Biomedicine & Pharmacotherapy 177 (2024) 117001

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Advances in biomedical applications of vitamin D for VDR targeted management of obesity and cancer

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ARTICLE INFO

Keywords:
Obesity
Vitamin D
$1,25(OH)_2D_3$
Cancer
VDR
Carcinogenesis

ABSTRACT

Background: $1,25(OH)_2D_3$ is a fat-soluble vitamin, involved in regulating Ca^{2+} homeostasis in the body. Its storage in adipose tissue depends on the fat content of the body. Obesity is the result of abnormal lipid deposition due to the prolonged positive energy balance and increases the risk of several cancer types. Furthermore, it has been associated with vitamin D deficiency and defined as a low $25(OH)_2D_3$ blood level. In addition, $1,25(OH)_2D_3$ plays vital roles in Ca^{2+}-P_i and glucose metabolism in the adipocytes of obese individuals and regulates the expressions of adipogenesis-associated genes in mature adipocytes.

Scope and approach: The present contribution focused on the VDR mediated mechanisms interconnecting the obese condition and cancer proliferation due to $1,25(OH)_2D_3$-deficiency in humans. This contribution also summarizes the identification and development of molecular targets for VDR-targeted drug discovery.

Key findings and conclusions: Several studies have revealed that cancer development in a background of $1,25(OH)_2D_3$ deficient obesity involves the VDR gene. Moreover, $1,25(OH)_2D_3$ is also known to influence several cellular processes, including differentiation, proliferation, and adhesion. The multifaceted physiology of obesity has improved our understanding of the cancer therapeutic targets. However, currently available anti-cancer drugs are notorious for their side effects, which have raised safety issues. Thus, there is interest in developing $1,25(OH)_2D_3$-based therapies without any side effects.

1. Introduction

The global increase in life expectancy has raised the cancer mortality rate in recent years [1]. Cancer is a highly heterogeneous group of diseases with abnormal cell growth [2]. The basic molecular mechanism underlying cancer involves the accumulation of genetic mutations, enhanced oncogene, and reduced tumor suppressor gene activities [3,4]. The genomic variabilities are modulated by epigenetic changes caused by chromatin-modifying enzymes and several transcription factors [4] for example, cytokines and chemokines in the cellular microenvironment [5]. Thus, epigenetic changes may have dual impacts on cancer development. The chemotherapy, radiotherapy, and surgical treatments of cancer are very expensive and have serious side effects [6]. Thus, there is an urgent need to develop cheap, and side-effect-free anti-cancer therapeutics. In this regard, $1,25(OH)_2D_3$ has attracted attention as a low-cost, readily available natural compound [7]. $1,25(OH)_2D_3$ is biologically synthesized in skin under the exposure of UV-B [8] [9]. $1,25(OH)_2D_3$ has a direct impact on the expression of several genes [10] via vitamin D receptor (VDR) [11]. Moreover, cytosolic VDRs have been reported to have non-genomic activities. Cytosolic VDRs

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https://doi.org/10.1016/j.biopha.2024.117001
Received 14 February 2024; Received in revised form 11 June 2024; Accepted 17 June 2024
Available online 26 June 2024

regulate signaling pathways affecting ion channels and enzymes (kinases and phosphatases) [12,13], and thus, $1,25(OH)_2D_3$ and its metabolites may effectively modulate intracellular signaling and impact cellular growth, differentiation, and apoptosis.

Obesity is a serious problem, characterized by the deposition of excess lipid and subsequent medical complications [14] [15]. Obesity is common in developed countries [16] and has been considered a major pathogenic factor for various diseases including cancer, which kills around 38.0 million people annually [17,18]. Furthermore, the incidences of overweight and obesity-linked diseases are increasing worldwide [19]. Obesity is usually diagnosed on the basis of body mass index (BMI) [20]. However, BMIs do not give information about the amount of body fat [21]. The BMI has been correlated with visceral fat accumulation, which is associated to the enhanced risks of several obesity-linked chronic ailments [22]. The subcutaneous adipose tissue (SAT) is metabolically less active than the visceral adipose tissue (VAT), which is responsible for synthesizing hormones and cytokines required for normal cellular functions. Furthermore, if the levels of these hormones and cytokines are altered, they can induce chronic inflammation and insulin resistance [23]. Several theories have been proposed to explain the relation between cancer and obesity. These theories are based on a strong correlation between VAT and SAT [24]. These adipose tissues (AT) have been shown to strongly resist the antilipolytic function of insulin, and thus, to alter insulin metabolism and enhance the release of glucose and lipoproteins [25]. In addition, in obese individuals, hypertrophic adipocytes secrete high levels of pro-inflammatory agents, such as leptin, IL-6, resistin, and TNF-α [26]. A number of clinical trials have reported that obesity lowers the serum vitamin D level [27]. Vitamin D is a fat-soluble secosteroid that exhibit an important role in calcium homeostasis and bone metabolism through VDR [28]. Since VDR has been reported to be present in almost all types of human cells, huge efforts have been made to determine the extra skeletal roles of $1,25(OH)_2D_3$. Moreover, the role of $1,25(OH)_2D_3$ in the development of cancer has been highlighted by several research groups. The elevated $1,25(OH)_2D_3$ concentrations have been linked with low risks of cancer development [29,30]. Also, VDR has been reported to be abundantly expressed in AT and performs a significant role in adipogenesis and energy metabolism. Furthermore, the expression of VDR decreases as adipocyte differentiation advances and contributes to obesity associated risks [31,32].

Several studies indicated that the decrease in $1,25(OH)_2D_3$ response and metabolism is linked with cancer progression [33]. However, the exact mechanism(s) related with the relationship between $1,25(OH)_2D_3$ and cancer development remains unclear. The relation between the status of $1,25(OH)_2D_3$ and obesity-associated cancers is still debatable. However, a bidirectional relationship cannot be ruled out. Therefore, this review was undertaken to highlight the complicated relationships between $1,25(OH)_2D_3$ deficiency, obesity, and cancer risk. This article also highlights the contributions of several factors, such as poor lifestyle choices, psychological and social factors, insufficient sun exposure, and VDR gene variations, to the risks of obesity and cancer development.

2. Factors responsible maintaining vitamin D homeostasis and biological roles

$1,25(OH)_2D_3$ is an important micronutrient and functions as a secosteroid prohormone [34]. Various $1,25(OH)_2D_3$ analogs have been reported to possess biological activities (Fig. 1). Vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol) are the main biological precursors of $1,25(OH)_2D_3$ synthesis.

The presence of $-CH_3$ and C═C at C_{24} in the structure of ergocalciferol makes it different from cholecalciferol. Therefore, the clearance of ergocalciferol was shown to be quicker than that of cholecalciferol [35]. The biological half-life of $1,25(OH)_2D_3$ has been reported to be lesser (4–15 h) [36,37] than $25(OH)_2D_3$ (21–30 days) [38]. Ergocalciferol is derived from food sources (mushrooms grown in UV light) [39], whereas cholecalciferol is derived from animal-based food sources [40]. The inactive form of pre-vitamin D is photochemically synthesized from 7-DHC in skin under UV-B exposure [41]. Furthermore, this inactive pre-vitamin D has been reported to metabolize in three major steps under the influence of different cytochrome P450 enzymes such as 25-hydroxylation by CYP2R1, 1α-hydroxylation by CYP27B1, and 24-hydroxylation by CYP24A1 [42,43]. In blood, the vitamin D-binding protein (VDBP) has been reported to transport photochemically synthesized pre-vitamin D to liver, where it is metabolized into $25(OH)_2D_3$ by 25-hydroxylase (CYP2R1 or 25-OHase) [44], which is the circulating form and used to determine as the marker of vitamin D deficiency [45]. The inactive $25(OH)_2D_3$ is transformed into active $1,25(OH)_2D_3$ in kidneys by 1α-hydroxylase (CYP27B1 or 1α-OHase) [44]. The active $1,25(OH)_2D_3$ exerts its biological functions through VDR in target tissues [46] (Fig. 2). Genes such as CYP450 family 2 subfamily R member 1/25-hydroxylase (CYP2R1) and 7-dehydrocholesterol reductase (DHCR7) have been reported to participate in the synthesis of $1,25(OH)_2D_3$ from 7-DHC. The major function of DHCR7 is to convert 7-DHC to form cholesterol and thus decreasing the synthesis of $1,25(OH)_2D_3$ [47–50]. It has been reported that almost 80 % of vitamin D_3 originates from skin and that the remaining 20 % originates from dietary ergocalciferol [51].

2.1. Abnormal metabolism

The serum level of $1,25(OH)_2D_3$ is influenced by several factors, such as limited sun exposure, garments, less outdoor activity, and the reduced synthesis capacity of skin in obese individuals [52,53]. Excess body fat can sequester cholecalciferol and make it unavailable for other tissues. Sequestration of cholecalciferol refers not only to their failure to dissolve in AT but also their inability to enter the liver through circulation as substrates for 25-OHase [54]. The low $25(OH)_2D_3$ serum levels in obese individuals may be attributable to the volumetric dilution in large adipose stores [55]. Body fat content and body weight are inversely associated with serum/tissue level of $25(OH)_2D_3$. This inverse relationship has been associated with larger distributable volumes of $1,25(OH)_2D_3$ and $25(OH)_2D_3$ in tissues, which suggests that volumetric dilution is the

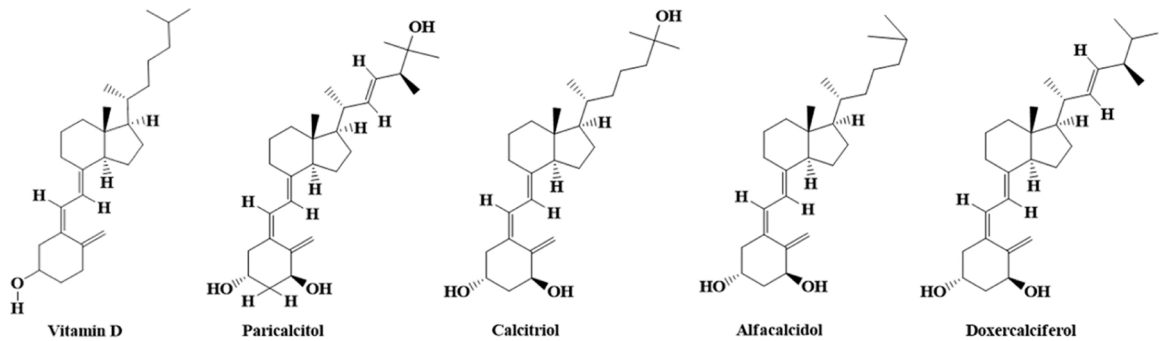

Fig. 1. Molecular structure of vitamin D and its major analogs.

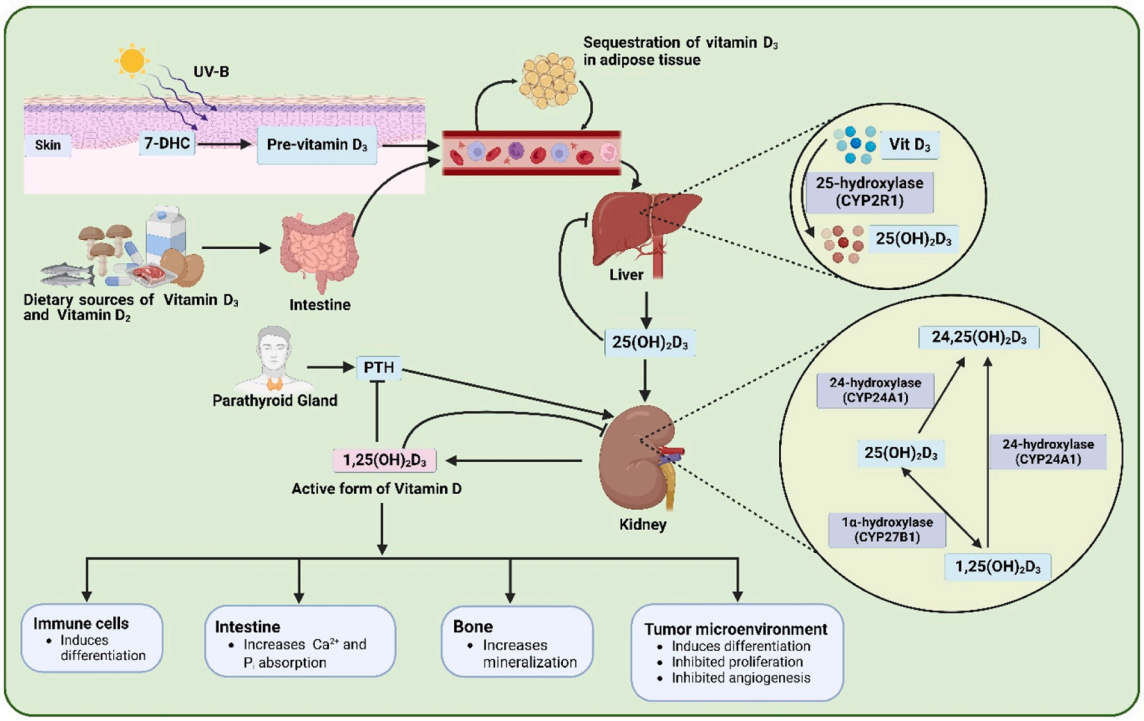

Fig. 2. Overview of $1,25(OH)_2D_3$ metabolism. The 7-DHC is photochemically converted to pre-vitamin D_3 under UV-B (290–315 nm). Vitamin D_3 is synthesized from the isomerization of pre-vitamin D_3 or dietary vitamin D_3 absorbed in the gut and transported to liver through the lymphatic system with the help of VDBP. Vitamin D_3 is hydroxylated into $25(OH)_2D_3$ by liver 25-OHase which further hydroxylated to form active $1,25(OH)_2D_3$ molecule by 1α-OHase in kidney. The hydroxylation of $25(OH)_2D_3$ is repressed by Ca^{2+}, Pi and $1,25(OH)_2D_3$ itself and encouraged by PTH. The degradation products formed after hydroxylation activity of 24-OHase (CYP24A1 gene) consequently excreted. **Abbreviations:** 7-DHC - 7-dehydrocholesterol; 25-OHase: 25-hydroxylase; $25(OH)_2D_3$: 25-hydroxycholecalciferol; PTH: parathyroid hormone; $1α,25(OH)_2D_3$: calcitriol; 1α-OHase: 1α-hydroxylase.

most cost-effective treatment for a $1,25(OH)_2D_3$ deficient obese individual [56]. A radiolabeling study indicated that almost 80 % of administered $25(OH)_2D_3$ was deposited in rat AT and then released slowly into blood [57]. The volumetric dilution hypothesis is founded on the concept of sequestration. Other authors proposed that $1,25(OH)_2D_3$ sequestration in AT decreases its bioavailability in obese individual [58]. $25(OH)_2D_3$ can be sequestered and trapped in the AT of obese individuals. However, concentrations of sequestered $25(OH)_2D_3$ have been reported to be non-uniform or non-consistent across fat deposits [59]. Furthermore, $1,25(OH)_2D_3$ metabolism can be altered by obesity due to changes in the levels of vitamin D-metabolizing enzymes in adipocytes. Interestingly, higher $25(OH)_2D_3$ levels have been described to increase energy expenditure by uncoupling oxidative phosphorylation in ATs [60]. Moreover, a lack of $25(OH)_2D_3$ may increase the concentration of PTH and Ca^{2+} influx in adipocytes and increase lipogenesis (acetyl co A is converted to triglycerides for fat storage and packed inside lipid droplets) [61]. Indeed, a low $25(OH)_2D_3$ status increases intracellular Ca^{2+} concentrations in adipocytes [62]. The thresholds level of serum $25(OH)_2D_3$ for defining sufficiency, and deficiency proposed by scientific societies has been reviewed previously [63].

Genetic factors such as VDR variants have also been shown to significantly maintain serum $25(OH)_2D_3$ concentrations [64]. Furthermore, the low level of $25(OH)_2D_3$ might also have an important role in the development of obesity-linked cancer. These multiple factors lead to a complex and multifactorial relationship between a low $25(OH)_2D_3$ level and obesity-related cancer development. The impaired hydroxylation of $25(OH)_2D_3$ in AT has demonstrated a linkage with obesity [65]. It has been reported that 25-hydroxylation is usually reduced in fatty liver patients, which is a common complication under obese conditions [66,67].

2.2. Reduced sunlight exposure

Sunlight is a crucial factor for endogenous $1,25(OH)_2D_3$ production [68]. Less skin exposure to the sun reduces the cutaneous capacity of 1, $25(OH)_2D_3$ synthesis [69]. It was proposed that obese individuals may produce more cutaneous $1,25(OH)_2D_3$ [70] than normal individuals based on skin area considerations [71]. However, the prevalence of 1,25 $(OH)_2D_3$ deficiency is highest among the obese individuals [72]. Obese individuals tend to live a sedentary life, avoid physical activity [73], and cover up when outside, thus restricting endogenous cholecalciferol production in skin [74]. However, season, latitude, altitude, time of day, air pollution, use of sunscreen, skin pigmentation, and aging have also been reported to play crucial roles in sunlight-induced $1,25(OH)_2D_3$ production [75]. Furthermore, sunlight exposure did not differ by BMI in different geographical regions [67,76]. The cutaneous synthesis of 1, $25(OH)_2D_3$ were identical when people with different BMIs were exposed to UV-B [67,77].

2.3. Lower Dietary Intake

$1,25(OH)_2D_3$ deficiency has been predicted to place a considerable burden on the healthcare system. The lifestyle patterns, including eating habits severely limits the intake of vitamin D-rich food options [78]. Obesity is associated with poor eating habits and possibly lower vitamin D consumption [79]. The lower intake of Ca^{2+} and vitamin D has also been reported to be related with obesity in humans [80]. This hypothesis is considered less important because dietary vitamin D contributes negligibly to the total requirements [67,81]. In USA, the food fortification has been another strategy to improve the dietary source of 1,25 $(OH)_2D_3$ [63,82–84]. However, in Japanese diet, fish has been considered as the main source of $1,25(OH)_2D_3$ [85].

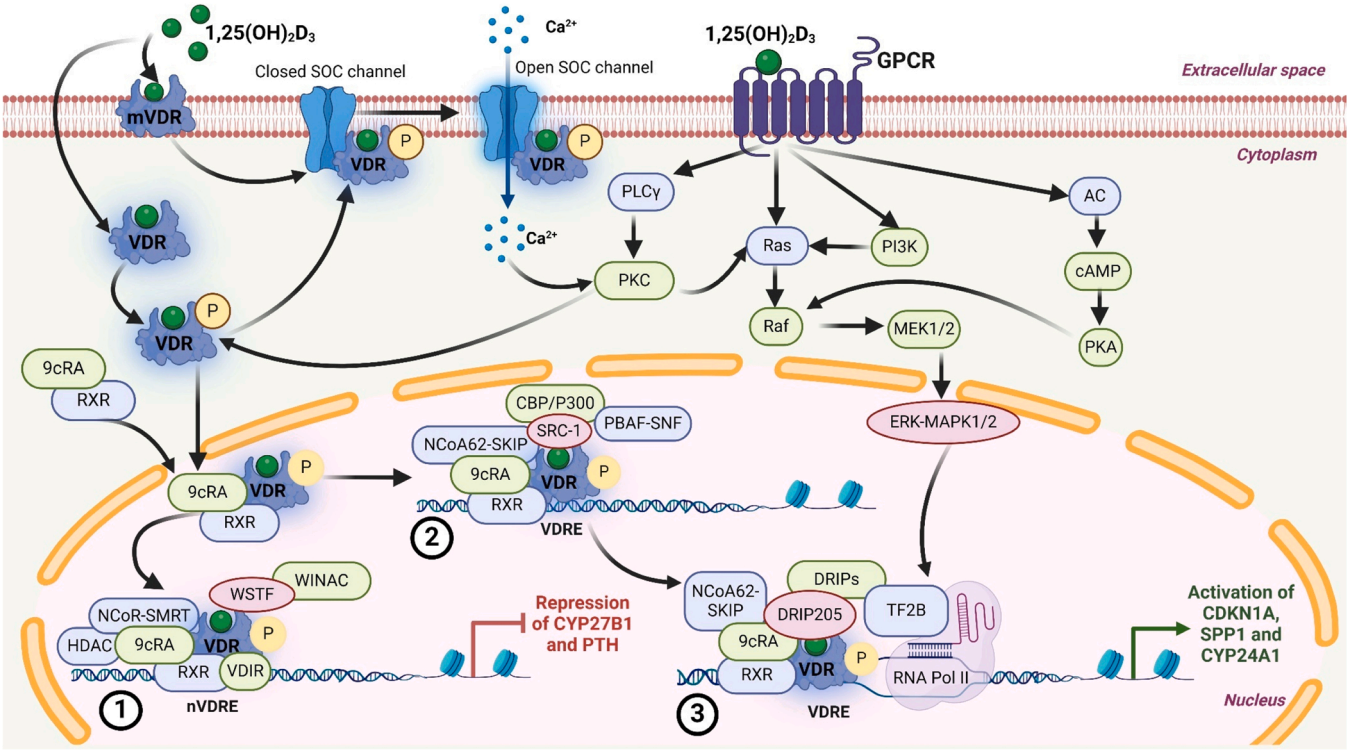

Fig. 3. $1,25(OH)_2D_3$-induced regulation of gene transcription by binding of VDR-RXR complex at VDREs. The activated PKC phosphorylates VDR which further binds with $1,25(OH)_2D_3$, activates Ca^{2+} influx through SOC channels which further activates MAPK-ERK pathway by activating Raf by PKC. $1,25(OH)_2D_3$ binds with GPCRs to activate several pathways (PLCγ, Ras, PI3K, AC and Raf-MAPK-ERK) to regulate gene expression. **(1)** $1,25(OH)_2D_3$-facilitates downregulation of CYP27B1 and PTH genes and involves the dissociation of HAT, association of VDR-RXR with VDIR and also recruits HDAC and WSTF to nVDREs. (2) The transcriptional activation involves co-activators (SRCs, NCoA62-SKIP, HATs, CBP-P300 and PBAF-SNF). **(3)** The binding of DRIP205 with VDR-RXR facilitates the association of other DRIPs to form VDR-RXR-NCoA62-SKIP-DRIP205 complex with RNA Pol II and TF2B for easing the transcription of genes such as CDKN1A, CYP24A1 and SPP1. Reproduced from [94] copyright 2007 Nature Publishing Group.

3. Biological functions of $1,25(OH)_2D_3$

3.1. $1,25(OH)_2D_3$ mediated regulation genomic functions

$1,25(OH)_2D_3$ exerts its regulatory actions on target genes through VDR (Fig. 2, and 3). $1,25(OH)_2D_3$-VDR-dependent modulation of transcription by the dimerization with RXR [86]. The activated $1,25(OH)_2D_3$-VDR-RXR binds to VDREs of the target genes [87] through basal transcription factors recruited by cofactors and chromatin-modifying proteins to promoter [88]. $1,25(OH)_2D_3$ induces conformational changes in VDR by phosphorylating it, and causes the release of NCoRs and SMRT-HDAC co-repressors complex that maintain transcriptionally repressed state of chromatin [89]. The conformational change in VDR also repositions it's AF2 domain to bind with coactivators NCoA62-SKIP, SRCs and chromatin modifiers CBP-p300 and PBAF, which facilitate transcription by histone acetylation [90]. When chromatin is activated, the DRIPs bind with AF2 domain of VDR and interacts with RNA Pol II and TF2B for transcription initiation. The epigenetic regulation of VDR has been suppressed by VDR-mediated signaling in cancer cells through rise in the expression of NCoR1 and SMRT [91,92]. $1,25(OH)_2D_3$ induced suppression of gene expression through binding of VDR-RXR heterodimer to negative VDRE of CYP27B1 and PTH genes [93,94]. The binding of $1,25(OH)_2D_3$ to VDR facilitates its interaction with VDIR and induces the dissociation of HAT and employment of HDAC for repression of CYP27B1 gene. Furthermore, WSTF enhances $1,25(OH)_2D_3$-induced repression of CYP27B1 by facilitating the association of WINAC, and chromatin-remodeling complex with chromatin [94]. The VDR induced repression also requires DNA methylation as well as histone deacetylation of CYP27B1 [94,95]. The key genes that has been reported to be regulated by $1,25(OH)_2D_3$ include PTH, CYP24A1, BGLAP, and CDKN1A [94,96–98].

3.2. Vitamin D mediated regulation of nongenomic functions

$1,25(OH)_2D_3$ performs numerous biological activities in the human body [99]. Besides maintaining Ca^{2+} and $[PO_4]^{3-}$ homeostasis [100] in serum via intestinal absorption, $1,25(OH)_2D_3$ plays several other crucial roles (Fig. 4). For example, it has been reported to regulate Ca^{2+} and $[PO_4]^{3-}$ homeostasis by improving bone resorption, thus preventing rickets and osteomalacia [41,101,102]. At the genomic level, $1,25(OH)_2D_3$ has been reported to influence gene expression in different types of cells through nuclear VDRs [103–105]. In contrast, $1,25(OH)_2D_3$ also exert non-genomic activities by functioning as hormones. These activities are facilitated by binding between $1,25(OH)_2D_3$ and VDRs on cell membranes and activating signal transduction [104,105]. The nongenomic signaling of $1,25(OH)_2D_3$ are independent from transcription. However, it may modulate transcription indirectly through crosstalk with other pathways [106]. The nongenomic actions involves the facilitation of the intestinal absorption of Ca^{2+} [107]. The binding of $1,25(OH)_2D_3$ to the membrane VDR resulted in the activation of several signaling cascades including PKC (Fig. 3). The PKC activation causes the opening of Ca^{2+} channels and significantly enhances the intracellular concentration of Ca^{2+}. The high content of Ca^{2+} subsequently activate the Raf-MEK-MAPK-ERK pathway which is attributed to the proliferation of normal colon and skeletal muscle cells [94,108]. $1,25(OH)_2D_3$ has also been reported to function as a major regulatory molecule for various biological processes including immunomodulation and cellular differentiation and proliferation [109]. Moreover, $1,25(OH)_2D_3$ was reported to suppress the apoptosis of β-cells in pancreas and have a regulatory effect on diabetes [104,106]. Furthermore, $1,25(OH)_2D_3$ also

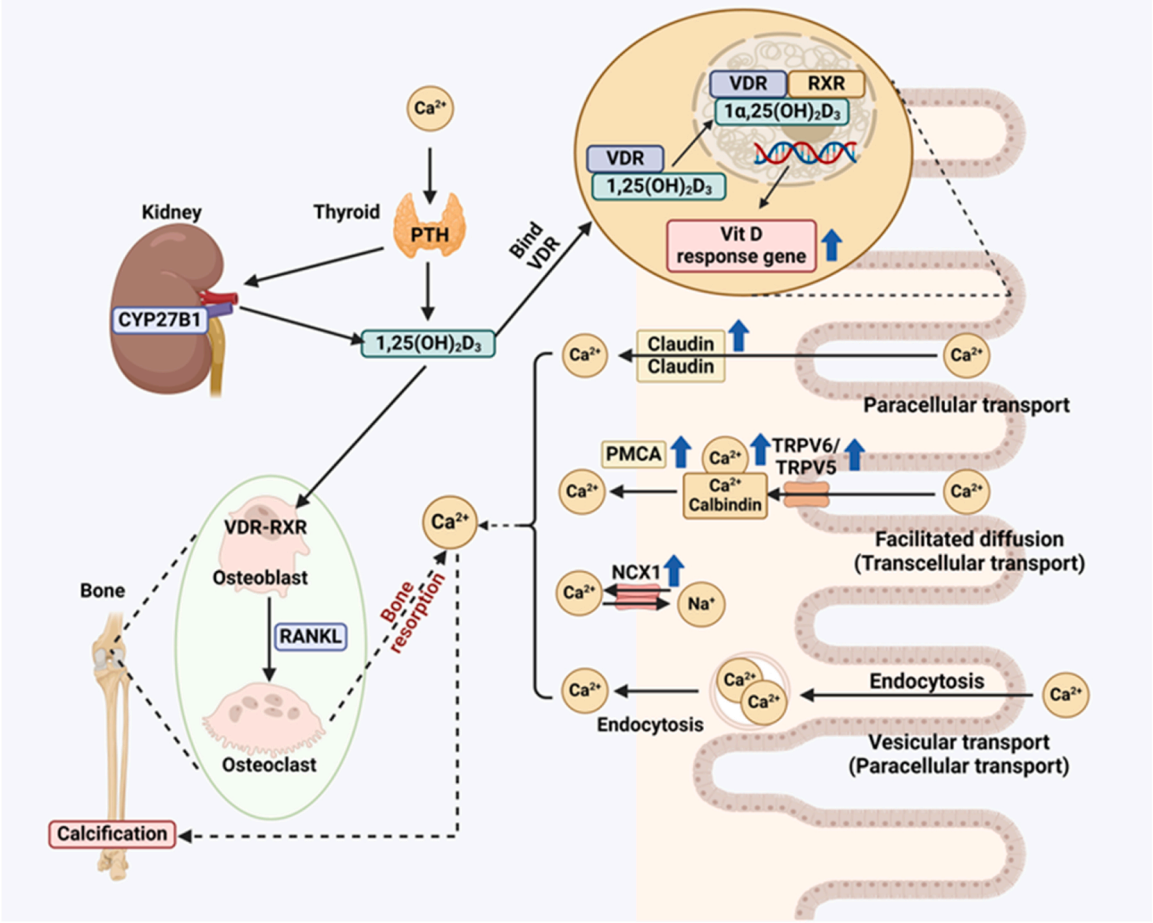

Fig. 4. Impact of $1,25(OH)_2D_3$ on Ca^{+2} homeostasis. Ca^{+2} is absorbed and transported by TRPV5/6 into intestinal absorptive cells forming Ca^{+2}-calbindin complex, which participates in bone calcification after entering in the systemic circulation.

decreases the risk of cardiovascular diseases and hypertension by regulating the renin-angiotensin system [109,110].

4. Role of $1,25(OH)_2D_3$ deficiency and VDR in cancer development

Adipogenesis is the process whereby preadipocytes change to mature adipocytes. The expansion of AT is caused by anomalous increases in the sizes and numbers of adipocytes and is linked to the prevalence of obesity. Numerous molecular interactions occur during this process, the most important of which are the expressions of C/EBPβ and PPARγ. In particular, adipogenesis is triggered by the α, β, and δ forms of C/EBP [111]. VDR also plays a key role and during adipogenesis mediated by $1,25(OH)_2D_3$ [80]. $1,25(OH)_2D_3$ has been reported to inhibit adipogenesis in mice by downregulating the expression of transcription factors C/EBPα, β, PPARγ, RXR [112]. $1,25(OH)_2D_3$ also has an antiadipogenic impact through the WNT/β-catenin pathway [113]. Thus, the $1,25(OH)_2D_3$-mediated antiadipogenic effect is an established mechanism that suggests $1,25(OH)_2D_3$ deficiency possess impact on obesity. $1,25(OH)_2D_3$ also increases the activities of lipogenesis-related enzymes such as fatty acid synthase (FAS) and PPARγ, which are transcription factors involved in adipogenesis in humans [114]. Also, in human subcutaneous adipocytes, $1,25(OH)_2D_3$ increases the expressions of FAS, lipase and fatty acid binding protein by increasing the expression of PPAR [115,116]. In contrast, some have suggested that $25(OH)_2D_3$ and $1,25(OH)_2D_3$ can stimulate the functions of hydroxylases [117]. Furthermore, $1,25(OH)_2D_3$ enhanced the secretions of adiponectin and the expression of leptin by stimulating the translocation of GLUT4 into the cell surface [118].The mechanism of $1,25(OH)_2D_3$ on adipogenesis is schematically illustrated in Fig. 5.

The nuclear VDR reportedly inhibits adipogenesis by binding with $1,25(OH)_2D_3$ [119,120]. The role of $1,25(OH)_2D_3$ is initiated by its interaction with VDR [121,122] and RXR heterodimer. This heterodimer binds with the VDREs of $1,25(OH)_2D_3$ regulated genes [122]. Around 1000 genes involved in physiological processes are regulated by $1,25(OH)_2D_3$ [123]. In mouse 3T3L1 cells, the $1,25(OH)_2D_3$ treatment inhibits adipogenesis [124] by early expression of VDR. VDR inhibits adipogenesis in the presence of $1,25(OH)_2D_3$ by downregulating the expressions of C/EBPβ and PPARγ, and inhibit their activities [122], thus, promote adipogenesis. Furthermore, $1,25(OH)_2D_3$ has increased the expression of PPAR-γ, FASN, and LPL to stimulate adipogenesis [115].

The VDR polymorphism can potentially affect VDR function [125,126]. Furthermore, it has been shown that the VDR polymorphism play a role in susceptibility to obesity [127,128] and increases the risk of obesity [119,129]. The link between the VDR polymorphism and obesity in different racial backgrounds, including European, American, and Asian populations, has also been investigated with focus on VDR genes associated with genetic susceptibility to obesity (Table 1) [117]. The identification of genetic variants related to susceptibilities to different ailments represents a major future area of advancement in public health. The VDR gene has been described to be highly polymorphic and to harbor several SNPs, such as Bsm I, Apa I, Taq I, Fok I, Tru 9I, and Eco RV [64,130], responsible for developing obesity and other diseases, including different types of cancer [131] (Fig. 6).

Obesity has been now reached pandemic proportions and is a key

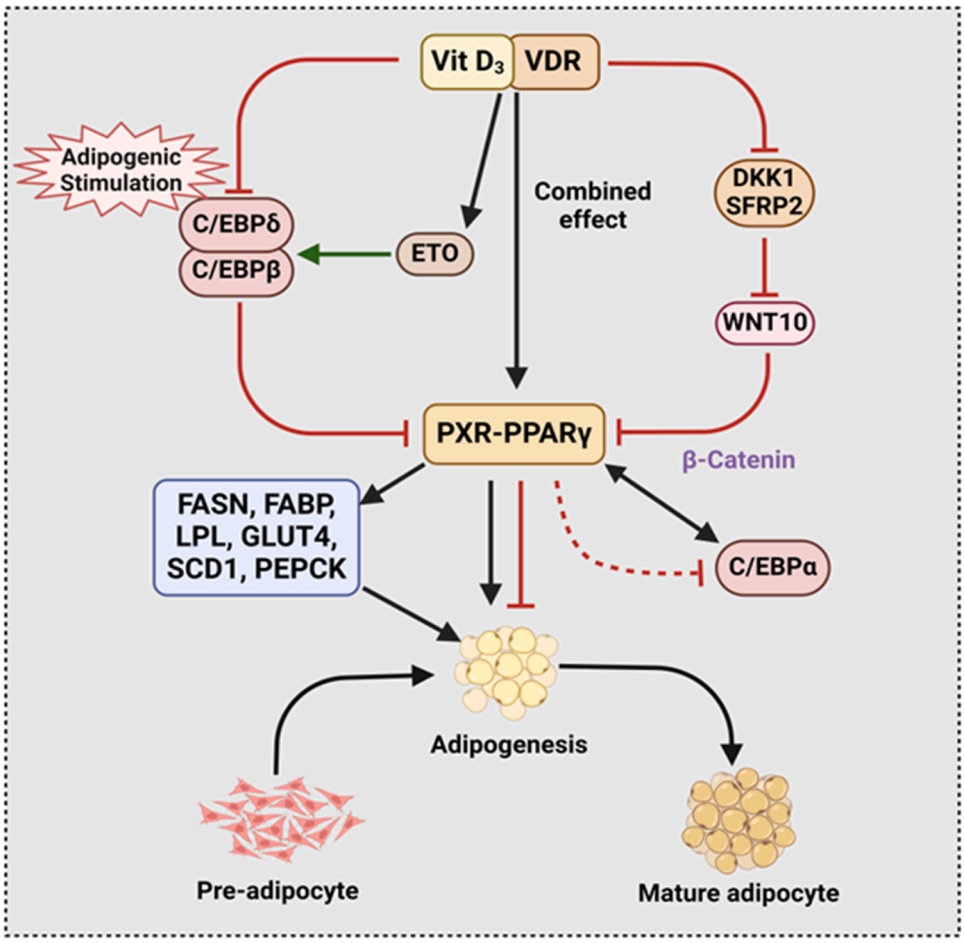

Fig. 5. Schematic representation of the mechanism of 1,25$(OH)_2D_3$-regulated adipogenesis. 1,25$(OH)_2D_3$ increases the expression of co-repressor, which suppresses the transcription of C/EBPβ. Further, 1,25$(OH)_2D_3$ directly downregulates the C/CEBP, PPARγ, and WNT/β-catenin pathways and sequesters RXR to inhibit adipogenesis in mice. 1,25$(OH)_2D_3$ prevented the development of mouse bone marrow cells by suppressing the expressions of DDK1 and SFRP2. In humans, 1,25$(OH)_2D_3$ stimulates adipogenesis by upregulating the expressions of FAS, FABP, and LPL.

contributor to the onset of several diseases, including cancers [18]. The worldwide increasing incidence of obesity [140] has also resulted in a ~60 % increase in obesity-induced cancers [19]. BMI has been considered an indicator of body weight status and fat content [20]. However, BMI does not give information about body composition [21]. Furthermore, VAT has been reported to secrete various hormones and cytokines, which, when secreted in excess, can result in several metabolic disorders [141] and influence the relative risk of obesity and associated cancer (Table 2).

The increase in obesity prevalence is directly proportional to the risk of cancer [173] and mortality [24]. A meta-analysis reported that general adiposity is positively associated with obesity and different cancers (breast and colorectal) [174]. Various mechanisms of action reported to connect 1,25$(OH)_2D_3$ levels to obesity-associated cancers [175]. VDR expression is known to reduce as adipocyte differentiation progresses. In addition, it has been suggested that 1,25$(OH)_2D_3$ has anti-tumor effects through the VDR system [176–178]. 1,25$(OH)_2D_3$ has been shown to modulate the functions of many genes through the VDR system. When 1,25$(OH)_2D_3$ associated VDR targets its corresponding gene, it binds with the transcription start sites accessible to Pol II and at least one VDR enhancer [179]. During carcinogenesis, noncancerous cells differentiate into cancerous cells (Fig. 7), which resulted in a huge increase in the accessible chromatin regions [180,181]. This evolution of tumor generally induces the transcription of MYC (an oncogene) [182] and decreases the expression of CDKN1A (a tumor suppressor gene) [183,184]. However, the absence of concrete evidence regarding the role of 1,25$(OH)_2D_3$ in the development of cancer needs an active research continues in this area [185].

As discussed earlier, 1,25$(OH)_2D_3$ has been reported to regulate the cell cycle progression and apoptosis by targeting several oncogenes and tumor suppressor genes [187–190]. However, many other cellular functions, including immune functions, are controlled by 1,25$(OH)_2D_3$-targeted genes [190–194]. Remarkably, the role of several VDR containing components of immune system (e.g., neutrophils, macrophages, and NK cells) have not been studied properly [195]. 1,25$(OH)_2D_3$ can disrupt dendritic cell-mediated antigen presentation and suppress their ability to activate T cells. Moreover, the activation of VDR can encourage the responses of T helper cells and exacerbate chronic disease states [196–198]. Hence, it appears that 1,25$(OH)_2D_3$ has immunosuppressive effects on cancer cells. In particular, 1,25$(OH)_2D_3$ counteracts the over reactions of adaptive immune system [193,199] through targeting genes like ACVRL1, CD93, CD14, CAMP, CEBPB, NINJ1, MAPK13, FN1, LILRB4, THBD, LRRC25, SRGN, SEMA6B, TREM1 and THEMIS2 [200]. 1,25$(OH)_2D_3$ influences the innate immune system through membrane-anchored glycoprotein CD14 [201]. In brief, 1,25$(OH)_2D_3$ treatment might modulate the transcriptome of healthy and malignant cells on multiple levels by inducing epigenomic changes, such as histone modifications, chromatin accessibility, VDR binding, and cellular growth [202]. The status of 1,25$(OH)_2D_3$ as an important factor for cancer therapy has been summarized in Table 3.

Table 1
Summary of studies on VDR gene polymorphisms and their associations with obesity risk.

S. No.	Country	Polymorphism (SNP)	Location on chromosome 12	Major /minor allele	References
1	Czech	rs1544410 (*Bsm*I)	Intron 8	C/T	[132]
		rs7975232 (*Apa*I)	Intron 8	C/A	
		rs2228570 (*Fok*I)	Initiator codon	C/T	
		rs731236 (*Taq*I)	Exon 9	A/G	
2	China	rs7975232 (*Apa*I)	Intron 8	C/A	[133]
		rs2228570 (*Fok*I)	Initiator codon	C/T	
3	Greek	rs731236 (*Taq*I)	Exon 9	A/G	[134]
4	Poland	rs1544410 (*Bsm*I)	Intron 8	C/T	[135]
		rs2228570 (*Fok*I)	Initiator codon		
5	Sweden	rs1544410 (*Bsm*I)	Intron 8	C/T	[136] [137]
6	USA	rs7975232 (*Apa*I)	Intron 8	C/A	[138]
		rs1544410 (*Bsm*I)	Intron 8	C/T	
		rs731236 (*Taq*I)	Exon 9	A/G	
7	UAE	rs1544410 (*Bsm*I)	Intron 8	C/T	[139]

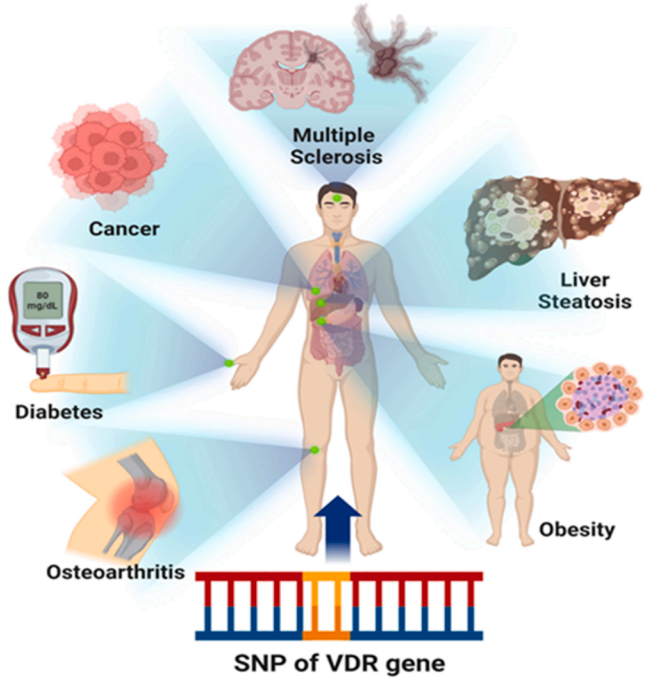

Fig. 6. Diagrammatic representation of VDR gene polymorphisms and their consequences. VDR is actively involved in the development of $1,25(OH)_2D_3$-deficient obesity and associated ailments.

5. $1,25(OH)_2D_3$ targeted pathways for cancer therapy

The administration of $1,25(OH)_2D_3$ has been reported to delay the progression of cancer in early-stage [243] by regulating proliferation, angiogenesis, and apoptosis [94,244,245]. The progression of cell cycle is regulated by association of cyclins, with CDKs and the CDK inhibitors (CKIs). The $1,25(OH)_2D_3$-VDR encourages the activation of CDKN1A which further encourages the differentiation and arrest of cell-cycle

Table 2
Summary of meta-analyses that showed obesity is associated with relative cancer risks.

S. No.	Cancer type	Number of studies	Types of studies	References
1	Bladder	11	Cohort	[142]
2	Breast	15	Cohort	[143]
		35	Case-control	
		11	Case-control	[144]
		8	Prospective	[145]
3	Colorectal	41	Prospective	[146]
		8	Cohort	[147]
		44	Prospective	[148]
		14	Retrospective	
		3	Case-control	[149]
		26	Cohort	
		23	Cohort	[150]
		8	Case-control	
		15	Cohort	[151]
		30	Prospective	[152]
4	Endometrial	4	Case-control	[153]
		1	Cohort	
5	Kidney	15	Cohort	[154]
		13	Case-control	
		6	Cohort	[155]
		22	Case-control	
6	Liver	12	Prospective	[156]
		26	Prospective	[157]
		11	Cohort	[158]
		21	Prospective	[159]
7	Lung	20	Cohort	[160]
		11	Case-control studies	
8	Melanoma	11	Case-control	[161]
		10	Cohort studies	
9	Ovarian	13	Case-control	[162]
		12	Cohort	
10	Pancreatic	23	Prospective	[163]
		14	Cohort	[164]
		7	Prospective	[165]
		8	Cohort	[166]
		6	Case-control	
11	Prostate	25	Prospective	[167]
		31	Cohort	[168]
		25	Case-control	
12	Gastrointestinal	12	Case-control	[169]
		10	Cohort	[170]
		3	Case-control	[171]
		8	Cohort	
		2	Cohort	[172]
		12	Case-control	

[94]. The $1,25(OH)_2D_3$ modulates the expression pattern of CDKN1A, CDKN1B, CCND1, CCND3, CCNA1, GADD45, TK1, MYC, INK4 family, TYMS and CCNE1 genes, which leads to the inhibition of pRb and CDK in several cancers (breast, colon, ovary and leukemia cells) [94,246]. The antiproliferative impact of $1,25(OH)_2D_3$ has been attributed to the repression of MYC gene [247]. $1,25(OH)_2D_3$ possess various indirect actions on cell-cycle regulation due to the cross-talk with other pathways such as by downregulating EGFR and upregulation of IGFBP3 and TGFβ-SMAD3 signaling [248] (Fig. 8). The $1,25(OH)_2D_3$ induced activation of VDR has inhibited cell proliferation in leukemia cell lines [245]. However, in hematopoietic cells, $1,25(OH)_2D_3$ inhibits the suppression of IL12 and down-regulation of CD40, CD80 and CD86 [249]. $1,25(OH)_2D_3$ also encourages the differentiation of SW480 cells by inducing CDH1 (encoding E-cadherin). The activation of CDH1 can restrain cellular growth by enabling the translocation of nuclear β-catenin to plasma membrane which results in the transcription inhibition.

The anti-angiogenesis actions of $1,25(OH)_2D_3$ has been reported to inhibit the growth of tumors [94,250] (Fig. 8). $1,25(OH)_2D_3$ upregulated the level of VEGF and THBS1 [250,251] to impede endothelial cell migration and tube formation in prostate cancer cells [252]. The tumor-derived endothelial cells were shown to be sensitive to 1,25

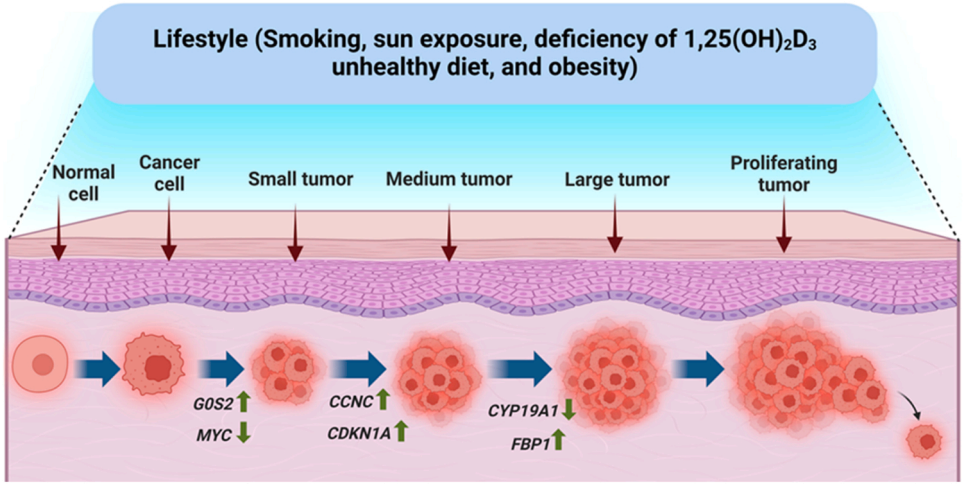

Fig. 7. $1,25(OH)_2D_3$ deficiency and the evolution of cancer. The malignant tumor developed due to an accumulation of mutations under $1,25(OH)_2D_3$ deficiency. The arrows indicate the direction of $1,25(OH)_2D_3$-targeted gene regulation. Reproduced from [186] Copyright 2022 Elsevier.

$(OH)_2D_3$ due to their ability to quench the expression of CYP24A1 gene [253]. Along with the antiproliferative and anti-angiogenic effects, 1,25 $(OH)_2D_3$ has exerted its anticancer effect by repressing the expression of BCL2 and BCL-XL proteins in MCF-7 and HL-60 cells, or upregulating the expression of BAK, BAX and BAD in prostate, and colorectal cancer **(**Fig. 8**)**. $1,25(OH)_2D_3$ inhibits ERK phosphorylation by upregulating the expression of VDR and cleaved MEK to deactivate its function by activating caspases [94]**.** The $1,25(OH)_2D_3$ also induces apoptosis by repressing the telomerase functions [254]. The anti-cancer effects of 1, $25(OH)_2D_3$ are studied well, however delineating the exact mechanism remains a challenge for future investigation.

6. $1,25(OH)_2D_3$ mediated regulation of mitochondrial respiration and VDR crosstalk in obesity and cancer

$1,25(OH)_2D_3$ controls several signaling pathways mediated by Ca^{2+}, which has been implicated in the regulation of apoptotic pathways [255–258]. Ca^{2+} has been considered as an extremely versatile, and ubiquitous intracellular messenger. $1,25(OH)_2D_3$ has been reported to maintain the cellular homeostasis of Ca^{2+} by triggering the voltage-dependent entry, release and mobilization of Ca^{2+} in breast cancer cells and normal cells [255,259] through TRPV6 proteins [260]. The $1,25(OH)_2D_3$ has been reported to inhibit the mitochondrial respiration through VDR in various cells such as cancer cell lines, keratinocytes [261] and brown adipocytes [262]. The VDR has also been reported to modulate the lipid metabolism in mitochondria and direct the metabolism towards the formation of precursors for biosynthetic pathway [262,263]. In proliferating cells, the mitochondrial acetyl-CoA is diverted towards the biosynthesis of cholesterol [263]. In addition, the VDR mediated inhibition of mitochondrial respiration may reduce the rate of β-oxidation. However, in the absence of VDR activity, the mitochondrial respiration and the expression of UCPs increased [264–266]. The increased mitochondrial respiration enhances the rate of β-oxidation. Moreover, the reduced content of acetyl-CoA derived malonyl-CoA in cytosol alleviates the inhibition of mitochondrial fatty acid import through carnitine acyltransferases present in the mitochondrial membrane, resulting in the increased β-oxidation (Fig. 9). The VDR mediated dual regulation of mitochondrial respiration and UCPs expression may be significant with the aim of preventing the extreme uncoupling and tuning of proton gradient.

Several investigations reported that $1,25(OH)_2D_3$ can inhibit the adipogenic effect of VDR and PPARγ [267,268]. The regulatory impact of VDR and PPARγ are interconnected and affects each other[269,270]. The overexpression of VDR has been reported to suppress the transactivation of PPARγ in preadipocytes [262]. In addition, the overexpression of PPARγ also decreases the $1,25(OH)_2D_3$-mediated transactivation of VDR. The excess PPARγ has also been reported to show compete with VDR for RXRα [271]. The PPAR has been reported to form a heterodimer structure with RXR to regulate the expression of genes responsible for adipogenesis, metabolic homeostasis, lipid metabolism, and anticancer effects. Since the risk of obesity and cancer has been strongly corelated, the crosstalk of VDR system and PPARγ was reviewed comprehensively [272,273]. PPARγ modulates the gene expression by binding with either natural or synthetic ligands along with RXR forming PPARγ-RXR complex. Subsequently, the PPARγ-RXR complex translocated to nucleus and binds with PPREs (PPAR response elements). The association of PPARγ-RXR complex and PPREs results into the regulation of genes involved in the cellular metabolism, proliferation and apoptosis [274–276]. The PPARγ functions can be compared to the functions of $1,25(OH)_2D_3$ and VDR in cancer [277,278] and obesity [273]. The communication of PPARγ and VDR through VDRE has already been established [279]. The PPARγ has a great binding ability towards VDR, thereby inhibits the $1,25(OH)_2D_3$-induced transactivation [271]. In another research the VDR system has been shown to inhibit the expression of PPARγ in adipocytes [280], which is conflicting with the pro-adipogenesis effects of $1,25(OH)_2D_3$ [281]. 1,25 $(OH)_2D_3$ has also been shown to elevate the expression level of fatty acid synthase and enhanced the lipogenesis through PPARγ [280]. However, the inability of PPARγ to look after the lipid storage above threshold level has lead towards the onset of obesity [282] and cancer. The disrupted VDR system leads to loss of total muscle mass [283], loss of fat and increases the energy consumption in mice [281].

7. Recent trends and future prospectives

In recent years, various studies have been focused on the extra skeletal therapeutic potential of $1,25(OH)_2D_3$. The cellular concentrations $1,25(OH)_2D_3$ have been described to be associated with the development of different cancers [284], such as lung, colon, lymphoma, breast, and prostate cancer [29,30,285]. Furthermore, it is well recognized that $1,25(OH)_2D_3$ reduces the proliferation of cancer cells through VDR [286]. $1,25(OH)_2D_3$ has also been reported to inhibit the progression and proliferation of cancer cells due to its modulating effect on the immune system and its anti-angiogenic effects [278]. Several mechanisms have been proposed to explain the anti-cancer effects of 1, $25(OH)_2D_3$ [287]. $1,25(OH)_2D_3$ has been reported to impede the cyclin-cyclin-dependent kinase complexes using P21 and P27 proteins, which are responsible for arresting cancer cells [174]. $1,25(OH)_2D_3$ has

Table 3
Summary of recent advancements in vitamin D system in the treatment of different cancers.

S. No.	Cancer	1,25 $(OH)_2D_3$ system/ VDR variants	Effects	References
1	Breast cancer	25$(OH)_2D_3$	Susceptible to younger/ obese patients.	[203]
		VDR Fok I	Increased the risk of breast cancer in female.	[204,205]
		VDR-IGF1R	Facilitated the growth of breast cancer.	[206]
		1,25 $(OH)_2D_3$, and EB1089	Enhanced the Era expression in triple-negative breast cancer via VDR signaling.	[207–209]
		CYP24A1	Suppressed the CYP24A1 sensitized cancer cells against 1,25$(OH)_2D_3$ therapy.	[210]
2	Bladder cancer	1,25 $(OH)_2D_3$	Improved cisplatin efficacy	[211]
3	Colorectal cancer	Vitamin D_3	Minimize the risk of colorectal cancer	[212]
		VDR, *CYP3A4*	Impaired the metabolic pathway of 1,25 $(OH)_2D_3$	[213]
		rs4588 A	Enhanced the 1α,25 $(OH)_2D_3$bioavailability	[214]
		1,25 $(OH)_2D_3$	Induced ferroptosis in stem cells of colon cancer.	[215]
		25$(OH)_2D_3$	Lowered the sporadic colon cancer.	[216]
		1,25 $(OH)_2D_3$	Encouraged the SIRT1 via auto-deacetylation, resulting in antiproliferative activity in colon cancer cell lines	[217]
		VDR, bile ascites	Suppressed the inflammation and cancer through VDR signaling in mice.	[218]
		VDR/p53	Enhanced the β-oxidation of peroxisomal fatty acid in mice and inhibited colorectal cancer	[219]
		Vdr ablation	Decreased the expression of Claudin-10, and thereby increased intestinal permeability, and bacterial infiltration	[220]
		Vitamin D_3	Induced the antiproliferative effects in colon cancer	[221,222]
4	Glioblastoma	VDR agonist, and 1,25 $(OH)_2D_3$	Stimulates cytotoxic autophagy and apoptosis.	[216,223]
		CY24A1	Induced CYP24A1 expression leading to impaired 1,25$(OH)_2D_3$ functions	[224]
5	Head and neck squamous cell carcinomas	VDR, and 1,25 $(OH)_2D_3$	Suppressed the PI3K/ Akt/mTOR pathway	[225]
		25$(OH)_2D_3$	Low content resulted in the development of mucositis and dermatitis against chemoradiation treatment	[226]
6	Melanoma	Vitamin D_3	Decreased the risk of melanoma	[227]
		25$(OH)_2D_3$	At a lower serum concentration reduced the survival rate of patients.	[228,229]
		1,25 $(OH)_2D_3$	Promoted apoptosis by inducing activated caspases and PTEN	[230,231]
7	Multiple myeloma	25$(OH)_2D_3$	Decreased peripheral neuropathy	[232]
		1,25 $(OH)_2D_3$	overcame bortezomib resistance	[233]
8	lung adenocarcinoma	CYP24A-targeted DNA aptamers	Induced antiproliferative effects	[234]
9	Osteosarcoma	1,25 $(OH)_2D_3$, and calcipotriol	Suppressed metastasis by modulating the ROS, NMD and EMT pathways	[235–237]
10	Ovarian cancer	25$(OH)_2D_3$	Elevated concentration of 25$(OH)_2D_3$ in serum decreased the risk of cancer in ovary by 37 %.	[238]
11	Prostate cancer	25$(OH)_2D_3$, and androgens	Decreased the *Lrp2* expression	[239]
		1,25 $(OH)_2D_3$	Encouraged unfolded protein response by inhibiting the expressions of the c-MYC and EMT genes	[240]
12	Squamous carcinoma	*VDR Fok* I, 25$(OH)_2D_3$ and Poly-A variants	A lower 25$(OH)_2D_3$ content increased disease progression.	[241]
		1,25 $(OH)_2D_3$	Suppressed cancer in both A431 cells and a mouse model by inhibiting mTOR and activating autophagy	[242]

also been described to reduce cancer progression by inducing apoptosis and reducing blood supply to developing tumors [288]. Other anti-cancer mechanisms include the suppression of angiogenesis in tumors by up-regulating Bax and downregulating Bcl-2. Moreover, 1,25 $(OH)_2D_3$ promotes the upregulation of E-cadherin, which suppresses cancer metastasis and invasion [289]. 1,25$(OH)_2D_3$ also prevents the growth of prostate and breast cancer by downregulating androgen and estrogen receptor signaling [287]. In addition, preclinical studies strongly support the anti-cancer effect of 1,25$(OH)_2D_3$ [278,290,291]. The supplementation of 1,25$(OH)_2D_3$ (4-ng/mL) have been shown to decrease the risk of colorectal cancer by 6 % [292]. However, the combined Ca^{2+} and 1,25$(OH)_2D_3$ therapy did not decrease the risk of colorectal cancer [293] [294–296]. Further preclinical and clinical investigations are required to explain the effects of 1,25$(OH)_2D_3$ supplementation [297]. The risk/benefit ratio of 1,25$(OH)_2D_3$ supplementation should be explored at higher doses of 1,25$(OH)_2D_3$ [298]. Currently, the FDA has approved the various drugs for obesity treatment such as orlistat, phentermine-topiramate in combination, naltrexone-bupropion in combination, liraglutide, setmelanotide (imcivree), and semaglutide [290]. However, the systemic activation of 1,25$(OH)_2D_3$ signaling presents a considerable risk of hypercalcemia [299]. Several efforts are being directed to develop VDR agonists with anti-cancer activity [94,300]. The data from clinical, preclinical, and

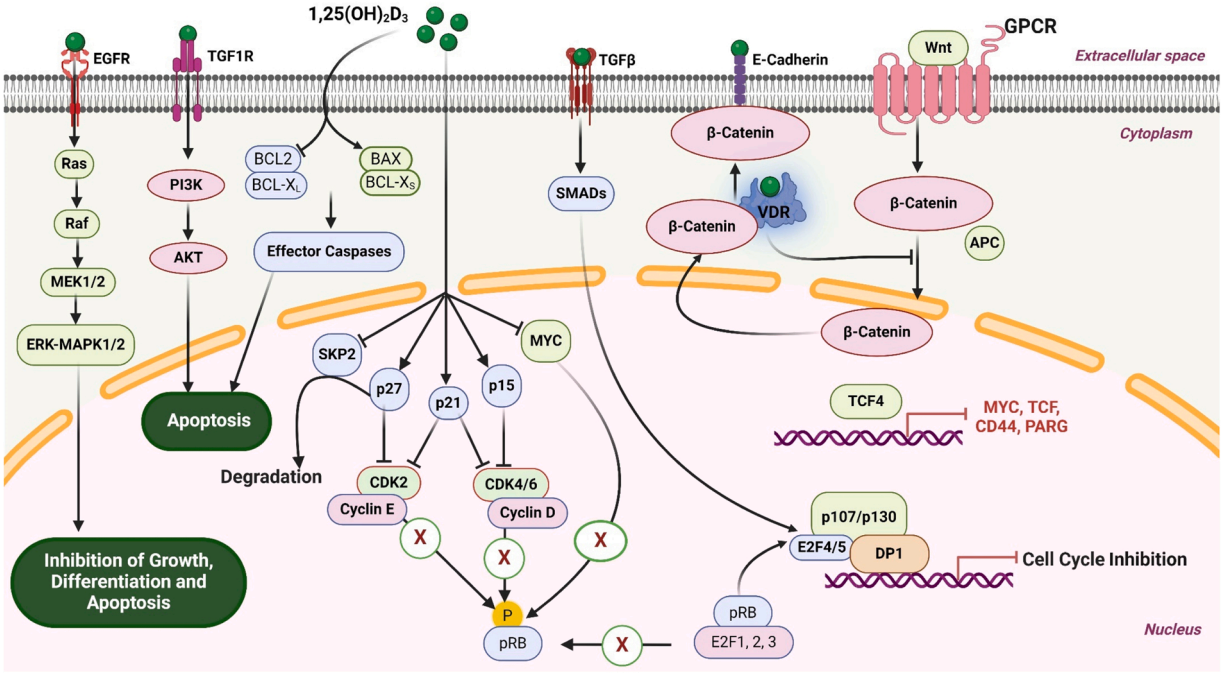

Fig. 8. $1,25(OH)_2D_3$ targeted major signaling pathways against cancer. $1,25(OH)_2D_3$ inhibits MAPK-ERK1/2 signaling through suppression of EGFR. $1,25(OH)_2D_3$ induced apoptosis in cancer cells through IGFR1-PI3K-AKT signaling. $1,25(OH)_2D_3$ downregulates BCL2, induces BAX and activates caspases leading to apoptosis. Progression of cell-cycle is modulated by $1,25(OH)_2D_3$ through SKP2 and TGFβ crosstalk, resulting to the inhibition of cell cycle. The perturbed cell-cycle finally affects the association of various factors (such as p107/p130, pRB, DP1 and E2F family of transcription factors) which are responsible for mediating the gene transcription. The interaction of E2F4/5-DP1 complex and E2F1,2,3-pRB complex with p107/p130 prevents the gene expression and restrain progression of cell-cycle. The expression of E-cadherin is facilitated by binding of $1,25(OH)_2D_3$ with VDR. The association of $1,25(OH)_2D_3$-VDR induces the nuclear β-catenin to move towards plasma membrane. The lack of nuclear β-catenin resulted in the inhibition of Wnt-β-catenin-TCF4 signaling. Reproduced from [94] Copyright 2007 Nature Publishing Group.

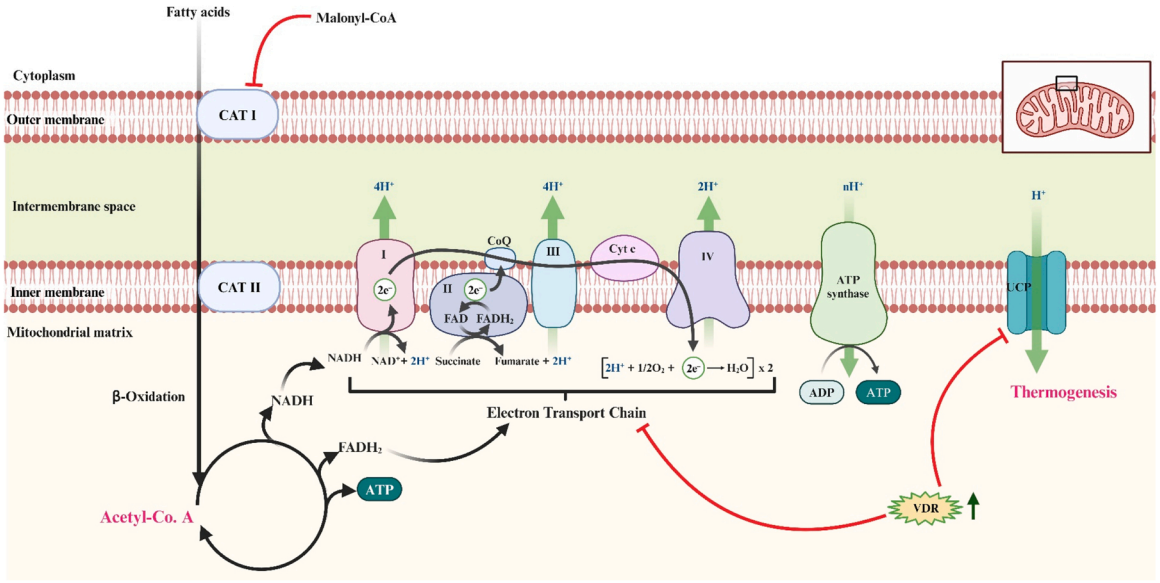

Fig. 9. Schematic illustration of VDR mediated regulation of mitochondrial respiration on lipid metabolism and cellular energetics. The dark green arrow indicated the elevated expression of VDR. The light green arrow indicates the movement of H^+ ions across proton gradient. The elevated expression level of VDR downregulates mitochondrial respiration and the UCP. The decreased utilization of $FADH_2$ and NADH reduces the rate of β-oxidation. The decreased mitochondrial respiration downregulates the lipid catabolism and encourages the channeling of acetyl-CoA into biosynthetic pathways. **Abbreviations**: UCP: uncoupling protein; CAT I: carnitine acyltransferase I and CAT II: carnitine acyltransferase II.

epidemiological investigations strongly recommend that the stimulation of $1,25(OH)_2D_3$ signaling may be an important therapeutic approach against many cancers [290].

The effect of alternative metabolism of $1,25(OH)_2D_3$ via CYP11A1 and VDR on cancer development is mostly unknown. Thus, exhaustive research should be conducted on the alternate metabolic pathways of $1,25(OH)_2D_3$ and their anti-cancer effects. In addition, enhancing the concentrations of $1,25(OH)_2D_3$ in cancer cells by inhibiting the

CYP24A1 may offers another possible approach [301]. Also, due to the low expressions of the VDR, CYP27B1, CYP11A1, and RORα/γ genes in cancer cells, the efficiency of $1,25(OH)_2D_3$ therapy might be inadequate and limited to the early disease stage. Thus, studies are required to identify and develop novel markers that predict the efficiency of $1,25(OH)_2D_3$ in cancer therapy. Relatively few studies have been endeavored to determine the nature of the relationships between $1,25(OH)_2D_3$/VDR polymorphisms and obesity-associated cancer development; thus, we suggest greater focus be placed on this area. Furthermore, since environmental and genetic factors have also influenced the $1,25(OH)_2D_3$ levels and obesity-associated cancer development, the research should be conducted in different parts of the world and on different ethnicities to delineate the implication of $1,25(OH)_2D_3$-based cancer therapy. The application of various nanoparticles have been used to enhance the therapeutic potential of anticancer drugs against various cancers [302–309]. However, the $1,25(OH)_2D_3$ conjugated nanoparticle-based study might be an interesting area of study for future investigation.

8. Conclusion

$1,25(OH)_2D_3$ has high affinity towards VDR that can directly regulate epigenetic modifications of normal and cancer cells. $1,25(OH)_2D_3$ influences cellular energetics, differentiation, proliferation, and programmed cell death through VDR and PPARs. Furthermore, the growth of malignant tumor cells is regulated either directly by genes and signaling pathways or indirectly by changes in the tumor microenvironment. However, the mechanisms accountable for the bidirectional relationship between $1,25(OH)_2D_3$ deficiency and obesity-related cancer remain unknown. $1,25(OH)_2D_3$ has been reported to activate VDR in adipocytes and regulates adipogenesis, metabolism in AT, and inflammatory gene expression. Several VDR influenced genes play key roles in the synthesis, metabolism, and function of $1,25(OH)_2D_3$ *in vivo*. The VDR gene is extremely polymorphic and possesses several SNPs that probably alter binding between $1,25(OH)_2D_3$ and VDR. VDR also influences adipocyte differentiation and cellular metabolism by modulating related signaling pathways. However, a VDR polymorphism study presented that genetic diversity of VDR gene is unlikely to perform a significant role in obesity or their consequences. Furthermore, VDR fingerprints can be used to predict increased risks of cancer development and help to identify novel therapeutic strategies. The analysis of literature revealed that $1,25(OH)_2D_3$ deficiency is related with the increased mortality among cancer patients, which suggests that the obesity-associated cancer development can be treated using lifestyle changes, a nutritious diet, and controlled exercise. Finally, this review highlights the need for further research to precisely establish the nature of the link between $1,25(OH)_2D_3$ deficiency and the onset of obesity-associated cancer.

Funding

This work was supported by a grant from the Korea Environmental Industry & Technology Institute (KEITI), funded by the Ministry of Environment (MOE) of the Republic of Korea (No. 2022002980004) and by grants from the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Korean government (MSIT) (Grant numbers: 2021R1A2C3011585 and 2022M3J7A1062940). This work was also supported by the Korea Basic Science Institute research (Grant number: A412310).

CRediT authorship contribution statement

Vivek Kumar Gupta: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Data curation, Conceptualization. **Lipina Sahu:** Writing – original draft, Visualization, Software, Formal analysis, Data curation, Conceptualization. **Sonam Sonwal:** Writing – original draft, Visualization, Software, Formal analysis, Data curation, Conceptualization. **Dong Hyeon Kim:** Visualization, Software. **Jigyeong Kim:** Visualization, Software. **Henu Kumar Verma:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Eluri Pavitra:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **LVKS Bhaskar:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Ganji Seeta Rama Raju:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Achanti Suneetha:** Conceptualization, Formal analysis, Software, Visualization, Writing – original draft, Writing – review & editing. **Hyun Uk Lee:** Funding acquisition, Project administration, Software, Supervision, Validation, Visualization, Writing – review & editing. **Yun Suk Huh:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

Acknowledgments

The author VKG is obliged to the Korea Environmental Industry & Technology Institute (KEITI), Ministry of Environment (MOE), Republic of Korea and the Korea Basic Science Institute research Republic of Korea.

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