Review

Ion Channels as Targets of the Vitamin D Receptor: A Long Journey with a Promising Future

Verna Cázares-Ordoñez *, Ramiro José González-Duarte, Michiyasu Ishizawa, Luis A. Pardo, Makoto Makishima *

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Ion Channels as Targets of the Vitamin D Receptor: A Long Journey with a Promising Future

Verna Cázares-Ordoñez [1,*], Ramiro José González-Duarte [1], Michiyasu Ishizawa [2], Luis A. Pardo [3] and Makoto Makishima [2,*]

[1] Centro Universitario de la Salud, Complejo Regional Nororiental, Benemérita Universidad Autónoma de Puebla, Teziutlán, Puebla 73800, México

[2] Division of Biochemistry, Department of Biomedical Sciences, Nihon University School of Medicine, Tokyo 173-8610, Japan

[3] Oncophysiology Group, Max Planck Institute for Multidisciplinary Sciences, City Campus, Hermann-Rein-Strasse 3, 37075 Göttingen, Germany

* Correspondence: verna.cazares@correo.buap.mx (V.C.-O.); makishima.makoto@nihon-u.ac.jp (M.M.)

Abstract

The vitamin D receptor (VDR) acts as both a nuclear transcription factor and a non-genomic mediator that regulates a broad spectrum of physiological processes beyond calcium and phosphate homeostasis. VDR plays an important role in the modulation of ion channels across multiple tissues, including osteoblasts, renal and intestinal epithelial cells, neurons, and vascular smooth muscle. These regulatory mechanisms encompass genomic actions through vitamin D response elements in target genes—such as *TRPV5*, *TRPV6*, *KCNK3*, and *KCNH1*—as well as rapid, non-genomic actions at the plasma membrane involving protein disulfide isomerase A3 and associated signaling cascades. VDR-mediated transcriptional control of calcium, potassium, and chloride channels contributes to the fine-tuning of cellular excitability, calcium transport, and mitochondrial function. Evidence also implicates VDR–ion channel crosstalk in various pathological contexts, including renal cell carcinoma, breast and cervical cancers, pulmonary arterial hypertension, and osteoporosis. Understanding the molecular interplay between VDR and ion channels provides new perspectives on the pleiotropic effects of vitamin D and offers promising therapeutic opportunities in oncology, cardiovascular disease, and skeletal disorders. This review synthesizes previous and current evidence on the genomic and non-genomic mechanisms underlying VDR–ion channel regulation and highlights novel frontiers in vitamin D signaling relevant to human health and disease.

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1. Introduction

In 1928, the German chemist Adolf Windaus successfully isolated two forms of vitamin D: one derived from plants, designated vitamin D_2 (also called calciferol), and the other derived from animal skin, identified as vitamin D_3 (also called cholecalciferol). Eight years after this discovery, he elucidated the chemical structure of vitamin D_3.

Vitamin D_3, is synthesized in the skin upon exposure to sunlight, and vitamin D_2 is derived from dietary sources. Vitamin D_3 is converted to 25-hydroxyvitamin D_3 ($25(OH)D_3$; also called 25-hydroxycholecalciferol) in the liver, which then circulates in the bloodstream and undergoes a second hydroxylation at the 1α-position in the kidney, producing the biologically active form that regulates calcium and phosphate homeostasis: 1α,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$; also called 1α,25-dihydroxycholecalceferol and calcitriol).

Dietary vitamin D_2 and vitamin D_3 are metabolized through the same activation process, involving 25-hydroxylation in the liver and subsequent 1α-hydroxylation in the kidney.

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Vitamin D is crucial for bone health, as it contributes to the maintenance of strong bones and teeth. Additionally, it plays a role in immune function and is vital for normal growth and development [1,2].

Vitamin D, while primarily recognized for its critical role in calcium metabolism and bone mineralization, is also implicated in a variety of physiological and pathological processes, including cancer, immune modulation, cardiovascular diseases, and metabolic syndrome. Most vitamin D's effects are mediated through the vitamin D receptor (VDR), which regulates a substantial number of target genes and consequently influences numerous cellular pathways. Notably, VDR is expressed in nearly all human cell types and have been shown to modulate the transcription of approximately 3% of human genes [3].

Research has demonstrated that steroid hormones exert rapid modulatory effects on ion channel activity across various cellular systems through multiple molecular mechanisms. For instance, the rapid actions of $1,25(OH)_2D_3$ on Cl^- and Ca^{2+} currents are linked to secretory activities in osteoblasts and bone mass formation [4]. However, the genomic effects of $1,25(OH)_2D_3$ on ion channels remain insufficiently explored. A comprehensive analysis of transcriptomic data from genes encoding ion channel proteins, which exhibit differential expression under $1,25(OH)_2D_3$ treatment, revealed that the majority of genes affected by $1,25(OH)_2D_3$ belong to the potassium channel family, including voltage-activated potassium channels, calcium-activated potassium channels, and two-pore domain potassium channels [5]. Given the significance of $1,25(OH)_2D_3$ and its receptor as biological regulators and their association with ion channels in the body, we deemed it pertinent to review the existing literature on the functional link between them, the associated molecular mechanisms, and their relationship with certain diseases.

2. VDR: Genomic and Non-Genomic Mechanisms

2.1. The VDR Functions as Both a Nuclear Transcription Factor and a Non-Genomic Mediator

VDR is a ligand-dependent transcription factor, with $1,25(OH)_2D_3$ and lithocholic acid (LCA) serving as endogenous ligands [6,7]. VDR is a member of the nuclear receptor superfamily [8], which encompasses receptors for glucocorticoids, mineralocorticoids, sex hormones, thyroid hormones, and vitamin A metabolites. The primary target tissues of VDR include the bone, kidney, and intestine, where it plays a crucial role in maintaining calcium homeostasis (calcemic effects). However, VDR is also expressed in various other tissues, contributing to non-calcemic effects, such as immune response, innate immunity, and the maintenance of barrier function in the skin and intestinal tract [9]. Upon ligand binding, VDR is activated and forms a heterodimer with the retinoid X receptor (RXR) [10], which subsequently binds to a gene region known as the vitamin D response element (VDRE) to regulate the transcription of target genes. While the principal function of VDR is transcription-mediated genomic action, it has been reported to partially participate in the acute phase calcium influx mechanism as part of the non-genomic actions of $1,25(OH)_2D_3$ [11] (Figure 1).

2.2. Structural Domains and Isoforms of VDR

VDR is a protein with a molecular weight of 50-60 kDa, which was cloned and sequenced in 1987 [6]. X-ray crystallographic analysis elucidated its binding model with $1,25(OH)_2D_3$ in 2000 [12], and with LCA in 2013 [13]. The nuclear receptor superfamily is characterized by an N-terminal domain containing a DNA-binding domain and a C-terminal domain containing a ligand-binding site. Compared to other nuclear receptors, VDR possesses a shorter N-terminal region located at the terminus of the DNA-binding domain. The DNA-binding domain comprises two zinc fingers that form tetrahedral structures with cysteine and zinc, adopting a loop or finger-like configuration. The zinc finger at the N-terminal side determines the specificity of the VDRE sequence. The C-terminal region encompasses a ligand-binding domain essential for heterodimerization with the RXR. Additionally, the activation function 2 domain at the C-terminal end is crucial for interactions with transcription cofactors, such as steroid receptor coactivator (SRC) and vitamin D receptor interacting

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protein (DRIP) [14]. VDR exists in several isoforms. Human VDRB1 is a transcript variant in which the N-terminal 50 amino acids of VDR are extended, exhibiting cell- and ligand-selective transcriptional activities distinct from those of the wild-type (VDRA) [15,16]. VDR1, in which intron 8 is transcribed following exon 8 of rat VDR, is expressed at low levels in the kidney and intestine and exhibits a dominant negative function compared to the wild-type (VDR0) [17]. The VDR gene contains multiple single nucleotide polymorphisms, with the representative BsmI single nucleotide polymorphism located in intron 8, which has been implicated in bone metabolism and muscle function [18,19]. In contrast, teleost fish, which underwent whole-genome duplication during evolution, possess VDRα and VDRβ. In medaka fish, VDRβ exhibits ligand responsiveness similar to that of terrestrial organisms, whereas the response of VDRα is notably weak [20].

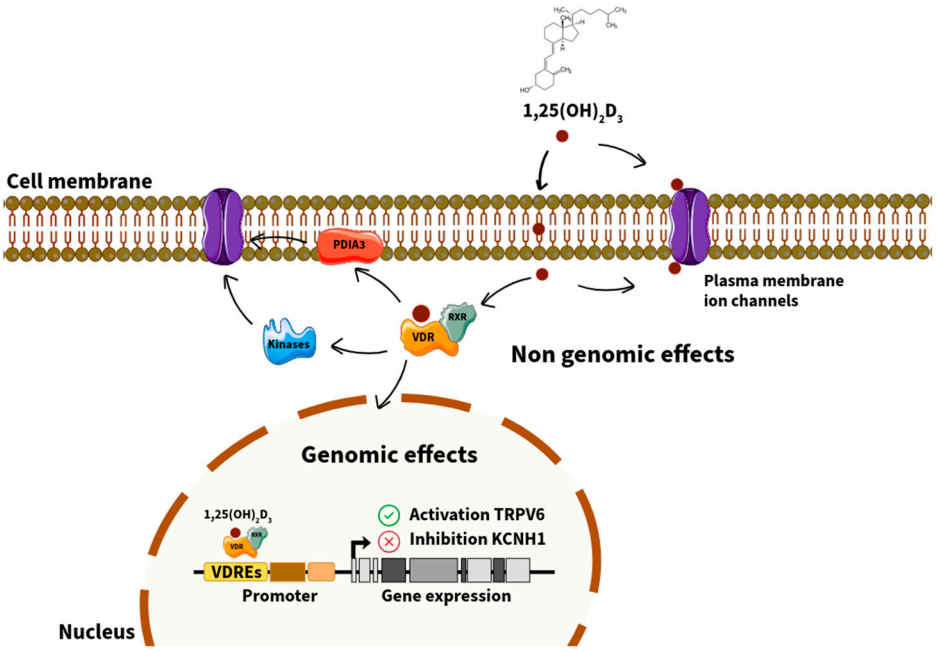

Figure 1. The dual role of the vitamin D receptor (VDR) as a genomic and non-genomic mediator. The active form of vitamin D, 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), binds to cytosolic or membrane-associated VDR to initiate rapid, non-genomic responses involving protein disulfide isomerase A3 (PDIA3), kinases, and plasma membrane ion channels. These interactions trigger secondary messenger cascades that modulate ion fluxes and cellular signaling within seconds to minutes. In parallel, nuclear VDR acts as a ligand-dependent transcription factor by binding to vitamin D response elements (VDREs) in the promoter regions of target genes, leading to transcriptional activation of transient receptor vanilloid 6 (TRPV6) and repression of the potassium channel KCNH1. Together, these mechanisms illustrate the integrated nature of VDR signaling, linking rapid extranuclear responses to long-term genomic regulation.

2.3. Regulation by $1,25(OH)_2D_3$ and Its Synthetic Analogs

VDREs present in VDR target genes are characterized by a direct repeat of two hexanucleotide half-elements with a three-nucleotide spacer (called direct repeat 3) or an everted repeat of two half-elements with a six-nucleotide spacer (called everted repeat 6). The VDR-RXR heterodimer on the VDRE then forms a transcription complex through interactions with cofactors, thereby facilitating transcription [21,22]. Synthetic analogs that bind to VDR are categorized into secosteroids and non-secosteroids. Alfacalcidol (1α-hydroxyvitamin D_3), a synthetic secosteroidal analog, is clinically used to treat osteoporosis. It is a prodrug that is converted to $1,25(OH)_2D_3$ by 25-hydroxylase in the body [23]. Maxacalcitol is used to treat psoriasis and secondary hyperparathyroidism. Compared to $1,25(OH)_2D_3$, maxacalcitol exhibits weaker VDR activation and binding affinity, as well as a shorter half-life, resulting in reduced hypercalcemia as a side effect [24]. While $1,25(OH)_2D_3$ and its prodrug

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alfacalcidol promote bone resorption as a side effect, eldecalcitol, introduced in 2011 in Japan, demonstrates an anti-osteoporotic effect with a milder bone resorption effect than alfacalcidol [25]. Although eldecalcitol is a weak VDR agonist, it is more stable and resistant to hydroxylation by the metabolic enzyme cytochrome P450 (CYP) 24A1 than $1,25(OH)_2D_3$, allowing it to exert a sustained effect in the body [26]. Paricalcitol, a 19-nor vitamin D derivative with the 19th exomethylene ring removed, has been used to treat secondary hyperparathyroidism. MART-10, another 19-nor vitamin D derivative, exhibits antitumor effects and resistance to degradation by metabolic enzymes [27,28]. Further development of these compounds is anticipated in the future. Various secosteroidal vitamin D derivatives have been synthesized by modifying the side chains; however, the complete separation of calcemic effects from other effects remains a challenge. LY2108491, a non-secosteroidal compound, improves psoriasis in models without elevating blood calcium levels [29]. Conversely, LCA acetate and LCA propionate, derivatives based on the LCA structure, activate VDR in the intestine and kidney without increasing blood calcium levels [30,31]. Dcha-20 is an LCA-type non-secosteroid compound that significantly enhances the VDR-binding affinity of LCA. The development of LCA-type VDR ligands is expected to yield selective VDR action and differences in stability and absorption efficiency in vivo, compared to secosteroid-type compounds [32].

2.4. Interactions with Co-Regulators and Membrane-Associated Signaling Proteins

The VDR transcriptional complex comprises coactivators and corepressors that modulate the transcriptional activity of VDR. These cofactor proteins possess LxxLL motifs, where 'L' denotes leucine and 'x' represents any amino acid, facilitating their binding to VDR. Upon ligand binding, the VDR recruits RXR and coactivators to form a transcription complex. Among these, SRC1, SRC2, and SRC3 exhibit histone acetyltransferase (HAT) activity [33], recruiting additional coactivators such as CBP/p300 and p/CAF, which also possess HAT activity [34]. HAT activity promotes transcription by loosening the chromatin structure. DRIP, another coactivator with LxxLL motifs, specifically DRIP205, lacks HAT activity [9], spans the region from the VDRE to the transcription start site, and directly associates with RNA polymerase II [35]. Furthermore, proteins such as PGC-1α [36], NCoA62 [37], Smad3 [38], and Ets-1 [39] have been identified to interact with VDR. In the absence of a ligand or upon antagonist binding, the VDR interacts with corepressors. The nuclear receptor corepressor (called NCoR) [40] and silencing mediator for retinoid or thyroid hormone receptors (called SMRT) [41], which function as VDR corepressors, recruit histone deacetylase 3 and methyltransferases to condense the chromatin structure [42]. Additionally, corepressors such as Hairless [43] and Alien [44] have been implicated in the suppression of VDR transcription.

The role of VDR on the cell membrane is limited, and the protein disulfide isomerase A3 (PDIA3, also called ERp60, ERp57, Grp58, or 1,25-MARRS) is implicated in the activity of vitamin D on the cell membrane [45]. Active vitamin D prompts an intracellular calcium influx within 1–10 min in ROS17/2.8 and chicken-derived muscle cells [46]. PDIA3 is involved in this acute calcium influx induced by active vitamin D [47], and the absence of PDIA3 negates vitamin D-mediated responses [48,49]. Additionally, vitamin D induces protein kinase C (PKC) activation in VDR-deficient ROS24/1 cells [50]. Both VDR and PDIA3 are localized on the cell membrane and interact with Caveolin-1 to engage in intracellular signaling. Consequently, an indirect interaction between VDR and PDIA3 cannot be excluded [51].

3. VDR Signaling and Ion Channels: Mechanistic Insights

VDR is integral to the modulation of ion channel activity across various cellular tissues. Investigating VDR as a regulator of gene expression and ion channel activity is essential for enhancing our understanding of the physiological roles of vitamin D in the human body. The regulation of ion channels by $1,25(OH)_2D_3$ is mediated through at least four mechanisms: a) the classical, long-term action of the ligated VDR within the nucleus; b) the rapid non-genomic action of $1,25(OH)_2D_3$ or ligated VDR at the plasma membrane and within the cytoplasm; c) alterations in the properties of the lipid bilayer housing the channels, which affect conductivity and the likelihood of

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channel openings; and d) direct binding to the channel protein, independent of the VDR [5]. Genes commonly regulated by $1,25(OH)_2D_3$ that encode channel proteins include transient receptor potential vanilloid (TRPV), two-pore-domain potassium channel (KCN) (KCN subfamily K; KCNK), calcium-regulated potassium (KCNN and KCNMA), and chloride intracellular channels [5,52].

3.1. Transcriptional Regulation of Ion Channel Genes via VDREs

VDR facilitates the transcription of calcium channels, TRPV5 and TRPV6, through the action of $1,25(OH)_2D_3$ [53]. The TRPV6 gene comprises five VDREs [54], while the TRPV5 gene contains four putative VDREs [55]. Notably, duodenal *Trpv6* mRNA expression is reduced by 90% in VDR knockout (KO) mice, indicating that VDR is the primary regulator of this gene [56]. Additionally, the transcriptional induction of *Trpv6* by $1,25(OH)_2D_3$ is ten-fold in the duodenum and four-fold in the kidney, suggesting the presence of tissue-specific induction mechanisms [57]. The mechanism of TRPV6 expression has been thoroughly examined among VDR-regulated ion channels and transporters. A detailed analysis using chromatin immunoprecipitation by Meyer et al. demonstrated that VDR and RXR form heterodimers on the VDRE of the human *TRPV6* promoter in a $1,25(OH)_2D_3$-dependent manner, resulting in the recruitment of SRC1 and RNA polymerase II in intestine-derived cells [54]. Consequently, these genes are direct targets of the VDR. The renal sodium-dependent phosphate transporter gene (called NaPi-3; gene symbol: *SLC23A1*) is also a VDR target and contains a VDRE in its promoter [58]. Comprehensive RNA-sequencing analysis revealed that ZnT10 (gene symbol: *SLC30A10*), a zinc-manganese transporter, is induced by $1,25(OH)_2D_3$ in Caco-2 cells, with the VDRE region on the ZnT10 gene confirmed [59]. Another endogenous VDR ligand, LCA, induces the expression of the intestinal manganese transporter *Slc30a10* through VDR-dependent regulation [60]. Thus, VDR not only regulates calcium transport, its primary physiological function, but also modulates the expression of phosphorus and other ion transporters.

3.2. Indirect Modulation Through Second Messengers and Kinase Cascades

The regulation of ion channel expression, particularly that of TRPV6, is influenced by various factors in both VDR-dependent and independent manners. Prolactin enhances local $1,25(OH)_2D_3$ levels by upregulating CYP27B1 expression, thereby increasing *TRPV6* mRNA expression [61]. VDR-mediated induction of prolactin expression may contribute to the amplification of TRPV6 induction [62]. The involvement of p38 and the p38-interacting molecule GADD45 in $1,25(OH)_2D_3$-induced TRPV6 expression has been noted, although it remains to be determined whether the p38 signaling cascade directly targets TRPV6 mRNA or other post-transcriptional modification factors, such as miRNA [63]. Additionally, p38 and c-Jun N-terminal kinase enhance VDR activity in conjunction with $1,25(OH)_2D_3$ in the breast cancer cell line MCF7 [64]. VDR activity is partially regulated by phosphorylation, with casein kinase II positively influencing transcription by phosphorylating serine 208 of VDR in a $1,25(OH)_2D_3$-dependent manner [65], which enhances the interaction between VDR and coactivator DRIP205 [66]. ATM, a DNA damage response molecule, targets serine residues 208 and 222 of VDR, positively regulating VDR activity [67]. Conversely, PKCβ [68,69] and protein kinase A target serine 51 and serine 182 of VDR, respectively, negatively regulating its activity. protein kinase A also inhibits the heterodimerization of VDR and RXR [70,71]. Phosphorylation of VDR may play a role in regulating ion channel expression in the intestine and kidney.

The regulation of TRPV6 expression independent of VDR may indirectly influence VDR-dependent TRPV6 expression. The induction of *TRPV6* mRNA in response to low calcium levels, independent of VDR, represents the most appropriate control mechanism [72]. Additionally, estradiol induces *TRPV6* expression in an estrogen receptor (ER) α-dependent manner, without involving the VDR [73]. Notably, ERα deficiency results in a 50% reduction in *TRPV6* expression, whereas ERβ does not contribute to this process [73]. Furthermore, *TRPV6* expression is induced by glucocorticoids [74], the plant compound quercetin [75], short-chain fatty acids, oligosaccharides [76], and the serum/glucocorticoid regulated kinases 1 and 3, and protein kinase B/Akt pathways [77]. The

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vitamin D-VDR pathway activates Akt signaling in VDR target tissues [78], suggesting potential intracellular crosstalk between these pathways.

3.3. Epigenetic and Post-Transcriptional Regulation

In addition to phosphorylation, VDR and its target ion channels are regulated by post-translational modifications, such as ubiquitination, SUMOylation, and miRNA interactions. The transcription cofactor SUG1 [79] and cell cycle-related CDK11p58 promote VDR ubiquitination [80]. Meanwhile, TRPV6 is one of the targets of the ubiquitin E3 ligase Neddd45-2 [81]. There are no reports on miRNAs that directly target *TRPV6*, but they may exert effects via miR-27b [82] and miR-125b [83], which target *VDR*. The localization of these miRNA expressions in VDR target tissues may be involved in the regulation of ion channels. SUMO2 is modified by PIDIA4 to suppress VDR activity and is deSUMOylated in a ligand-dependent manner [84]. In addition, SUMO specific peptidases 1 and 2 selectively act on intestinal and kidney cell lines to enhance VDR transcriptional activity [85].

4. Regulation of Ion Channel Function by VDR in Different Cellular Contexts

VDR is integral to the regulation of ion channel function in various cells and tissues (Figure 2). This regulation is mediated through both genomic and non-genomic mechanisms, which affect the expression and activity of ion channels. The specific outcomes of VDR-mediated ion channel regulation are contingent on the cellular context, underscoring the complexity and versatility of this regulatory mechanism. Among the initial studies demonstrating the regulatory influence of vitamin D on ion channel expression are those concerning the epithelial calcium channel TRPV6. Herein, we present scientific evidence detailing some of the most extensively studied examples of VDR's influence of VDR on the expression and activity of ion channels.

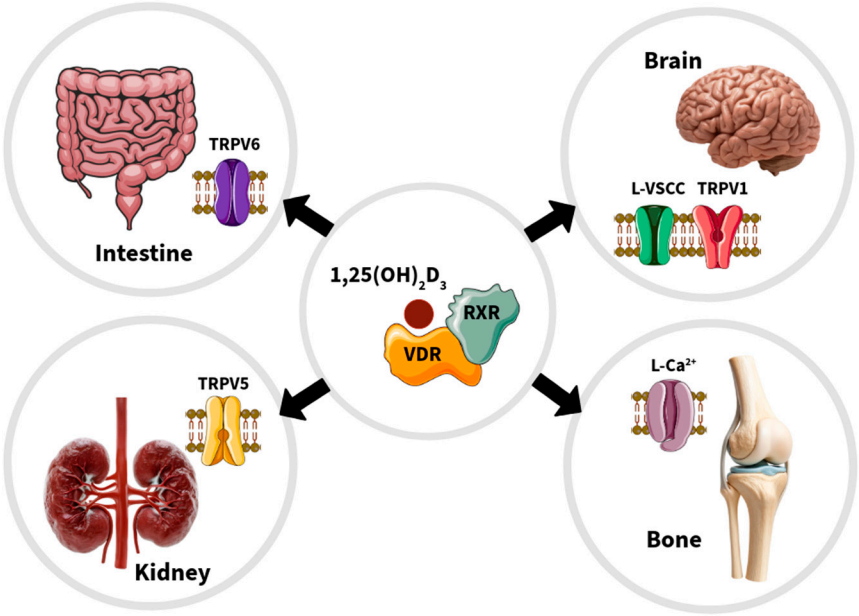

Figure 2. Regulation of ion channel function by the vitamin D receptor (VDR) in different tissues. The active form of vitamin D, 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$], binds to VDR to regulate the expression and/or activity of multiple ion channels across diverse cellular contexts. In the intestine, VDR controls the transcription of the epithelial calcium channel transient receptor potential vanilloid 6 (TRPV6); in the kidney, it regulates TRPV5, which mediates calcium reabsorption. In bone, $1,25(OH)_2D_3$–VDR signaling modulates L-type voltage-sensitive calcium channels (L-VSCC) in osteoblasts, while in the brain, VDR has been associated with the regulation of TRPV1 and neuronal calcium homeostasis. Together, these interactions highlight the broad influence of vitamin D signaling on ion transport and calcium balance in mammalian physiology.

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4.1. Osteoblast Cells

Osteoblasts have been extensively investigated to elucidate the mechanisms of action associated with vitamin D and VDR. Given that osteoblasts contain various ion channels within their plasma membrane [86,87], they have been deemed appropriate for initial studies on the effects of VDR on ion channel function [4]. For instance, the hormone $1,25(OH)_2D_3$ facilitates the activation of voltage-dependent L-type calcium channels in ROS 17/2.8 osteosarcoma cells [88]. Furthermore, $1,25(OH)_2D_3$ augments chloride currents through mechanosensitive anion channels under conditions of significant membrane depolarization [89]. These rapid actions of $1,25(OH)_2D_3$, which modulate the voltage sensitivity of Ca^{2+} channels and enhance the amplitude of Cl^- currents, suggest that vitamin D may engage distifnct signaling mechanisms at the plasma membrane in osteoblasts. In another study, the modulation of ion channel activity by $1,25(OH)_2D_3$ was examined in calvarial osteoblasts isolated from VDR-KO and wild-type mice. The authors concluded that $1,25(OH)_2D_3$ modulates ion channel activities exclusively in calvarial osteoblasts with functional VDR, and this effect is linked to exocytosis [90].

4.2. Intestinal and Kidney Cells

The action of $1,25(OH)_2D_3$ to sustain calcium and phosphorus homeostasis through the facilitation of intestinal calcium absorption and renal calcium reabsorption was linked in early research to its ability to induce the expression of calbindin D9K and/or D28K, as well as plasma membrane calcium ATPase 1b [91,92]. TRPV6 is the principal ion channel in the intestinal epithelial cell membranes that is responsible for calcium entry [54]. TRPV5 represents a class of highly selective calcium channel proteins predominantly located in the kidney, associated with calcium transport, and plays a crucial role in maintaining intracellular calcium concentration stability [93]. The TRPV5/V6 channels in kidney and intestinal cells are among the primary targets for the regulation of calcium homeostasis by hormones [94].

$1,25(OH)_2D_3$ has been shown to induce the expression of TRPV6 and calbindin D9K in the intestine and TRPV5, calbindin D9K, and D28K in the kidneys of wild-type mice in a time- and dose-dependent manner [57]. The capacity of $1,25(OH)_2D_3$ to induce TRPV6 gene expression and facilitate calcium transport has also been demonstrated in vitro using human colon-derived Caco-2 cells [95]. These studies suggest that $1,25(OH)_2D_3$ regulates the expression of TRPV genes, which are essential for the intestinal absorption and renal reabsorption of calcium. Subsequent research identified VDREs in the upstream region of the TRPV6 gene, which mediate the *cis*-actions of $1,25(OH)_2D_3$ to modulate intestinal *TRPV6* expression [54]. Additional reports indicate that $1,25(OH)_2D_3$ induces *TRPV6* mRNA expression at lower concentrations than those required for the induction of *CYP24A1*, a VDR target gene involved in vitamin D inactivation, in human intestinal SW480 cells. This suggests an alternative mechanism for vitamin D signaling in *TRPV6* induction. $1,25(OH)_2D_3$ treatment induced the expression of *GADD45A*, which encodes the growth arrest and DNA damage inducible α (GADD45α) MAPK kinase activator, prior to *TRPV6* expression, and GADD45A knockdown reduced *TRPV6* induction by $1,25(OH)_2D_3$l. These findings suggest that GADD45α plays a role in enhancing vitamin D signaling in *TRPV6* expression [63].

Research conducted by Wood et al. (2001) demonstrated that $1,25(OH)_2D_3$ induces a tenfold increase in *TRPV6* mRNA expression in the Caco-2 human intestinal cell line. Furthermore, the study observed a significant elevation in *TRPV6* mRNA levels, exceeding a five-fold increase, as early as four hours after $1,25(OH)_2D_3$ treatment. This finding suggests a pivotal role for this calcium transporter in vitamin D-dependent calcium absorption [96]. In a separate investigation involving VDR-KO mice, researchers assessed the expression of TRPV calcium channels implicated in transcellular calcium transport. The calcium transport protein TRPV6 was found to be abundantly expressed at the mRNA level in the duodenum; however, its expression was markedly reduced by more than 90% in VDR-KO mice maintained on a normal-calcium diet. This observation indicates that the expression of the duodenal epithelial calcium channel TRPV6 is dependent on vitamin D [97].

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4.3. Neuron Cells

In addition to its classical roles in regulating the absorption of calcium and phosphorus in the intestines, bones, and kidneys, as well as bone mineralization, vitamin D_3 has been shown to possess neuroprotective functions. These functions are mediated through neuronal calcium regulation, antioxidative pathways, immunomodulation, and detoxification [98]. Direct neuroprotective effects of $1,25(OH)_2D_3$ have been observed at low concentrations, including the selective downregulation of L-type voltage-sensitive Ca^{2+} channel expression in brain neurons [99]. These findings suggest that the Ca^{2+}-regulatory functions of $1,25(OH)_2D_3$ extend to neurons and may contribute to neuronal survival. TRPV1, a calcium-selective channel, is activated by heat, low pH, and various endogenous and exogenous agonists [100]. This channel is expressed in various tissues throughout the human body, including neurons, immune T-cells, nociceptive C fibers that innervate the airways, and airway epithelial cells [101,102].

$25(OH)D_3$ acts as a partial agonist of the TRPV1 channel. This vitamin D metabolite directly binds to TRPV1 within the same vanilloid binding pocket as capsaicin, enabling it to weakly activate the channel while concurrently antagonizing the effects of full agonists such as capsaicin and oleoyl dopamine. In addition to direct activation, $25(OH)D_3$ inhibits PKC-mediated potentiation of TRPV1 activity, thereby demonstrating multiple regulatory pathways. This discovery identifies TRPV1 as a novel receptor for the biological actions of vitamin D, thereby expanding our understanding of the traditional nuclear vitamin D receptor [103]. This finding provides evidence supporting the concept of a novel vitamin D/TRPV1 axis, which may elucidate some of the beneficial effects of vitamin D in disease states in which TRPV1 expression and vitamin D deficiency are known to coincide [104].

4.4. Ion Channels from the Plasma and Mitochondrial Membranes

Numerous studies have established a significant association between $1,25(OH)_2D_3$ and mitochondrial function in various cell types. Various ion channels have been identified in the mitochondrial membranes, with the majority classified as potassium channels. To date, eleven distinct potassium channels have been identified in the inner mitochondrial membrane: (1) small-conductance calcium-regulated potassium channel (mitoSKCa; encoded by *KCNN1-3*); (2) intermediate-conductance calcium-regulated potassium channel (mitoIKCa; encoded by *KCNN4*); (3) large-conductance calcium-regulated potassium channel (mitoBKCa; encoded by *KCNMA1*); (4) large-conductance potassium channel DEC isoform (mitoBKCa-DEC; encoded by *KCNMA1*); and (5) two-pore domain potassium channel [5]. A study has demonstrated for the first time that $1,25(OH)_2D_3$ modulates mitochondrial potassium channels, directly influencing the activity of the mitochondrial large-conductance Ca^{2+}-regulated potassium channel (mitoBKCa) in human astrocytoma cells, while not affecting the mitochondrial calcium-independent two-pore domain potassium channel (mitoTASK-3) in human keratinocytes [105].

5. Pathophysiological Relevance of VDR–Ion Channel Interactions

5.1. Cancer

Epidemiological research suggests that vitamin D insufficiency may play an etiological role in the development of various cancers. Over the decades, $1,25(OH)_2D_3$ and vitamin D analogs have been extensively investigated in preclinical studies because of their potential as anticancer agents. These compounds exhibit antiproliferative effects, activate apoptotic pathways, inhibit angiogenesis, and may exert effects through immune mechanisms [106,107]. In addition to its other functions, $1,25(OH)_2D_3$ regulates microRNAs, which are crucial in cancer biology, by modulating their expression profiles and influencing certain components of the miRNA processing machinery [108,109]. VDR is implicated in the regulation of cancer cell proliferation through complex mechanisms involving ion channels and metabolic regulation (Table 1).

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Table 1. Ion channels regulated by vitamin D and vitamin D receptor (VDR) in cancer.

Ion Channel/ Protein	Type of Regulation (Genomic/Non-genomic)	Functional/Physiological Effect	References
TRPV5	Genomic. Vitamin D response elements (VDREs) present in *TRPV5* promoter region; transcriptional regulation by VDR.	Maintains calcium transport in renal cells; VDR acts as a tumor suppressor in renal cell carcinoma by modulating *TRPV5* to inhibit proliferation, migration, and invasion.	Van Cromphaut et al., 2001; Hoenderop et al., 2001; Chen et al., 2018.
KCa1.1 (BKCa, KCNMA1)	Genomic. Transcriptional repression mediated by VDR activation.	Decreases depolarization responses and inhibits cell proliferation in breast cancer cells.	Khatun et al., 2016; Oeggerli et al., 2012.
Kv10.1	Genomic. Negative VDRE (E-box) identified in *KCNH1* promoter.	Reduces potassium channel expression, leading to lower proliferation and oncogenic potential in breast and cervical cancer cells.	Avila et al., 2010; García-Becerra et al., 2010; Cázares-Ordoñez et al., 2015; Cázares-Ordoñez & Pardo, 2017.

Summary of ion channels modulated by 1,25-dihydroxybitamin D_3/VDR, their regulatory mechanism, and functional consequences in tumor biology (renal cell carcinoma, breast, and cervical cancer).

5.2. Renal Cell Carcinoma (RCC)

$1,25(OH)_2D_3$ and VDR have been implicated in reducing the risk of renal cell carcinoma (RCC) [110,111]. The expression of VDR in normal kidney tissue diminishes during malignant transformation to RCC and is correlated with RCC prognosis [112,113]. These observations suggest that VDR may play a critical role in RCC development and progression. VDR and $1,25(OH)_2D_3$ have been reported to regulate the activity of TRPV5. In vitamin D-deficient or VDR-KO mice, the mRNA and protein expression levels of TRPV5 were reduced, whereas $1,25(OH)_2D_3$ administration significantly increased *TRPV5* mRNA expression in the kidneys. Consequently, TRPV5 expression is highly dependent on vitamin D intake. Furthermore, the human *TRPV5* promoter contains several consensus vitamin D-responsive elements [56,114]. Functional experiments documented in a published study demonstrated that VDR overexpression decreased cell proliferation, migration, and invasion, while promoting apoptosis in RCC cells. Conversely, VDR knockdown had the opposite effect. TRPV5 expression levels are inversely correlated with VDR, with VDR overexpression downregulating TRPV5 expression and knockdown upregulating it in RCC cells [115]. These findings indicate that VDR acts as a tumor suppressor in RCC cells by inhibiting proliferation, migration, and invasion through the regulation of TRPV5 expression.

5.3. Breast and Cervical Cancer

Numerous studies have demonstrated an association between low VDR levels and aggressive breast cancer. Furthermore, a reduction in VDR is linked to neoplastic transformation, which diminishes cancer cell sensitivity to the antiproliferative effects of $1,25(OH)_2D_3$ [116]. This underscores the significance of VDR activity in regulating the gene interaction network. The large-conductance Ca^{2+}-activated K^+ channel, KCa1.1, is associated with high-grade and poorly differentiated tumors in breast cancer [117]. A study has elucidated the effects of VDR agonists on the expression and activity of KCa1.1 in human breast cancer cells. Treatment with VDR agonists resulted in decreased KCa1.1 expression at both the transcript and protein levels in MDA-MB-453 cells, leading to the inhibition of depolarization responses induced by paxilline, a specific KCa1.1 blocker. This provides mechanistic insights, indicating that the Ca^{2+}-activated K+ channel KCa1.1 is a downstream target of VDR signaling [118].

Interactions between VDR and ion channels play crucial roles in cellular proliferation. Specifically, $1,25(OH)_2D_3$ suppresses the expression of the Kv10.1 potassium channel (also called

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EAG1; encoded by the gene *KCNH1*), a member of the ether-à-go-go (EAG) family of voltage-gated potassium channels, through VDR-dependent mechanisms, resulting in decreased proliferation of breast cancer cells [119]. Furthermore, $1,25(OH)_2D_3$ downregulates Kv10.1 channels in cancer cells derived from the breast and cervix, leading to a reduction in Kv10.1 protein levels at various incubation periods [120]. Kv10.1 is considered clinically significant because of its transformative activity and ectopic expression in clinical tumors [121]. Ectopic expression has been observed in various tumor cell lines and is associated with cell proliferation [122,123]. Additional studies have demonstrated the overexpression of Kv10.1 in tumors from clinical samples, suggesting its potential as a promising target for cancer therapy [124]. Research on cervical cancer cells has indicated that the effect of $1,25(OH)_2D_3$ on *KCNH1* expression is VDR-dependent. It has been proposed that this mRNA repression by $1,25(OH)_2D_3$ involves an E-box type VDRE, which functions as a negative regulatory element in the *KCNH1* promoter [125].

5.4. Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a complex chronic condition characterized by pulmonary vascular remodeling and vasoconstriction of the pulmonary artery (PA). This vascular remodeling results from the excessive and uncontrolled proliferation and resistance to apoptosis of PA smooth muscle cells (PASMCs) and endothelial cells, leading to intimal thickening and PA obliteration. Vitamin D deficiency is significantly more prevalent in patients with PAH than in the general population or even in patients with other cardiovascular diseases. In both PAH patients and animal models, lower vitamin D levels are associated with a worse functional class [126,127]. A recent report indicated that VDR is expressed in several cell types within the lung, including PASMCs, and is downregulated in the lungs and PASMCs of PAH patients. Treatment with $1,25(OH)_2D_3$ can restore VDR expression, upregulate *KCNK3* and bone morphogenetic protein 4, and downregulate survivin gene expression in PASMCs, exerting an antiproliferative effect by modulating the survivin and bone morphogenetic protein signaling pathways [128]. Notably, low levels of lung VDR are associated with several pulmonary diseases, including chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis, and correlate with a poor prognosis [129,130].

Several studies have indicated that *KCNK3* may be a target of VDR [131–133], and a VDRE has been identified in the promoter region of the *KCNK3* gene [134]. $1,25(OH)_2D_3$ has been shown to significantly upregulate *KCNK3* mRNA expression in cultured PASMCs from both control subjects and patients with PAH (26). However, the antiproliferative effects of $1,25(OH)_2D_3$ appear unaffected by *KCNK3* inhibition, suggesting that the upregulation of *KCNK3* does not contribute to the antiproliferative effects induced by $1,25(OH)_2D_3$ [128]. Voltage-dependent (Kv) or K2P potassium channels are crucial in pulmonary circulation as they regulate the membrane potential, arterial tone, cell proliferation, and survival of PASMCs. Ionic channel remodeling, primarily characterized by dysfunctional Kv1.5 and TASK-1 channels, is a common feature of PAH in both animal models and humans [135–138].

Kv7 channels are critical regulators of vascular tone in both healthy and diseased states. Activation of Kv7 channels induces an outward efflux of K^+, leading to hyperpolarization and relaxation, as well as exerting antiproliferative effects on vascular smooth muscle cells [139–141]. Previous studies have identified potential VDREs in the promoters of genes encoding Kv7.1, Kv7.3, and KCNE4 channels [142]. Vitamin D deficiency is highly prevalent among patients with PAH, affecting 95% of this population [126,127]. Low levels of vitamin D are associated with poor prognosis, and both VDR mRNA and protein are downregulated in the lungs of patients with PAH.

A recent investigation examined the function of VDR within the pulmonary vasculature of mice, specifically assessing whether the ablation of *Vdr* in mice leads to pulmonary arterial dysfunction, with a focus on the regulation of Kv7 channels. The study identified upregulation of the ancillary subunit KCNE4 in the lungs of VDR-KO mice, which aligns with the discovery of a consensus VDRE in both human and mouse KCNE4 genes. Notably, PASMCs from VDR-KO mice exhibited enhanced Kv7 currents and an increased relaxant response to the Kv7 channel activator retigabine. Mice

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deficient in VDR did not exhibit an evident PAH phenotype [143]. Collectively, these findings indicate a negative regulatory role of VDR on KCNE4 within the pulmonary vasculature, adversely affecting Kv7 channel activity [143] (Table 2).

Table 2. Ion channels regulated by vitamin D and vitamin D receptor (VDR) in pulmonary arterial hypertension.

Ion Channel/ Protein	Type of Regulation (Genomic/Non-genomic)	Functional/Physiological Effect	References
TASK-1	Genomic. VDRE identified in promoter.	Improves repolarization; partial antiproliferative effect. However, KCNK3 inhibition does not block 1,25(OH)$_2$D$_3$-induced antiproliferation.	Callejo et al., 2020; Milani et al., 2013; Shalhoub et al., 2010; Campos et al., 2013; Callejo et al., 2024.
Kv7 regulatory subunit 4	Genomic. VDRE present in KCNE4 promoter	Overexpression enhances Kv7 activity and K^+ currents, increasing PASMC relaxation.	Olivencia et al., 2023; Wang et al., 2005.
Kv7.x (KCNQ1, KCNQ3, Kv7.1–Kv7.5)	Genomic. Predicted VDREs	Activation causes K^+ efflux, hyperpolarization, and relaxation with antiproliferative effects in PASMCs.	Wang et al., 2005; Barrese et al., 2018; Mondejar-Parreño et al., 2020; Mackie & Byron, 2008.
Kv1.5	Non-genomic/indirect (no VDRE reported)	Loss of Kv1.5 currents favors depolarization and PASMC proliferation.	Antigny et al., 2016; Gurney et al., 2003; Lambert et al., 2018; Yuan et al., 1997.
TASK-1/K2P (two-pore domain K^+ channels)	Genomic. VDRE present in KCNK3 promoter	Regulates pulmonary arterial tone and PASMC proliferation.	Callejo et al., 2020; Tanaka et al., 2017.

Summary of ion channels modulated by 1,25-dixydroxyvitamin D$_3$ (1,25(OH)$_2$D$_3$)/VDR, their regulatory mechanism, and functional consequences in pulmonary artery hypertension. VDRE, vitamin D response element; KCN, potassium channel; PASMC, pulmonary artery smooth muscle cell.

5.5. Osteoporosis

Osteoporosis is a systemic skeletal disorder characterized by reduced bone mass and deterioration of bone microarchitecture, leading to increased bone fragility and a heightened risk of fractures [144]. A prevalence report that included 86 studies from five continents indicated that the global prevalence rate of osteoporosis is 18.3%, with only 31-36% of individuals over the age of 70 years maintaining normal bone health [145]. The etiology of osteoporosis may be idiopathic or secondary to factors such as hypogonadism, vitamin D deficiency, insufficient calcium intake, and prolonged excessive alcohol consumption, ultimately resulting in an osteopenic skeleton and an increased risk of developing osteoporosis [146].

Bone mineral density (BMD) is commonly employed as an indicator of bone strength, and the diagnosis of osteoporosis is based on its assessment. BMD is affected by both genetic and environmental factors, including physical activity, smoking, and dietary habits [147]. Bone remodeling is a continuous process throughout life that encompasses osteoclast-mediated bone resorption and osteoblast-driven bone formation [148]. Furthermore, osteocytes, which are embedded within the bone matrix, contribute to this remodeling process and are currently regarded as the primary source of molecules that regulate osteoclast and osteoblast activities. The formation and differentiation of osteoclasts are regulated by complex interactions between cytokines, hormones, immune factors, gut microbiota, and cellular aging. Among the various cytokines and

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hormones that influence osteoclast formation and function, macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor-kB ligand (RANKL) are critical [149].

Genes postulated to contribute to osteoporosis include those implicated in bone formation and remodeling (e.g., LRP5), those involved in hormone signaling pathways (e.g., VDR and ESR1), and those encoding bone structural proteins (e.g., COL1A1) [150].

Dysregulation of the Vitamin D/VDR system has been associated with various bone pathologies, including osteoporosis. Recent advancements have elucidated the role of the VD/VDR system in modulating the activity of bone cells, such as osteoblasts and osteoclasts, and have highlighted how VDR polymorphisms may influence bone mineral BMD and fracture risk [151].

Activation of the VDR modulates the equilibrium between osteoblast-mediated bone formation and osteoclast-mediated bone resorption by regulating the expression of receptor activator of nuclear factor κB ligand (RANKL) and osteoprotegerin (OPG) [152,153]. RANKL serves as a critical osteoclastogenic factor, whereas OPG functions as a decoy receptor, inhibiting RANKL and thereby preventing osteoclast activation [152,153]. VDR activation in osteoblasts reduces RANKL expression and increases OPG expression, thereby suppressing osteoclastogenesis and maintaining bone homeostasis. Extensive research has been conducted globally on the association between VDR gene polymorphisms, particularly ApaI, TaqI, and BsmI, and osteoporosis [154,155].

Bone metabolism in osteoporosis is intricately associated with the expression of Ca^{2+} channels in osteocytes, rendering their regulation essential for effective disease management. Calcium channels play a pivotal role in skeletal homeostasis by facilitating processes that govern extracellular and intracellular Ca^{2+} equilibrium. The differentiation and apoptosis of osteoclasts are extensively regulated by Ca^{2+} channels located in the cell membrane [149].

Transient receptor potential (TRP) channels, recognized for their high calcium permeability, have several members that are significantly associated with osteoporosis. These channels, comprising six subfamilies—TRPC, TRPV, TRPP, TRPM, TRPA, and TRPML—are integral to the regulation of Ca^{2+} balance during bone homeostasis [156]. Specifically, TRPV1 facilitates osteoclast differentiation, as evidenced by TRPV1-deficient mice, which exhibit a reduced number of osteoclasts [157]. Furthermore, TRPV5 and TRPV6 are involved in the regulation of osteoclast size and number, with TRPV6 acting as a negative regulator [158–160]. TRPV6 knockdown is associated with a significant increase in bone resorption [161] (Table 3).

Although the precise mechanisms through which VDR-mediated transcription facilitates osteogenesis and osteoblastic bone formation while concurrently inhibiting osteocyte senescence and osteoclastic bone resorption remain to be elucidated, the critical role of the VDR in bone formation and its contribution to bone-associated pathologies continues to represent an important area of investigation [162]. Given the critical involvement of the VDR pathway in osteoporosis pathogenesis, targeting this pathway presents substantial therapeutic potential.

Table 3. Ion channels regulated by vitamin D and vitamin D receptor (VDR) in bone physiology and their potential role in osteoporosis.

Ion Channel/ Protein	Type of Regulation (Genomic/Non-genomic)	Functional/Physiological Effect	References
TRPV1	Non-genomic/indirect. Ca♂-mediated signaling.	Increases osteoclastogenesis and bone resorption via Ca♂ influx.	He et al., 2017.
TRPV5	Genomic. VDRE present in promoter; transcriptional activation by VDR.	Controls osteoclast size and Ca♂ transport; deficiency reduces calcium reabsorption and bone mineralization.	Chen et al., 2014; van der Eerden et al., 2005.
TRPV6	Genomic. VDRE-dependent regulation.	Reduces osteoclast activity; TRPV6 knockdown increases bone resorption.	Chamoux et al., 2010; Ma et al., 2021; Chen et al., 2014.

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TRP Channel Family (TRPC, TRPV, TRPM, TRPA, TRPML)	Mixed genomic and non-genomic.	Regulate Ca^{2+} influx, osteoclast differentiation, and osteocyte signaling for bone remodeling.	Li, 2017; Hao et al., 2024.

Summary of ion channels modulated by $1,25(OH)_2D_3$/VDR, their regulatory mechanism, and functional consequences in osteoporosis. TRP, transient receptor potential; TRPV, transient receptor vanilloid; VDRE, vitamin D response element.

6. Conclusions and Perspectives

The intricate relationship between the VDR and ion channels represents an essential and evolving area of research in molecular and cellular physiology. Over the past few decades, substantial progress has been made in elucidating how vitamin D and its active metabolites influence ion fluxes through both genomic and non-genomic mechanisms. Genomic actions, primarily mediated by ligand-activated VDR binding to VDREs, regulate the transcription of key channel genes, such as TRPV5, TRPV6, KCNK3, and KCNH1. These interactions control calcium and potassium channel expression, contributing to the maintenance of calcium-phosphate balance, membrane potential, and cellular excitability. In parallel, non-genomic actions occurring within seconds to minutes modulate channel activity through membrane-associated VDR, alternative binding pockets, and signaling intermediates, including protein kinase C and cyclic AMP. Together, these dual mechanisms enable the VDR to coordinate both the expression and function of ion channels, ensuring a finely tuned homeostatic network across tissues.

Experimental studies in osteoblasts and renal and intestinal epithelial cells have revealed that 1,25-dihydroxyvitamin D_3 rapidly modulates voltage-gated calcium and chloride currents, underscoring the receptor's involvement in exocytosis, secretion, and bone formation. Simultaneously, the transcriptional control of TRPV channels and calbindins underlies vitamin D–dependent calcium absorption and reabsorption. Furthermore, mitochondrial ion channels have recently emerged as novel VDR targets, highlighting the potential link between vitamin D signaling and bioenergetic regulation. Growing evidence suggests that VDR–ion channel interactions extend beyond calcium homeostasis to include broader physiological functions, from cell proliferation and differentiation to neuronal excitability and cardiovascular control.

Clinically, disturbances in VDR signaling and ion channel expression are associated with multiple diseases, including osteoporosis, chronic kidney disease, pulmonary hypertension, and various forms of cancer. In this context, dysregulated calcium and potassium fluxes may contribute to aberrant cell proliferation, resistance to apoptosis, and altered metabolic profiles. Thus, understanding the molecular interplay between VDR and ion channels not only enhances our knowledge of basic physiology but also provides new therapeutic opportunities.

Traditional Chinese medicine (TCM) and bioactive compounds derived from natural sources have attracted increasing interest from scholars. Notably, TCM formulations and TCM-derived bioactive compounds have demonstrated the potential to modulate VDR activity [162]. Numerous medicinal herbs used in TCM, commonly referred to as kidney tonics, have been evaluated for their effects on bone metabolism in the treatment of osteoporosis in both laboratory settings and clinical trials [163]. Bu-Shen-Jian-Pi-Yi-Qi therapy, a traditional Chinese medicine, was assessed for its potential therapeutic efficacy in an alcohol-induced osteoporosis rat model, and its underlying mechanism was investigated. Bu-Shen-Jian-Pi-Yi-Qi therapy inhibited bone loss and promoted bone formation in an alcoholic osteoporosis model, as evidenced by increased BMD and elevated VDR expression at the mRNA level [164], suggesting a relationship between VDR expression and bone metabolism in alcoholic osteoporosis.

Further investigation is required to substantiate the biological relationship between VDR function and osteoporosis. Considering the physiological linkage between VDR and various ion channels in bone metabolism, elucidating the cell signaling networks and biological mechanisms

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connecting these elements within the context of osteoporosis is anticipated to facilitate the development of novel therapeutic strategies.

Several questions remain unanswered. The precise molecular identity of membrane-associated VDR complexes, structural basis for VDR–channel protein interactions and downstream signaling cascades require further elucidation using high-resolution biochemical and biophysical methods. Moreover, integrating transcriptomic and electrophysiological approaches is crucial for capturing the dynamic nature of VDR-mediated ion channel regulation. Future studies should also explore the tissue-specific variability of these mechanisms and their relevance in pathological states and aging.

In conclusion, the VDR–ion channel axis constitutes a multifaceted signaling paradigm that bridges genomic and rapid extranuclear pathways. Continued exploration of this field promises not only to expand our comprehension of vitamin D biology but also to open promising perspectives for precision medicine, where the modulation of receptor–channel interactions could become a key strategy for restoring ionic and metabolic homeostasis in human health and disease.

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Abbreviations

The following abbreviations are used in this manuscript:

$1,25(OH)_2D_3$	1,25-dihydroxyvitamin D_3
$25(OH)D_3$	25-hydroxyvitamin D_3
BMD	Bone mineral density
CYP	Cytochrome P450
DRIP	Vitamin D receptor interacting protein
EAG	Ether-à-go-go
ER	Estrogen receptor
HAT	Histone acetyltransferase
KCN	Potassium channel
KO	knockout
LCA	Lithocholic acid
OPG	osteoprotegerin
PDIA3	Protein disulfide isomerase A3
PA	Pulmonary artery
PAH	Pulmonary artery hypertension
PASMC	Pulmonary artery smooth muscle cell
PKC	Protein kinase C
RANKL	Receptor activator of nuclear factor kB ligand
RCC	Renal cell carcinoma
RXR	Retinoic X receptor
SRC	Steroid receptor coactivator

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TCM	Traditional Chinese medicine
TRP	Transient receptor potential
TRPV	Transient receptor potential vanilloid
VDR	Vitamin D receptor
VDRE	Vitamin D response element

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