α hydroxylase (CYP27B1) to form the active metabolite and ligand for the vitamin D receptor (VDR), namely 1,25 dihydroxyvitamin D ($1,25(OH)_2D$). The $1,25(OH)_2D$/VDR complex acted as a transcription factor in combination with the retinoid X receptor (RXR) to induce the genes that enabled intestinal calcium and phosphate transport, renal reabsorption of calcium, and flow of calcium and phosphate in and out of the skeleton.

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Conflicts of interest

The author declares no conflicts of interest.

With the observations that the VDR in found in nearly every cell in the body and that CYP27B1 and 25 hydroxylases are widely expressed, this paradigm has undergone major revisions. Now the concept is that all cells may be targets for $1,25(OH)_2D$ at least at some stage of their differentiation[1], that many of these cells make their own $1,25(OH)_2D$ and so are not dependent on the renal production of this metabolite[2], that the VDR may act without its classical ligand and/or use alternative ligands,[3,4] that RXR is not the only partner for VDR in its transcriptional actions,[5,6] and that vitamin D signaling may involve non-genomic as well as genomic mechanisms of action.[7–9] These observations underlie the rapid explosion in publications about the mechanism of vitamin D action, not just in regulating bone and mineral homeostasis but in essentially in all biologic processes, with the hope that vitamin D and its metabolites might play an important role in the prevention and treatment of a vast number of diseases—not just rickets, osteomalacia, and osteoporosis, as important as this role is. Pubmed lists 67,463 publications on vitamin D at the time of this writing, with acceleration over the past decade. The number of publications over the past 5 years illustrate this trend: 3154 in 2011, 3613 in 2012, 3890 in 2013, 3995 in 2014, 4236 in 2015, with 1771 so far by May 1, 2016.

Recent studies in which the number of VDR binding sites (putative vitamin D response elements or VDREs) have been determined using Chip-seq have identified anywhere from 1000 to 13,000 in a variety of cells that have been examined, possibly involving 3–4% of the genome.[5,10] The majority (67%) of the sites are cell specific.[10] Each gene may have multiple VDR binding sites that can be essentially anywhere in the gene, often at great distances from the transcription start site.[5,10] Most of the sites are probably not functional (most have not been tested). Using RNA-seq to identify regulated genes, studies have shown anywhere from 100–500 up or down regulated genes in different cells, with limited overlap in the genes regulated among the different cell types.[5,10–12] Although it is beyond the scope of this review to discuss the reasons for tissue specificity—likely involving tissue-specific expression of the various coactivator and corepressors that differentially regulate $1,25(OH)_2D$ action,[5,13] and epigenetic differences in different tissues that regulate access of the VDR to its VDREs, or even of VDR expression itself[14]—the tissue-specific effects of vitamin D signaling certainly make it possible to understand the diversity of $1,25(OH)_2D$ effects on different cell types.

In this review, I will explore some of this diversity in a number of cell types and tissues that are not obviously linked to bone and mineral homeostasis (Fig. 1). With each cell/tissue type, I will examine the translational implications of these findings in terms of both the very promising association studies and the less compelling randomized placebo controlled clinical trials (RCTs). I will refer to “vitamin D signaling” or “action” to indicate the impact of the active vitamin D metabolites, $1,25(OH)_2D$ in particular, interacting with its various receptors and cofactors to induce change within the cell by mechanisms to be described. By “vitamin D status” I refer primarily to the levels of circulating 25OHD levels, the most widely used method of assessing vitamin D status. In this review “vitamin D” refers to both vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol). Similarly, “25OHD” refers to both $25OHD_3$ (calcifediol or 25-hydroxycholecalciferol) and $25OHD_2$ (25-hydroxyergocalciferol), and “$1,25(OH)_2D$” refers to both $1,25(OH)_2D_3$ (calcitriol) and $1,25(OH)_2D_2$ (ercalcitriol).

Cancer

The antiproliferative, prodifferentiating effects of vitamin D signaling on many, if not most, cell types has raised the hope that vitamin D, $1,25(OH)_2D$, or one or more of its analogs, would prove useful in the prevention and/or treatment of cancer. Indeed, PubMed lists 8875 articles on the subject at the time of writing. I will briefly review several of the main mechanisms by which vitamin D signaling is thought to prevent/treat cancer, giving examples of some of the cells studied and the animal data for several of the most common and best studied tumors, then examine whether these promising mechanistic and animal studies have been successfully translated to the clinic.

Cellular studies and mechanisms

Alterations in VDR levels and vitamin D metabolism—Most tumors express the VDR, and mutations in the VDR are uncommon.[15] However, the expression of the VDR is often lost as a tumor undergoes progressive dedifferentiation, and loss of its expression in a tumor is a bad prognostic sign.[16] Similarly, CYP27B1 is expressed in many tumors and mutations are uncommon;[15] but like the VDR, expression of CYP27B1 typically declines with progressive dedifferentiation.[17,18] On the other hand, CYP24A1 expression is often increased in tumors and is associated with resistance to $1,25(OH)_2D$.[18,19] This increase is secondary to the CYP24A1 gene being part of a region of gene duplication seen in some tumors;[20] its overexpression is a poor prognostic sign.[21]

Regulation of miRNAs and lncRNAs—As discussed previously, VDR binding sites in the genome are numbered in the thousands, and VDR coding transcripts number in the hundreds. However, a substantial level of regulation occurs via microRNAs (miRNAs) and long noncoding RNAs (lncRNAs), a difference being that miRNAs are typically around 20 nucleotides in length, whereas lncRNAs are 200 or more nucleotides. A number of miRNAs have been identified to be regulated by $1,25(OH)_2D$–VDR and relevant to its antiproliferative actions.[22] These include increased expression of miR145, which blocks the expression of E2F3, a key regulator of proliferation,[23] or miR-32 that blocks the proapototic protein Bim, which somewhat paradoxically protects the cell (human myeloid leukemia) from AraC induced apoptosis.[24] In VDR-null ($Vdr^{-/-}$) keratinocytes, a number of oncogenic lncRNAs are increased, whereas tumor suppressor lncRNAs are decreased.[25]

Antiproliferation—$1,25(OH)_2D$ typically causes arrest at the G_o/G_1 and/or G_1/S transitions in the cell cycle; this is associated with a decrease in cyclins (varies with cell type) and an increase in the inhibitors of the cyclin-dependent kinases (CDK) such as $p21^{cip1}$ and $p27^{kip1}$, again in a cell-specific fashion.[26,27] Given the importance of calcium in vitamin D signaling, it was of interest that the antiproliferative actions of $1,25(OH)_2D$ in CRC cell lines are dependent on the expression of the calcium sensing receptor.[28] Forkhead box O (FoxO) proteins are transcription factors that suppress proliferation and increase apoptosis. $1,25(OH)_2D$ promotes an increase in the interaction between several of the FoxOs with VDR and FoxO regulators, including Sirt1 and protein phosphatase 1, keeping FoxO dephosphorylated and transcriptionally active, as shown in the SCC25 cell line.[29] $1,25(OH)_2D$ reduces the levels of other genes linked to proliferation, genes such as *MYC*,

FOS, and *JUN* as illustrated in colon cancer cell lines.[30] $1,25(OH)_2D$ stimulates the expression of IGF binding protein 3 (IGFBP3) in prostate and breast cancer cells, thus limiting the ability of IGF I and II to stimulate tumor growth.[31,32] The expression of TGF-β2, which is antiproliferative in epithelial cells, is stimulated by $1,25(OH)_2D$ in a number of cell types, including breast and prostate cancer cells.[33, 34, 35] Overexpression of components of the Hedgehog (HH) pathway is a major cause of basal cell carcinomas (BCC).[36] In the epidermis of VDR-null mice the HH pathway is up regulated; on the other hand $1,25(OH)_2D$ blocks the expression of these components.[37] $1,25(OH)_2D$ inhibits EGF stimulation of proliferation by inhibiting the expression of EGFR in breast cell lines[38] and was shown to target the EGF–EGFR complex to endosomes in the epidermoid cell line A431.[39] Mutations in APC, leading to constitutive activation of the Wnt/β-catenin pathway, are the cause of most colorectal cancers (CRC). When activated, β-catenin enters the nucleus where it binds to TCF/LEF sites in genes promoting proliferation (e.g., cyclin D1). $1,25(OH)_2D$/VDR competes with TCF/LEF for binding to β-catenin and by stimulating the formation of the E-cadherin–catenin complex in the cell membrane limits the amount of β-catenin that can be activated and translocated to the nucleus.[40] A similar mechanism exists in the skin, contributing to the ability of vitamin D signaling to protect against skin cancer.[41] Moreover, $1,25(OH)_2D$ can increase the expression of the Wnt inhibitor dickkopf (DKK)-1,[42] while inhibiting that of the Wnt activator DKK-4[43] in colon cancer cells. The ability of calcium to enhance the antiproliferative actions of $1,25(OH)_2D$ in these tissues is due, in part, to its role in stimulating E-cadherin–catenin complex formation and reducing the induction of cyclin D1.[44]

Apoptosis—$1,25(OH)_2D$ promotes the apoptosis of a number of cell types, including gastric and colon carcinoma cells,[45,46] by stimulating the expression of a number of pro-apoptotic genes such as *G0S2* (G_0/G_1 switch gene 2) in colon cancer,[27] *BAX* in the chronic myeloid leukemia cell line K562,[47] *DAP* (death-associated protein)-3, *CFKAR* (caspase 8 apoptosis-related cysteine peptidase), *FADD* (Fas-associated death domain) and a number of caspases (e.g., caspase 3, 4, 6, and 8 genes) in breast cancer cells,[34] or by suppressing the expression of a number of pro-apoptotic genes such as Bcl-2 (*BCL2*) and Bcl-X_L (*BCL2L1*) in K562 cells,[47] thus sensitizing cells to apoptosis induced by reactive oxygen species (ROS) and cytokines (e.g., TNF-α), as seen in breast cancer cells.[48,49] Moreover, the $1,25(OH)_2D$–induced increase in intracellular calcium further increases apoptosis by activating the calcium dependent μ-calpain and calcium/calpain-dependent caspase 12, shown in breast cancer cells.[50] $1,25(OH)_2D$ also promotes autophagy[51] in some cancer cells, such as the MCF-7 breast cancer cell line, by inhibiting the anti-autophagy mTOR gene (*MTOR*) and increasing the levels of the pro-autophagy beclin-1 gene (*AMBRA1*).

DNA damage repair (DDR)—DNA damage repair mechanisms have probably been best described in the skin. Sunlight induces DNA damage both through its UVB component that damages DNA directly[52] and its UVA component that damages DNA through oxidative stress.[53] UVB induced DNA damage includes the formation of cyclobutane pyrimidine dimers (CPD) and pyrimidine (6–4) pyrimidone photoproducts (6–4PP) that if not repaired result in C to T or CC to TT mutations.[54] VDR-null mouse epidermis is slow to clear CPDs and 6,4PPs following UVB,[37,55] but topical $1,25(OH)_2D$ is protective (in VDR-containing

skin). In other tissues, chromosomal damage is due to oxidative and other stresses, and is more prevalent in vitamin D deficiency[56] or VDR-null mice,[57] where it is associated with increased levels of 8-OH-2′-deoxyguanosine (8-OHdG), a marker of oxidative DNA damage.[58] 800 IU of vitamin D as a daily supplement has been shown to reduce the levels of oxidative DNA damage in human colons.[58] $1,25(OH)_2D$ induces several genes important for DDR, including *XPC* (xeroderma pigmentosum complementation group C), *DDB2* (damage-specific DNA binding protein 2, also known as XPE), and *GADD45* (growth arrest and DNA-damage inducible).[59,60] Similarly,$1,25(OH)_2D$ induces a number of antioxidant enzymes, including thioredoxin reductase 1,[33] superoxide dismutase,[33] glucose-6 phosphate dehydrogenase,[61] and glutathione peroxidase,[27] that protect against oxidative DNA damage.

Inhibition of angiogenesis—Angiogenesis is critical for tumor growth and metastasis. $1,25(OH)_2D$ inhibits the proliferation of endothelial cells, reduces hypoxia-induced expression of VEGF in a variety of cancer cell lines including colon cancer cells,[62] and, by inhibiting VEGF-induced endothelial cell sprouting and elongation, reduces neovascularization of tumors such as in breast cancer cells (Fig. 2).[63]

Inhibition of metastasis—$1,25(OH)_2D$ reduces the migration and invasion capacity of tumor cells by several mechanisms.[64] It reduces the expression of the matrix protein laminin and its receptors α6 and β4. $1,25(OH)_2D$ also reduces the degradation of the matrix by matrix metalloproteinases and cathepsins produced by cancer cells that otherwise would facilitate their metastasis by inducing inhibitors of these enzymes, as occurs in prostate cancer.[65] $1,25(OH)_2D$ increases the expression of the PDZ-LIM domain–containing protein 2, a scaffold protein linking different components of the cytoskeleton, enabling the proadhesion, anti-migration, anti-invasion effects of $1,25(OH)_2D$, as shown in breast cancer cells.[66] The increased expression of E-cadherin and decreased expression of CEACAM1 (carcinoembryonic antigen-related cell adhesion molecule 1) by endothelial cells limits binding of cancer cells to endothelial cells, a requirement for their ability to metastasize.[67]

Animal studies

Although a number of different types of tumors have been examined in animal models, I will focus on just four: colorectal cancer (CRC), breast cancer (BCa), prostate cancer (PCa), and non-melanoma skin cancer (NMSC), as these are common malignancies that have received substantial attention in human studies. I will briefly describe several illustrative examples of vitamin D regulation of tumor development/metastasis for each of these tumor types.

Colorectal cancer—A Western diet low in calcium and vitamin D fed to mice increases their risk of CRC, a risk reversed by supplementing the diet with calcium and vitamin D.[68] Chronic inflammation likewise increases CRC in both mice and humans.[69] VDR-null mice are particularly sensitive to the inflammatory effects of dextran sulfate sodium (DSS).[70] Tumors induced by the combination of azoxymethane (AOM) and DSS can be at least partially prevented with the administration of vitamin D metabolites.[71] As previously mentioned, activation of the Wnt/β-catenin pathway is a major cause of CRC. Mice with a mutation in adenomatous polyposis coli (Apc^{Min}), a regulator of the Wnt/β-catenin pathway, develop tumors much faster on a Western diet,[72] on a vitamin D–deficient diet,[73] or when

bred with VDR-null mice.[74] 1,25(OH)$_2$D and its analogs are protective when animals are fed the vitamin D–deficient diet.[73,75]

Breast cancer—Similar to CRC, the number of BCa induced, in this case, by dimethylbenzanthracene (DMBA) is increased when the rats are fed a Western diet[76] or when DMBA is given to VDR-null mice.[77] VDR agonists prevent the growth of breast cancer xenografts regardless of estrogen receptor status.[78] The growth of bone metastases is increased with dietary vitamin D deficiency,[56] whereas VDR agonists can reduce their growth.[79]

Prostate cancer—Using xenograft models, studies have demonstrated that vitamin D analogs can inhibit the growth of PCa regardless of androgen receptor status.[80] The growth of PC3 prostate cancer cells in bone is increased when mice are fed a vitamin D–deficient diet.[81] When the transgenic prostate tumor model LPB-Tag is bred with VDR-null mice, tumors developed more rapidly.[82] High doses of 1,25(OH)$_2$D suppress the development of tumors in the TRAMP model (transgenic adenocarcinoma of mouse prostate).[83]

Non-melanoma skin cancer—Included in this category are squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), the most common of human tumors. In animals, these tumors are induced by chemical induction with DMBA topically or orally, often followed by repeated topical application of phorbol esters or by chronic exposure to UVB. When VDR-null mice are treated with DMBA, nearly all the mice develop skin tumors. Similar results are seen following chronic UVB exposure.[84,37] Surprisingly, mice lacking the ability to produce 1,25(OH)$_2$D (*CYP27B1* null) do not show increased susceptibility to tumor formation following either DMBA[84] or UVB,[37] suggesting that the role of VDR in these situations is not 1,25(OH)$_2$D dependent. However, topical 1,25(OH)$_2$D is protective at least of the early effects of UVB,[85] and as discussed in the previous section describing mechanisms, 1,25(OH)$_2$D does induce mechanisms that would be expected to protect against tumor development in the skin.

Clinical studies

At this point most, evidence for the role of vitamin D in tumor prevention comes from epidemiologic studies, with few randomized placebo-controlled clinical trials of sufficient size, duration, and compliance of subjects to make conclusive comments regarding its efficacy. The epidemiologic studies are suggestive of benefit, however.

Colorectal cancer—A number of meta-analyses have been performed of studies, totaling thousands of subjects, examining both the relationship of vitamin D intake and/or serum levels of 25OHD on the incidence of CRC.[86, 87] One such study found a risk reduction to 0.88 (CI 0.8–0.96) comparing the highest to lowest levels of vitamin D intake[86] and 0.67 (CI 0.54–0.80) comparing the highest to the lowest serum 25OHD levels;[86] further reduction was found when dietary calcium was taken into account (higher calcium is better). These meta-analyses confirm earlier results from a American Cancer Society cohort study (120,000 men and women)[88] and from the National Institutes of Health study (16,000 participants)[89] that identified a beneficial association of vitamin D intake or serum 25OHD levels on CRC.

That said, from the Women's Health Initiative 400 IU vitamin D per day did not,[90] although this study has been criticized for poor compliance and inadequate vitamin D supplementation. Thus, there is a reasonably consistent set of data supporting the protective effect of vitamin D (and calcium) on CRC development.

Breast cancer—The largest cohort studies[91,92] (Nurses Health Study with 88,891 participants and Womens Health Study with 31,487 participants) showed a relative risk (RR) of 0.72 (CI 0.55–0.94) and 0.65 (CI 0.42–1.00), respectively, but only in premenopausal women. Several meta-analyses of both case control and cohort studies have been performed. One such study demonstrated a risk reduction of 0.55 (CI 0.38–0.80) comparing the highest quintile of 25OHD levels to the lowest.[93] Another meta-analysis showed a RR of 0.89 (0.82–0.98) for a 10 ng/ml increase in 25OHD when all studies were included, and 0.83 (0.79–0.87) when only case control studies were pooled.[94] The Womens Health Initiative (not to be confused with the Womens Health Study mentioned above) did not show a protective role for vitamin D in breast cancer. Thus, the evidence supporting a role for vitamin D in breast cancer prevention is somewhat mixed.

Prostate cancer—In a recent summary of 14 studies examining the association between 25OHD levels and the development of prostate cancer, 11 showed no association.[95] Similarly, meta-analyses of studies examining either the association of dietary vitamin D intake to PCa or of serum 25OHD and PCa did not find a benefit for vitamin D.[96,94] A RCT examining the effect of high dose $1,25(OH)_2D$ and docetaxol initially showed promise in the treatment of castration-resistance PCa (ASCENT I), but this was not confirmed in a larger trial (ASCENT II).[97] Thus, the clinical evidence weighs against vitamin D supplementation being beneficial in the prevention/treatment of prostate cancer.

Non-melanoma skin cancer—Although skin cancer is by far the most common cancer, studies of the epidemiology of BCCs and SCCs are handicapped by the failure of most national registries to list them. Moreover, since UVB is the common etiologic agent for both NMSC and vitamin D production, 25OHD levels can be both a marker of vitamin D sufficiency and UVB exposure, making association studies between vitamin D sufficiency and NMSC problematic. Sudies that have been reported are mixed. In a nested case control study of NMSC incidence in the Osteoporotic Fractures in Men (MrOS) study, those with the highest baseline serum 25OHD levels (30 ng/mL) had a RR of 0.53 (CI 0.3–0.93) compared to those with the lowest baseline 25OHD levels.[98] On the other hand, several studies found that higher 25(OH)D levels were associated with an increased risk of BCC.[99, 100] Therefore, whether the harm of UVB exposure to the skin outweighs the benefits of UVB exposure with respect to vitamin D production remains controversial.

Cardiovascular

Cellular and animal studies

VDR- and CYP27B1-null mice have increased levels of renin,[101,102] which converts angiotensinogen to angiotensin I, which is further converted to angiotensin II, a powerful vasoconstrictor as well as stimulator of aldosterone production. In these mice blood pressure

is increased, with increased cardiac hypertrophy, impaired systolic and diastolic function, and increased arterial stiffness.[101–103] Angiotensin inhibitors block cardiac hypertrophy in these mice.[101,102] The increased arterial stiffness is associated with a reduction in nitric oxide synthase (NOS) activity,[103] and deletion of *Vdr* specifically in endothelial cells demonstrates impaired relaxation and reduced NOS expression.[104] *In vitro* studies show that $1,25(OH)_2D$ suppresses myocyte hypertrophy,[105] and vitamin D deficiency results in smaller myofibrils but increased fibrosis[106] *in vivo*. In global VDR gene knockout mice, renin expression is reduced both in the kidney and the heart, as is the cardiac expression of atrial naturetic factor (ANP).[107] However, in the cardiomyocyte-specific VDRKO, increased renin expression is not found, yet cardiac hypertrophy still ensues.[108] The cardiac hypertrophy seen in VDRKO mice includes an increase in fibrosis. $1,25(OH)_2D$ suppresses endothelin expression in cardiac fibroblasts,[109] a known profibrotic/hypertrophic factor for the heart, whereas the expression of several metalloproteinases are increased and their inhibitors are decreased.[110] VDRKO mice are also prone to develop accelerated atherosclerosis,[111] whereas $1,25(OH)_2D$ can reduce such lesions in ApoE gene knockout mice, a mouse model of accelerated atherosclerosis, in part by suppressing the immune response in the atherosclerotic plaques.[112] Mouse models of hypertension such as the Dahl salt-sensitive rat[113] or the spontaneously hypertensive rat[114] develop cardiac hypertrophy that can be prevented with the administration of $1,25(OH)_2D$ or one of its analogs. VDRKO mice are also prone to increased thrombosis, with increased platelet aggregations and decreased thrombomodulin.[115] $1,25(OH)_2D$, on the other hand, can increase the expression of thrombomodulin and decrease the procoagulant tissue factor.[116] Thus, these models suggest an important role for vitamin D signaling in the prevention of cardiovascular disease including heart failure, hypertension, and atherosclerosis.

Clinical studies

Severe vitamin D deficiency is associated with cardiomyopathy and congestive heart failure in children, which are reversible with vitamin D supplementation.[117] Epidemiologic studies demonstrate an association between low 25OHD levels and increased risk of cardiac events including death,[118,119] whereas other studies have shown this relationship with strokes,[120] coronary artery calcification,[121] and atherosclerosis.[122,123] Not all such studies are positive;[124] but recent meta-analyses of a number of these studies have demonstrated an association.[125,126] Several large studies of patients on hemodialysis treated with active forms of vitamin D analogs have demonstrated a reduction in cardiovascular mortality,[127,128] although these are retrospective reviews not RTCs. Similarly, a number of studies have shown an association between 25OHD levels and blood pressure, with meta-analyses showing a risk reduction of 16%[129] to 30%.[130] One interesting study employed a Mendelian randomization approach with allelic variants of *CYP2R1* and *DHCR7* (previously shown in GWAS studies to influence 25OHD levels)[131] to demonstrate a positive association between the 25OHD allelic score and lower blood pressure.[132] Endothelial function was found to improve in vitamin D–deficient diabetic patients when given vitamin D.[133] However, RCTs have generally been disappointing. In one multicenter trial evaluating the use of paricalcitol in renal failure patients, the authors demonstrated a reduction in parathyroid hormone (PTH), but no effect on cardiac function.[134] A meta-analysis of 51 RCTs found no significant effect on death, myocardial infarction, stroke, or blood pressure.[135] Similar

results were found in a separate meta-analysis of four RCTs.[126] However, a different meta-analysis of RCTs using vitamin D supplementation with or without calcium did indicate a modest reduction in mortality when vitamin D plus calcium were given.[136] In a review of 10 vitamin D trials for hypertension, with vitamin D doses ranging from 400–8751 IU/day, the overall analysis showed no significant effect whether or not calcium was included in the supplement, even when the negative results from the Women's Health Initiative were excluded.[126] Thus, the promise of the animal and human association studies regarding the potential benefit of vitamin D supplementation on prevention and treatment of cardiovascular disease has been difficult to confirm in RCTs.

Metabolism

Pancreas and diabetes mellitus type 2

Cellular and animal studies—The beta cell within pancreatic islets expresses both VDR[137] and CYP27B1.[138] $1,25(OH)_2D$ stimulates insulin secretion *in vivo* and *in vitro*,[137,139,140] and by stimulating the expression of the insulin receptor promotes glucose uptake by peripheral tissues.[141] On the other hand, insulin secretion is reduced in vitamin D deficiency[142] and in VDRKO mice.[143] However, calcium is important for insulin secretion, and low calcium levels can be suppressive.[144] Therefore, the early results with vitamin D deficiency may also have reflected the low calcium levels in this condition, and when VDRKO mice were placed on a rescue diet to maintain normal calcium levels, insulin secretion was not different from wild-type mice.[145] The renin/angiotensin system (RAS) may also play a role by impairing beta cell function and insulin sensitivity. As noted previously, $1,25(OH)_2D$ suppresses the RAS in VDRKO mice and has this property in mouse islets, perhaps contributing to the ability of $1,25(OH)_2D$ to stimulate insulin secretion (Fig. 3).[146]

Clinical studies—Most association studies have shown an increased risk of diabetes mellitus type 2 (DM2) with low 25OHD levels.[126,147–150] These studies have linked low 25OHD levels to both increased insulin resistance and impaired insulin secretion.[150–152] However, not all studies show this relationship,[126] and when corrected for BMI and obesity, the association may weaken.[153] RCTs have been mixed and generally small. One study in 35 vitamin D–deficient adolescent obese females given 4000 IU vitamin D per day or placebo showed a reduction in fasting insulin levels and HOMA-IR over a 6-month period.[154] A study of 89 obese vitamin D–deficient African Americans on a similar protocol showed increased insulin secretion following vitamin D supplementation, but insulin sensitivity was reduced.[155] A study using very high doses of vitamin D (mean 88,865 IU/wk for 1 year) versus placebo in 109 prediabetic subjects with 25OHD levels >30 ng/ml failed to demonstrate an effect on insulin secretion, insulin sensitivity, or progression to frank DM2. Serum calcium levels were not reported, but subjects on vitamin D achieved mean 25OHD levels of 70 ng/ml throughout the study. Pittas has recently initiated a large multicenter placebo controlled RCT to study the role of vitamin D in DM2, which hopefully will delineate this role definitively (NIH list of clinical trials).

Adipocyte and obesity

Cellular and animal studies—The adipocyte expresses both the VDR[156,157] and CYP27B1.[158] The impact of $1,25(OH)_2D$ on adipogenesis is dependent on species and level of differentiation of the cell at the time $1,25(OH)_2D$ is added to the medium—not unlike the situation in bone,[159] perhaps not surprisingly since adipocytes and osteoblasts can share a common precursor at least in the bone marrow. In particular, $1,25(OH)_2D$ promotes adipogenesis from human mesenchymal progenitor cells[160,161] but is inhibitory in mouse preadipocytes[162,163] at least in part by inhibiting the expression of inhibitors of Wnt/β-catenin signaling, thus promoting Wnt/β-catenin stimulation of osteoblastogenesis rather than adipogenesis. Human fibroblasts with VDR mutations are less likely to differentiate into adipocytes in adipogenic medium than normal fibroblasts.[164] Mice null for either the VDR or CYP27B1 have less adipose tissue then their normal controls[165] even on rescue diets to normalize serum calcium. These results correlate with increased energy expenditure and increased expression of the uncoupling protein UCP1 in their mitochondria. Moreover, these mice are resistant to diet-induced obesity. $1,25(OH)_2D$ inhibits the expression of UCP1 in brown adipose tissue, and overexpression of the VDR in adipocytes decreases energy expenditure leading to increased fat mass.[166]

Clinical studies—Obesity is associated with reduced 25OHD levels.[167] The explanation(s) for this association varies from increased tissue distribution (i.e., increased storage in fat),[168] decreased sunlight exposure due to lower outdoor activity levels, to decreased efficiency of vitamin D production in the skin.[169] However, clinical trials with vitamin D and calcium have had limited success with respect to reducing obesity or increasing energy expenditure.[170,171] Bariatric surgery, although correcting a number of metabolic consequences of obesity such as diabetes mellitus, does not reverse the vitamin D deficiency of obesity. Rather, because of its negative impact on vitamin D absorption, such surgery can make vitamin D deficiency worse, requiring higher than the usually recommended doses of vitamin D to correct the deficiency.[172,173]

Muscle and falls

Cellular and animal studies

The role of VDR and CYP27B1 in myocytes has been controversial. Although both are expressed in muscle precursor cells, their expression decreases with differentiation into adult muscle fibers[174] and was not found in earlier studies.[175] That said recent studies indicate that even in adult muscle, VDR is still expressed albeit at very low levels.[176] In myoprogenitors both 25OHD and $1,25(OH)_2D$ decrease proliferation and myotube formation, while increasing myotube size by regulating the expression of cell cycle regulators associated with changes in the forkhead box O3 and notch pathways.[174,177] The nongenomic actions of $1,25(OH)_2D$ have also received attention in muscle. Calcium, of course, is critical for muscle contraction and relaxation. $1,25(OH)_2D$ stimulates rapid calcium influx in a VDR-dependent fashion through store-operated and voltage-dependent channels, as well as stimulating the release of calcium from intracellular stores (Fig. 5).[178,179] These rapid effects involve the translocation of VDR from the nucleus to the membrane, where it is found in caveolae.[180–182] In the membrane, the VDR and/or or the

non-VDR receptor for 1,25$(OH)_2$D, namely Pdia3 (protein-disulfide isomerase-associated 3, aka MARRS/Erp57/GRp58/ER60), mediate 1,25$(OH)_2$D activation of the cyclic AMP, phospholipase C, and MAP kinase pathways.[178,179] However, the physiologic significance of these nongenomic pathways remains controversial. In humans, as well as rodents, vitamin D deficiency leads to a preferential loss of type II muscle fibers associated with fatty infiltration, fibrosis, and loss of strength.[183] This results, at least in part, from activation of the ubiquitin proteasome pathway.[184] Vitamin D replacement reversed these changes, but supplementation with high dietary calcium alone was only partially protective.[184]

Clinical studies

Vitamin D deficiency is associated with increased falls.[185] However, trials evaluating the ability of vitamin D to prevent falls have produced mixed.[186–189] A large meta-analysis of 26 RTCs in elderly females showed benefit with respect to fall risk reduction especially in vitamin D deficient subjects who were supplemented with both vitamin D and calcium,[188] although the effect was generally modest.[190] One interesting study evaluating vitamin D supplementation of vitamin D–deficient adults used NMR spectroscopy to measure phosphate labeled metabolites in muscle. These investigators observed faster recovery of phosphocreatine levels in muscle after exercise associated with correction of symptoms of muscle weakness in those receiving the vitamin D.[191] However, efforts to provide very large doses of vitamin D (or calcifediol) at infrequent intervals (e.g., 500,000 IU annually or 60,000 IU every mo) have not been successful, and may even increase the fall risk.[192,193]

Skin and skin diseases

The skin consists of the epidermis to which the hair follicle is attached underlain (epidermis) or surrounded by the dermis with which these structures have strong interactions. Hair follicle cycling, for example, is critically dependent on a specialized group of mesenchymal cells known as the dermal papilla. Both the dermis and epidermis contain specialized immune cells and melanocytes that play important roles in various skin diseases. Both the hair follicle and epidermis are examples of continuously regenerating tissues: the hair follicle undergoing repeated cycles of growth (anagen), collapse (catagen), and rest (telogen) before being reactivated, while the epidermis is continuously renewing itself as stem cells in the stratum basale divide to form transit amplifying cells (TAC) that proliferate then start the differentiation process forming first the stratum spinosum where mature keratins (K1, K10), involucrin (an important component of the cornified envelope), and transglutaminse K (the enzyme cross linking involucrin and other structural components of the cornified envelope), are first expressed. The cells from the stratum spinosum further differentiate into the stratum granulosum, where the bundling protein filaggrin and another critical component of the cornified envelope, loricrin, are made. Furthermore, in the stratum granulosum lipid producing and processing enzymes are expressed that make the specialized ceramides and other lipids that are packaged into lamellar bodies for secretion into the cornified envelope, and that serve to waterproof this terminally differentiated, enucleated layer. 1,25$(OH)_2$D and calcium are critical regulators of these events (Fig. 4).[194]

Cellular and animal studies

As is well known, the epidermis is the major source of vitamin D_3 in the body, produced from 7-dehydrocholesterol in the epidermis under the influence of UVB to form first pre-vitamin D_3, which is subsequently isomerized to vitamin D_3. The epidermis also expresses the 25-hydroxylase CYP27A1, possibly CYP2R1,[195,196] the 1α-hydroxylase CYP27B1,[197] and the VDR.[198] Thus, the keratinocyte can make its own $1,25(OH)_2D$ from its own substrates, and respond to the $1,25(OH)_2D$ it produces. The highest levels of VDR and CYP27B1 are found in the stratum basale. The VDR is also highly expressed in the stem cells of the hair follicle (bulge region), and deletion or mutations of VDR block post-natal hair follicle regeneration in humans, as well as in mice.[199–201] Of particular interest is that hair follicle cycling does not require $1,25(OH)_2D$, in that mice or humans lacking or having mutations in CYP27B1 do not demonstrate abnormal hair follicle cycling.[202,203] Activation of the stem cells in the bulge[204,205] and epidermis[204,206] involve β-catenin signaling and both require the VDR to do so. However, subsequent differentiation, at least in the epidermis, is blocked by Wnt/β-catenin signaling. What is less clear is the role played by $1,25(OH)_2D$ in this function of the VDR. β-Catenin binds to the VDR in the AF2 domain.[207] Like that of the coactivators to be discussed below, this binding is $1,25(OH)_2D$ dependent. Such binding can promote ligand-dependent VDR transcriptional activity, but block that of β-catenin regulated proliferation.[207,208] This appears to be central to the ability of $1,25(OH)_2D$ to promote differentiation of keratinocytes (Fig. 4). On the other hand, β-catenin can bind to the VDR in a $1,25(OH)_2D$-independent fashion,[209] perhaps mediating its stem cell–activating role in both epidermal and hair follicle stem cells, promoting differentation. In the keratinocyte, the function of the VDR is also regulated by two major coactivator complexes: mediator (originally known as DRIP or VDR interacting protein) and the steroid hormone receptor complexes (SRC) 2 and 3.[13] Mediator 1 (Med1), the main VDR-binding component of the Mediator complex, is expressed primarily in the proliferating cells of the stratum basale and hair follicle, whereas SRC3 is expressed primarily in the more differentiated layers of the epidermis.[13] These different coactivator complexes control different aspects of VDR action, with Med 1 more involved in proliferation and hair follicle cycling, whereas SRC2 and SRC3 are more involved in maintenance of the barrier function of the skin including its innate immune function.[210–212] That said, these coactivator complexes regulate more than just VDR, and in the case of hair follicle cycling, deletion of Med1 accelerates this process unlike VDR deletion that blocks it.[213]

Calcium is also critical for epidermal differentiation, acting in concert with $1,25(OH)_2D$.[214] The epidermis and hair follicle express the calcium sensing receptor (CaSR) that is critical for calcium induction of keratinocyte differentiation.[215,216] Keratinocyte-specific deletion of CaSR results in impaired epidermal differentiation and barrier function, but hair follicle cycling is not affected.[217] Both calcium/CaSR and $1,25(OH)_2D$/VDR are required for the formation of the E-cadherin–catenin complex. This complex plays a central role during epidermal differentiation through its regulation of phosphoinositide processing in the membrane via phosphatidylinositol 3 kinase (PI3K) and phosphatidyl inositol phosphate 5 kinase 1α (PIP5K1a), the subsequent activation of PLCγ1 by phosphatidylinositol trisphosphate (PIP3) (the product of PIP5K1α acting on phosphatidylinositol bisphosphate

(PIP2)), generating the important signaling molecules inositol trisphosphate (IP3) and diacylglycerol (DG) that stimulate intracellular calcium release and protein kinase C activity, respectively.[194] Moreover, by binding β-catenin (preventing its activation and nuclear transcription) and α-catenin (the link between the E-cadherin–catenin complex and the cytoskeleton), this complex blocks proliferation while facilitating cell–cell adhesion and further downstream signaling via the cytoskeleton.[214] Recent studies have shown the importance of the VDR and the CaSR in both stem cell activation and E-cadherin–catenin complex formation in the response of the skin to wounding[218] and skin tumor formation.[219]

Clinical studies

Psoriasis, a hyperproliferative disease of the skin, is one of the few non skeletal actions of vitamin D to have a well-validated clinical application for $1,25(OH)_2D$ and its analogs. Psoriasis is a complex disease of autoimmunity, so the mechanisms by which $1,25(OH)_2D$ suppresses the immunologic aspects of psoriasis will be discussed in the immune section. That said, the erythematous scaling plaques associated with psoriasis are the result of increased keratinocyte hyperproliferation and decreased differentiation driven by the inflammatory component.[220] A number of clinical trials have demonstrated the efficacy and safety of $1,25(OH)_2D$ and its analogs in the treatment of psoriasis, as monotherapy or in combination with topical glucocorticoids.[221–224] Successful treatment of other skin diseases with $1,25(OH)_2D$ and its analogs has been less clear. Given that $1,25(OH)_2D$ promotes barrier formation[211] and cathelicidin production in keratinocytes,[225] the efficacy of $1,25(OH)_2D$ treatment on atopic dermatitis has been examined, but the results, while encouraging, are not conclusive (Fig. 4).[226] Ichthyosis is a disorder of keratinization. Individuals with ichthyosis can have very low 25OHD levels and rickets.[227] However, it is likely that ichthyosis is the cause of the vitamin D deficiency rather than the other way around, and a trial with the $1,25(OH)_2D$ analog calcipotriol did not improve the disease.[228]

Immune system and immunologic diseases

The immune system is comprised of two major but interacting forms of immunity: adaptive and innate. Adaptive immunity is initiated by cells specialized in antigen presentation, dendritic cells (DCs) primarily, and the cells responsible for antigen recognition, T and B lymphocytes, by which they are activated to carry out specialized functions including cytokine production, antibody production, and cell killing. The broad classification of T helper and regulatory cells differentiating from parent $CD4^+$ T lymphocytes includes Th1, Th2, Th9, Th17, and Treg cells. This response is adaptive because the cells tailor their response to the antigen presented. The innate immune response involves the activation of Toll-like receptors (TLRs, of which there are 10 in the human genome) that can be expressed by a number of cell types, including polymorphonuclear cells (PMNs), monocytes, macrophages, and a wide variety of epithelial cells, including keratinocytes of the skin, gingiva, intestine, vagina, bladder, and lungs. TLRs are pathogen-recognition receptors that recognize various products of infectious agents, including bacteria and viruses, and trigger the TLR-expressing cell to produce cytokines or various antimicrobial peptides (AMPs), the best studied of which is cathelicidin. This response is innate because it is inherent to a cell

from its inception, requiring no adaptation.[229] The overall picture is that vitamin D signaling suppresses adaptive immunity, but promotes innate immunity.

The VDR and CYP27B1 are expressed in most if not all cells of the immune system including the epithelial cells at least when activated (Fig. 6).[230–232] Moreover, several of these cells express CYP2R1 and so theoretically can produce $1,25(OH)_2D$ from circulating vitamin D.[232] The regulation of CYP27B1 in these cells differs substantially from that in the kidney, being insensitive to hormonal regulators such as PTH and FGF23, its product $1,25(OH)_2D$, and calcium and phosphate levels. In these immune cells CYP27B1 is stimulated by cytokines such as tumor necrosis (TNF) α and interferon (IFN) γ.[233–236] Moreover, transcription of the enzyme that controls $1,25(OH)_2D$ levels within cells, CYP24A1, is absent, defective, or blocked,[232,237,238] essentially leaving $1,25(OH)_2D$ with minimum regulation. Thus, activation of these immune cells in diseases such as sarcoidosis or lymphomas can lead to hypercalcemia with elevated $1,25(OH)_2D$ levels.

Adaptive immunity

Cellular studies—$1,25(OH)_2D$ decreases the maturation of DCs, as noted by the decreased expression of HLA-DR and costimulatory molecules such as CD40, CD80, and CD86, thus decreasing their ability to present antigen.[239] By suppressing IL-12 production (important for Th1 development) and IL-23 and IL-6 production (important for Th17 development), the number of Th1 and Th17 cells is reduced, as is their ability to secrete IFN-γ and IL-2 (from Th1 cells) and IL-17 (from Th17 cells).[240–242] These actions limit further recruitment of T cells and their proliferation. The suppression of IL-12 also increases the development of Th2 cells and their production of IL-4, IL-5, and IL-13 further suppressing Th1 and shifting to a Th2 predominance (Fig. 6A). Th9 cells are induced by TGF-β and IL-4. $1,25(OH)_2D$ reduces IL-9 production by these cells.[243] $1,25(OH)_2D$ induces the differentiation of Treg cells as shown by increased FoxP3 expression.[244] Treg cells produce the regulatory cytokine IL-10 that suppresses the development of Th1 and Th17 leading to immune tolerance.[245] $1,25(OH)_2D$ can also modify the homing properties of T cells, for example by inducing the expression of CCR10, the receptor for CCL27, a keratinocyte specific cytokine, while suppressing CCR9, a gut homing receptor[232], potentially accounting for the different effects of $1,25(OH)_2D$ on the inflammatory process within different tissues. The regulation of a number of cytokines involved in the inflammatory process can be both direct and indirect and complex. For example $1,25(OH)_2D$ inhibition of IL-2 expression involves blocking NFAT binding to the IL-2 gene promoter and sequestration of Runx1 by the VDR.[241,246] Suppression of IFN-γ expression involves a negative VDRE in the IFN-γ gene promoter.[247] The mechanism of IL-17 expression involves blocking NFAT binding to the IL-17 gene promoter, sequestering Runx1 by the VDR, and induction of Foxp3.[241] $1,25(OH)_2D$ blocks NF-κB by inhibiting its nuclear translocation and binding to its consensus sequences and inhibiting the degradation of IκB (inhibitor of NF-κB).[248] Moreover, a negative VDRE has been found in the promoter of the RelB gene, an NF-κB family member[249]

Animal studies: Animal studies have demonstrated both the good and problematic aspects to the suppression of adaptive immunity by $1,25(OH)_2D$. Overall myelopoiesis and

composition of lymphoid tissue are normal in VDRKO mice, although abnormalities in immune responses to stimuli have been observed, some of which could be reversed with the rescue diet to normalize serum calcium.[250] However, a number experimental models of autoimmune diseases including rheumatoid arthritis, psoriasis, type 1 diabetes mellitus (NOD mouse), systemic lupus erythematosus (SLE), experimental allergic encephalitis (EAE, model for multiple sclerosis), and inflammatory bowel disease (IBD) have been prevented/ameliorated with the use of $1,25(OH)_2D$ or one of its analogs.[251] The importance of IL-10 in the immunomodulatory actions of $1,25(OH)_2D$ is demonstrated by the increased severity of IBD when IL-10 gene knockout mice are bred with VDRKO mice.[69] Moreover, transplantation models involving the aorta, bone, bone marrow, heart, kidney, liver, pancreatic islets, skin, and small bowel have demonstrated a reduction in rejection when the animals are treated with $1,25(OH)_2D$ or one of its analogs.[252] On the other hand, the promotion of Th2 numbers and function may have adverse effects on allergic diseases such as asthma and atopic dermatitis. In these diseases, Th2 cells, not Th1 and Th17 cells, dominate the inflammatory response. Calcipotriol, an analog of $1,25(OH)_2D$, stimulated thymic stromal lymphopoietin (TSLP) in keratinocytes leading to an increased expression of Th2 cytokines and increased inflammatory responses to allergen induced atopic dermatitis and asthma.[253] Other studies have been mixed. In normal mice $1,25(OH)_2D$ was shown to be protective against experimentally-induced asthma, including a reduction in IL-4 production and eosinophilic infiltration.[254] Part of this may relate to suppression of IL-9, a potent part of the inflammatory response in lungs.[243] However, using a very similar protocol, other studies have shown that mice lacking the VDR are also protected from experimentally-induced asthma.[255] Although the acute phase of atopic dermatitis is also marked by increased production of Th2 cytokines (IL-4, IL-5, IL-13) that can lead to suppression of antimicrobial peptides such as cathelicidin and increased susceptibility to infection, Th1 cells are predominant in the chronic phase.[256] $1,25(OH)_2D$, via its effects on the permeability barrier, increased numbers of Treg cells, and induction of the innate immune system can counter these effects and actually suppress Th2 function.[257] The effects of $1,25(OH)_2D$ on infections is also mixed. $1,25(OH)_2D$ inhibition of IFN-γ stimulation of reactive oxygen species and nitric oxide production,[258] or suppression of IL-17 (limiting its induction of AMPs and neutrophil recruitment)[259] have been shown to reduce resistance to infectious organisms such as Leishmania,[258] toxoplasma,[260] and Citrobacter.[261]

Clinical studies—Association studies have found inverse correlations between 25OHD levels and/or vitamin D intake and a number of autoimmune diseases including multiple sclerosis,[262] type 1 diabetes,[263,264] Crohns disease,[265] rheumatoid arthritis,[266] lupus,[267] and Graves thyroiditis.[268] Similarly, an inverse correlation was found between maternal 25OHD levels and the development of eczema and asthma in children[269] and, in adults, between 25OHD and asthma in the NHANES survey.[270] The majority, although not all, of studies have shown an inverse correlation between 25OHD and atopic dermatitis.[271] RTCs have not been plentiful, large, or consistent,[272–274] although a meta-analysis of 4 trials with vitamin D supplementation in atopic dermatitis demonstrated benefit.[275]

Innate immunity

Cellular and animal studies—Stimulation of TLR 2/1 in macrophages[276] or TLR2 in keratinocytes[225] leads to an increase in CYP27B1 and VDR expression. With adequate substrate (25OHD), these cells produce $1,25(OH)_2D$ that in turn induces AMPs such as cathelicidin and defensins (Fig. 6B). Cathelicidin, in turn, can kill intracellular organisms such as *Mycobacterium tuberculosis*. In keratinocytes, $1,25(OH)_2D$ also induces the TLR coreceptor CD14. Cathelicidin also promotes the chemotaxis of neutrophils, monocytes, macrophages, and T cells into the skin, and in this way links the adaptive and immune responses in the skin and other tissues.[277] It had been appreciated for some time that $1,25(OH)_2D$ was capable of inhibiting the growth of *M. tuberculosis in vitro*,[278] and the elucidation of the TLR–CYP27B1–VDR–cathelicidin pathway demonstrated the mechanism. Moreover, the dependence of the final induction of cathelicidin on the ambient 25OHD concentrations[279] explained the susceptibility of vitamin D–deficient subjects to this disease.[280] The murine cathelicidin gene lacks a VDRE and so is not responsive to $1,25(OH)_2D$. However, $1,25(OH)_2D$ stimulates the inducible NOS pathway by which it induces *M. tuberculosis* killing in macrophages.[281] Not all aspects of $1,25(OH)_2D$ induction of the innate immune system are beneficial, however. Chronic activation resulting in overexpression of cathelicidin may lead to the formation of a self–DNA complex that can be detected by plasmacytoid DCs, which become activated and contribute to the psoriatic process.[282]

Clinical studies—As noted earlier, in atopic dermatitis, production of cathelicidin and other AMPs is reduced by IL-4 and IL-13, and patients with atopic dermatitis are susceptible to microbial superinfections.[283] This likely contributes to the improvement of atopic dermatitis in most studies noted earlier. Unfortunately, the ability of vitamin D to treat *M. tuberculosis* even in vitamin D–deficient populations has not been universally successful.l[284–287]

Summary and conclusions

The extraskeletal actions of vitamin D are legion as befits a molecule ($1,25(OH)_2D$, the active metabolite of vitamin) whose receptor is found in nearly all cells, many of which also contain the enzyme (CYP27B1) that can produce $1,25(OH)_2D$ in the same cell. Indeed, thousands of cellular and animal studies indicate that vitamin D signaling has a profound effect on most physiologic processes, including cancer prevention, improved cardiovascular function, diabetes prevention, prevention of obesity, improved muscle function, enhanced barrier function of the skin, hair follicle cycling, and prevention of immune related diseases. Indeed, association studies in humans have linked vitamin D deficiency to diseases resulting from disruption of these physiologic processes. However, large RCTs that clearly demonstrate the promising potential of vitamin D in the prevention and treatment of these diseases have either not been done or have produced mixed results. Part of the problem relates to lack of pharmaceutical support for large RCTs involving a drug (i.e., vitamin D) that cannot be patented, or the inability to give high enough doses of the active metabolite or its analogs to get an effect without serious side effects, such as hypercalcemia and

hypercalciuria. However, several large government supported RCTs are ongoing and the results from which are eagerly awaited.

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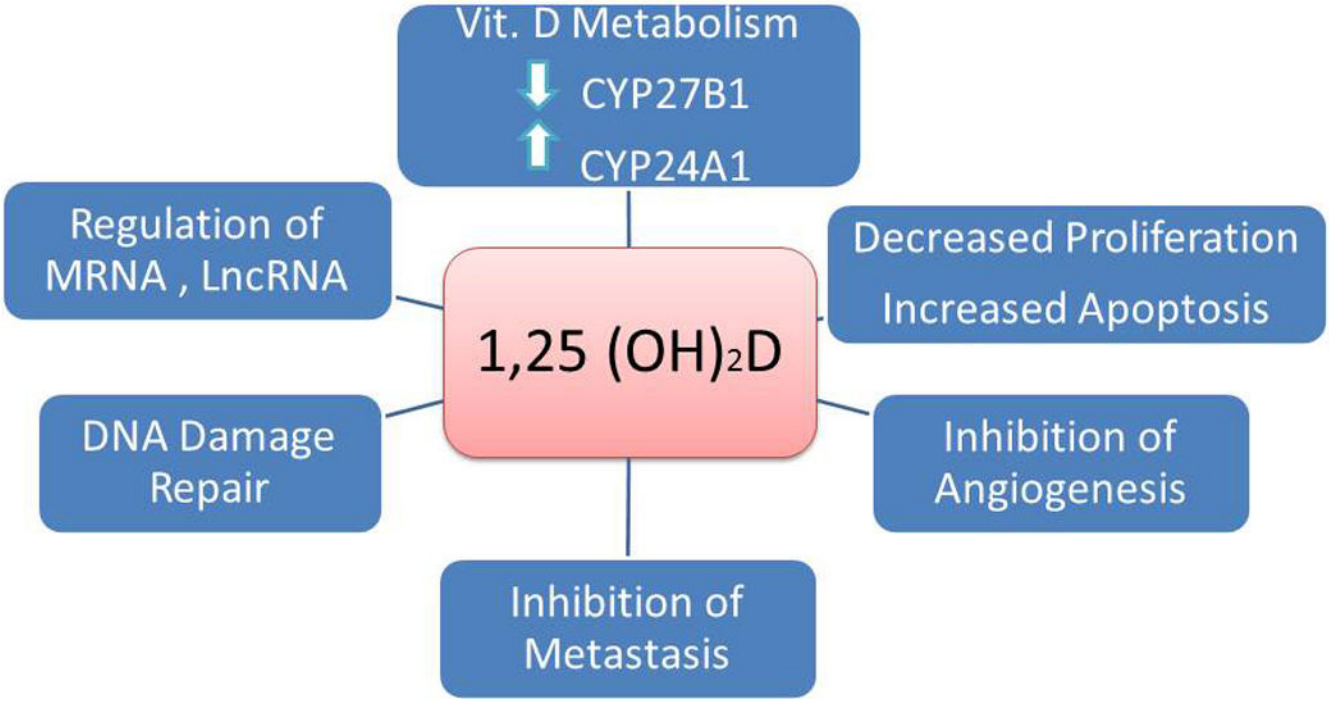


Figure 1.
Mechanisms by which 1,25(OH)2D suppresses cancer formation.

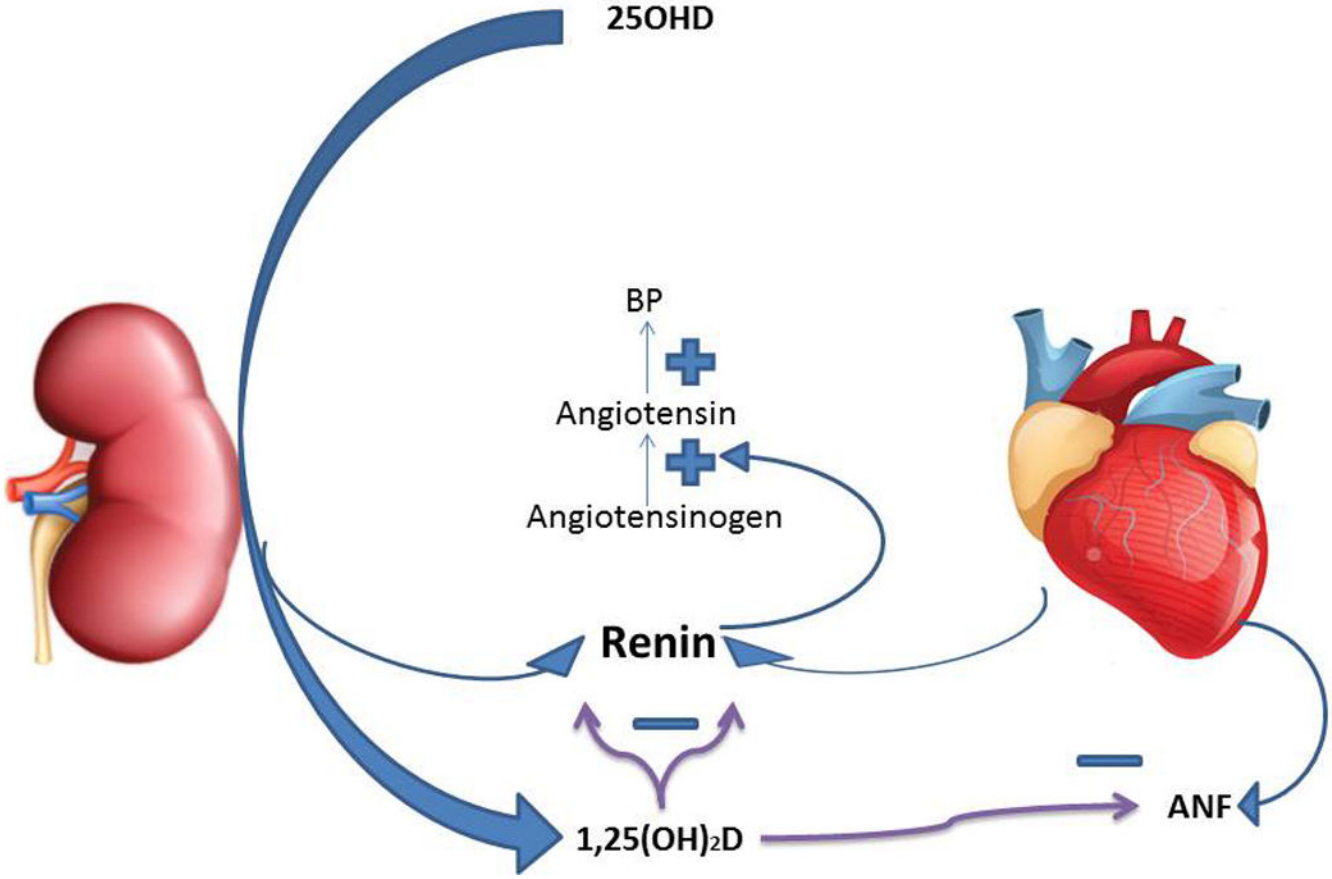


Figure 2.

Regulation of cardiovascular function. 1,25(OH)2D inhibits the production of renin by both the kidney and heart as well as ANF by the heart. Renin in turn catalyzes the production of angiotensin, a powerful vasculoconstrictor as well as stimulator of aldosterone production, that results in hypertension.

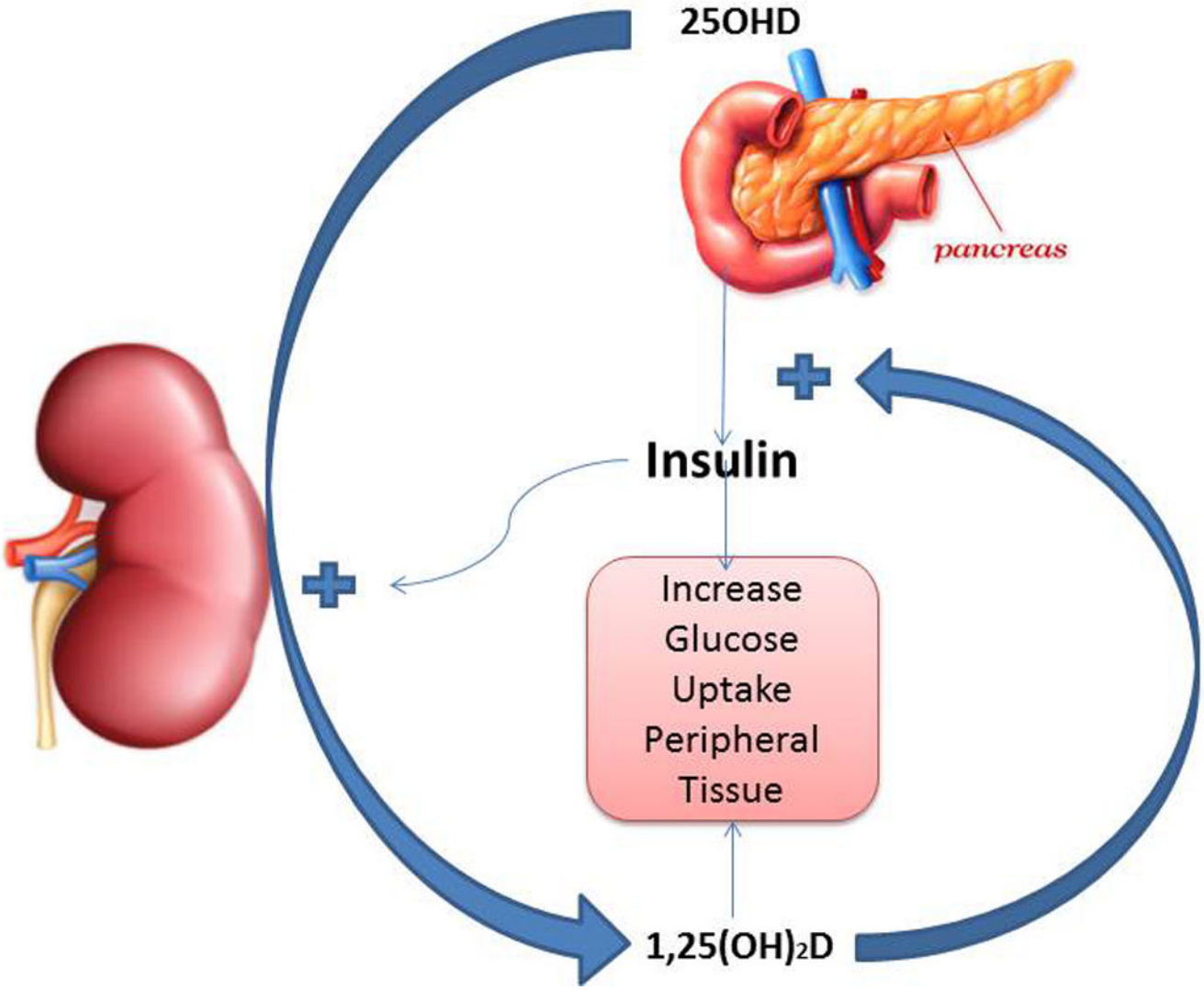


Figure 3.
Regulation of insulin secretion and peripheral action. 1,25(OH)2D along with calcium promotes the secretion of insulin and its stimulation of gluose uptake by peripheral tissues. Insulin in turn promotes the production of 1,25(OH)2D by the kidney.

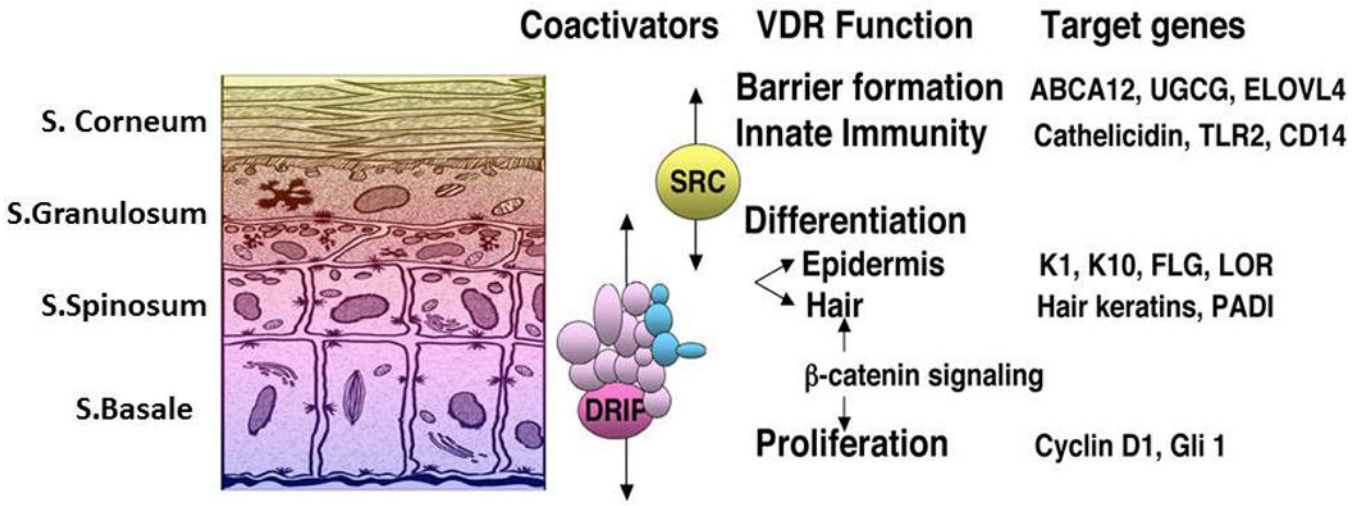


Figure 4.

Sequential regulation of epidermal differentiation by 1,25(OH)2D–VDR and its coactivators. The DRIP (Mediator) complex is located primarily in stratum basale/spinosum and modulates 1,25(OH)2D–VDR regulation of proliferation, hair follicle cycling, and the early stages of differentiation, whereas SRC2/3 complexes are preferentially expressed in the upper layers of the epidermis where they modulate 1,25(OH)2D/VDR regulation of barrier function and innate immunity.

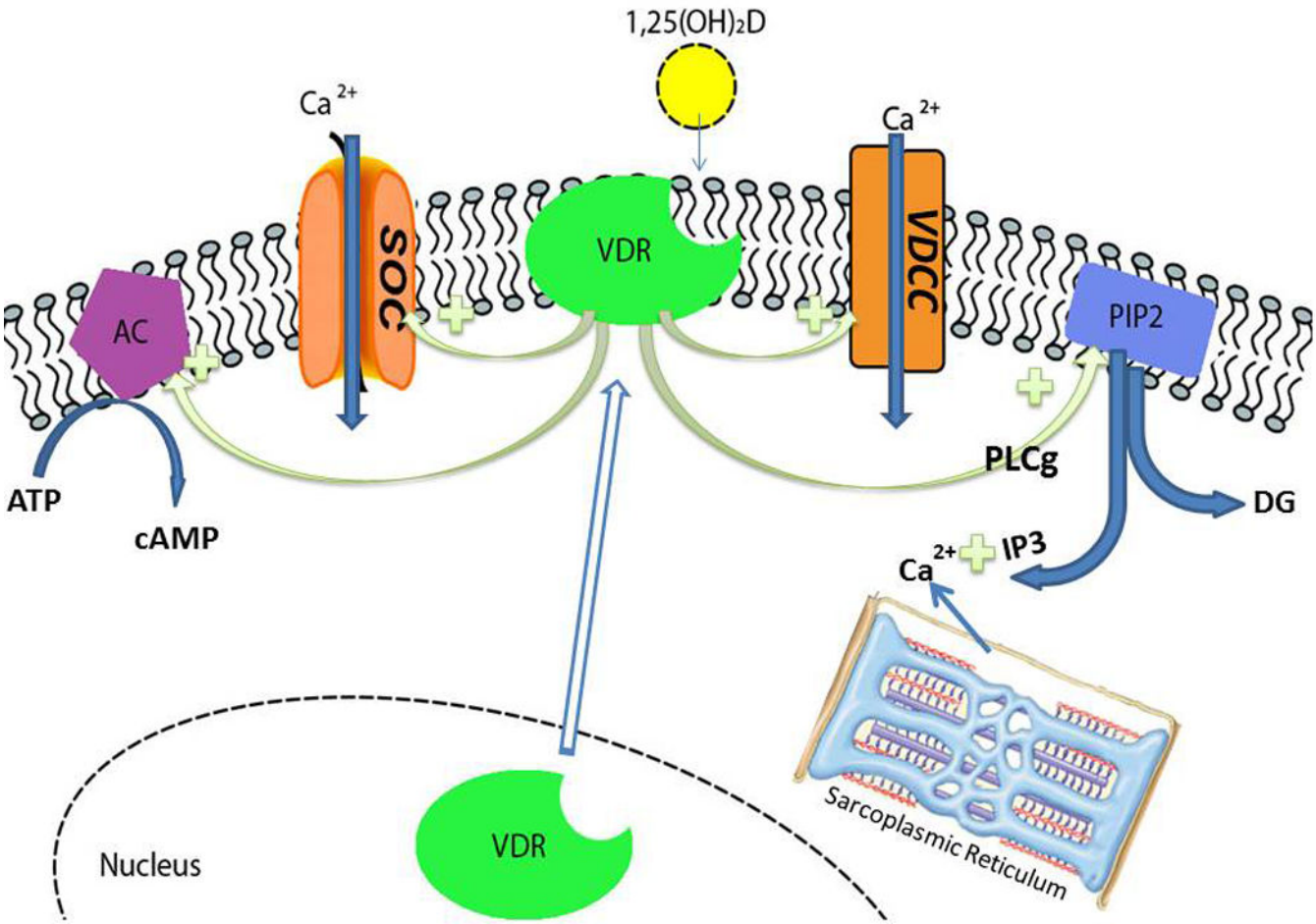
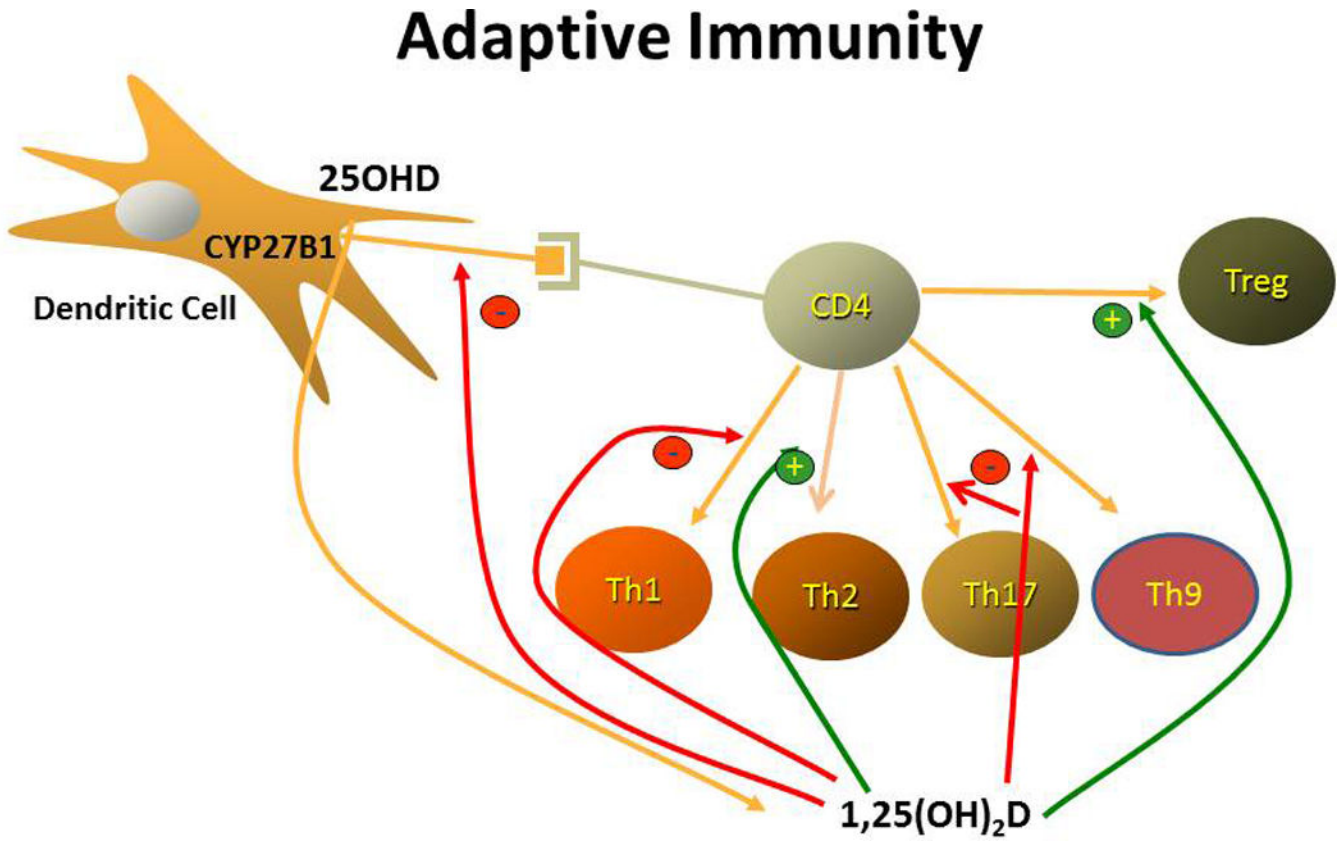


Figure 5.

The rapid actions of 1,25(OH)2D–VDR on calcium flux within the muscle cell. VDR is translocated from the nucleus to the membrane where it is activated by 1,25(OH)2D to stimulate calcium influx through store operated (SOC) and voltage dependent (VDCC) calcium channels. 1,25(OH)2D–VDR also activates phospholipase C γ (PLCγ) that in turn hydrolyzes phosphatidylinositol bisphosphate (PIP2) to inositol trisphosphate (IP3) and diacyl glycerol (DG). IP3 stimulates the release of calcium from the sarcoplasmic reticulum; DG activates protein kinase C. 1,25(OH)2D/VDR also activates adenyl cyclase (AC), producing cAMP, and activates the mitogen activated protein kinase (MAPK) pathway (not shown).



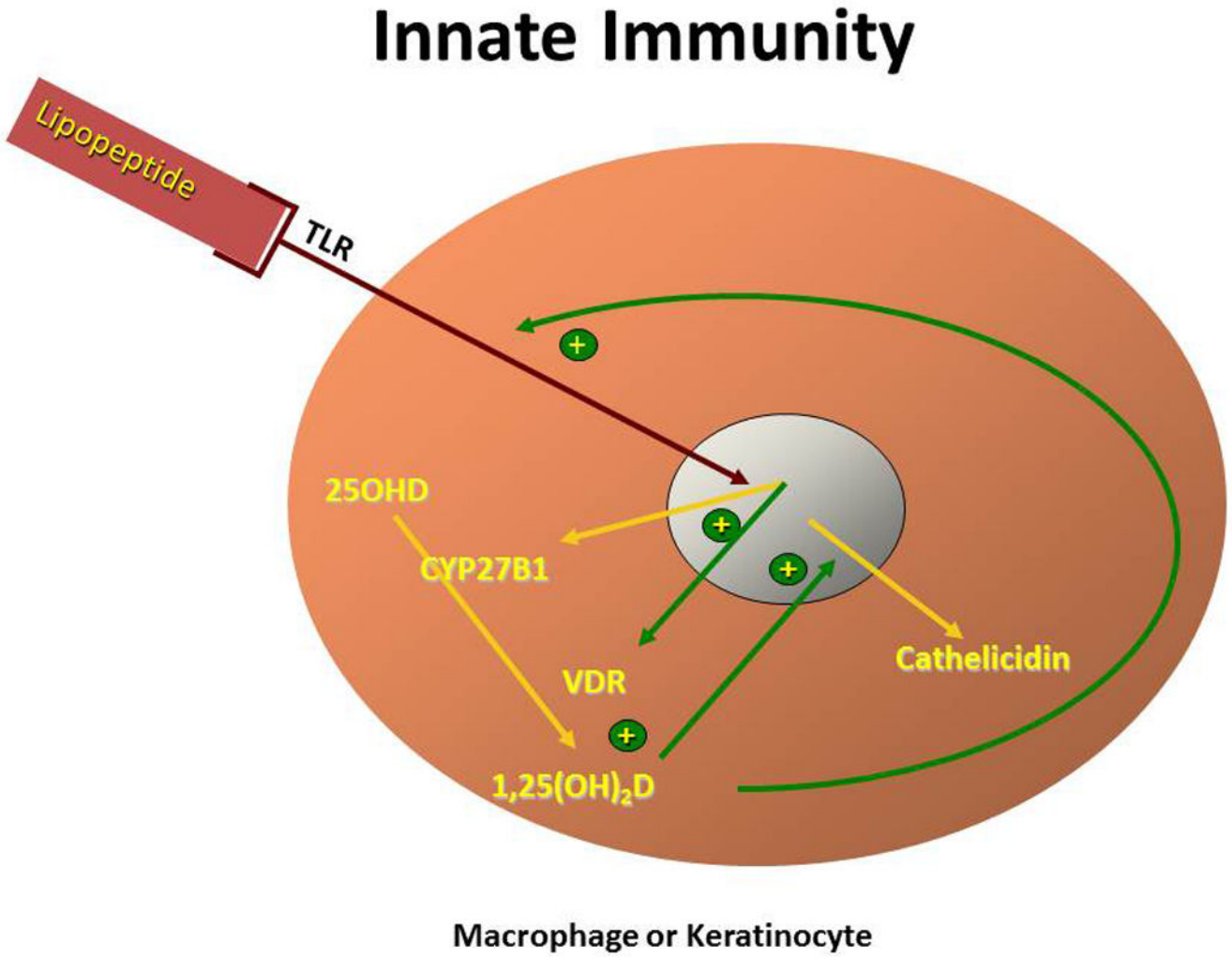


Figure 6.

Regulation of the adaptive and innate immune pathways. (A) Adaptive immunity. 1,25(OH)2D, which is produced by dendritic cells, decreases the maturation and antigen presenting ability of dendritic cells and alters the profile of T helper cells that differentiate from the activated CD4 parent cell. In particular, 1,25(OH)2D reduces the formation of Th1, Th17, and Th9 cells, while promoting the differentiation of Th2 and Treg cells. The result is overall suppression of the adaptive immune pathway. (B) Innate immunity. Activation of selective Toll-like receptors (TLR1/2) by products of infectious organisms such as the lipopeptides from *M. tuberculosis* results in the induction of both the VDR and CYP27B1. In the presence of adequate substrate (25OHD), 1,25(OH)2D is produced that, in combination with the VDR, induces the formation of antimicrobial peptides such as cathelicidin, whichi are capable of killing intracellular organisms like *M. tuberculosis*.