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Genomic and non-genomic action of vitamin D on ion channels – Targeting mitochondria

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ABSTRACT

Recent studies revealed that mitochondria are not only a place of vitamin D_3 metabolism but also direct or indirect targets of its activities. This review summarizes current knowledge on the regulation of ion channels from plasma and mitochondrial membranes by the active form of vitamin D_3 ($1,25(OH)_2D_3$). $1,25(OH)_2D_3$, is a

Abbreviations: $1,25(OH)_2D_3$ calcitriol, the active form of vitamin D_3; $1,25D_3$-MARRS, membrane-associated rapid response to steroid; $25(OH)_2D_3$, calcidiol; 7DHC, 7-dehydrocholesterol; A431, squamous carcinoma cell line; ADAM10, A disintegrin and metalloproteinase domain 10; ANO1, anoctamin 1; APP, amyloid precursor protein; BODIPY, boron-dipyrromethene; C2C12, mouse myoblast cell line; CAV1, caveolin-1; Cav1.3, L-type Ca^{2+} channels; CAV3, caveolin-3; CLCN2, chloride voltage-gated channel 2; CLIC, chloride intracellular channels; CLIC4, chloride intracellular channel type 4; CLIC5, chloride intracellular channel type 5; CO-IP, co-immunoprecipitation; COXII, cytochrome c oxidase subunit II; CPT1b, carnitine palmitoyltransferase 1; CRAC1, cholesterol binding motif; CYP1B1, cytochrome P450 family 1 subfamily B member 1; CYP24A1, cytochrome P450 family 24 subfamily A member 1; CYP27A1, cytochrome P450 family 27 subfamilies A member 1; CYP27B1, cytochrome P450 Family 27 Subfamily B Member 1; Cyp2R1, cytochrome P450 family 2 subfamily R member 1; DEGs, differentially expressed genes; D-loop, displacement loop; DRP1, dynamin-related protein 1; EAG1, ether à-go-go-1 channel; Elovl3, elongation of very long chain fatty acids-3; ERp57, endoplasmic reticulum resident protein 57; ETC, electron transport chain; FIS1, mitochondrial fission 1 protein; GHS, hypercalciuric stone-forming; HDAC, histone deacetylase; HEKn, human epidermal keratinocytes neonatal; HK-2, a proximal tubular cell line derived from normal kidney; HPEKp, primary human epidermal keratinocytes; K^+-ATP, ATP-regulated potassium channels; K^+-Ca^{2+}, calcium–regulated potassium channels; KCNE4, potassium voltage-gated channel subfamily E regulatory subunit 4; KCNH1, potassium voltage-gated channel subfamily H member 1; KCNJ11, potassium inwardly rectifying channel subfamily J member 11; KCNK9, two-pore domain potassium channels type 9; KCNMA1, potassium calcium-activated channel subfamily M alpha 1; KCNMA1 STREX, potassium calcium-activated channel subfamily M alpha 1 with stress-axis regulated exon; KCNMB4, potassium calcium-activated channel subfamily M regulatory beta subunit 4; KCNN, intermediate/small conductance calcium-activated channel, subfamily N; KCNN1, potassium calcium-activated channel subfamily N member 1; KCNN2, potassium calcium-activated channel subfamily N member 2; KCNN3, potassium calcium-activated channel subfamily N member 3; KCNN4, potassium calcium-activated channel subfamily N member 4; KCNQ1, potassium voltage-gated channel subfamily Q member 1; KCTD14, potassium channel tetramerization domain containing 14; Kv, voltage-regulated potassium channels; Kv7, potassium *voltage-gated channel subfamily Q member 1; LRP2/CUBN, megalin/cubilin; L-type VDCC, L-type voltage-gated channels; MCF-7, breast cancer cell line; MCU, mitochondrial calcium uniporter; MFN1/2, mitofusin-1/2; MG-63, human osteosarcoma cell line; mitoBK$_{Ca}$, mitochondrial large conductance calcium-regulated potassium channel; mitoBK$_{Ca}$, DEC mitochondrial large conductance potassium channel DEC isoform; mitoDEGs, mitochondrial differentially expressed genes; mitoHCN, mitochondrial hyperpolarization-activated cyclic nucleotide-gated channel; mitoIK$_{Ca}$, mitochondrial intermediate conductance calcium-regulated potassium channel; mitoK$_{ATP}$, mitochondrial ATP-sensitive potassium channel; mitoKv1.3, mitochondrial 1.3 voltage-gated potassium channel; mitoKv1.5, mitochondrial 1.5 voltage-gated potassium channel; mitoKv7.4, mitochondrial 7.4 voltage-gated potassium channel; mitoSK$_{Ca}$, mitochondrial small conductance calcium-regulated potassium channel; mitoSLO2, mitochondrial sodium-activated potassium channel; mitoTASK-3, mitochondrial two-pore domain potassium channel; MT-ATP6, mitochondrially Encoded ATP Synthase Membrane Subunit 6; MT-ATP8, mitochondrially Encoded ATP Synthase Membrane Subunit 8; MTCO1, mitochondrially Encoded Cytochrome C Oxidase I; mtDNA, mitochondrial DNA; MT-ND3, mitochondrially encoded NADH:ubiquinone oxidoreductase core subunit 3; MT-ND4, mitochondrially encoded NADH:ubiquinone oxidoreductase core subunit 4; MT-ND5, mitochondrially encoded NADH:ubiquinone oxidoreductase core subunit 5; OPA1, optic atrophy 1; OXPHOS, oxidative phosphorylation; PASMC, pulmonary artery smooth muscle cells; PC, phosphatidylcholine; PDIA3, protein disulfide isomerase family A member 3; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1alpha; PKA, protein kinase A; PLA2, phospholipase A2; PTP, permeability transition pore; RXRA, retinoid X receptor alpha; SERCA, sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase; SHH, sonic hedgehog signaling; SH-SY5Y, neuroblastoma cell line from a metastatic bone tumor; STREX, stress-axis regulated exon; TASK, TWIK-related acid-sensitive K+ channel, two-pore domain; TFAM, mitochondrial transcription factor A; TGFβ, transforming growth factor-β; THP-1, human monocytic cells; TMEM16A, transmembrane Protein 16A; TOM/TIM, mitochondrial translocase; TRPV, transient receptor potential cation channel subfamily V; TRPV5, transient receptor potential cation channel subfamily V type 5; TRPV6, transient receptor potential cation channel subfamily V type 6; UCP3, uncoupling Protein 3; UVB, ultraviolet B; VDAC, voltage-dependent anion channel; VDR, vitamin D receptor; VDRE, vitamin D receptor response elements.

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naturally occurring hormone with pleiotropic activities; implicated in the modulation of cell differentiation, and proliferation and in the prevention of various diseases, including cancer. Many experimental data indicate that $1,25(OH)_2D_3$ deficiency induces ionic remodeling and $1,25(OH)_2D_3$ regulates the activity of multiple ion channels. There are two main theories on how $1,25(OH)_2D_3$ can modify the function of ion channels. First, describes the involvement of genomic pathways of response to $1,25(OH)_2D_3$ in the regulation of the expression of the genes encoding channels, their auxiliary subunits, or additional regulators. Interestingly, intracellular ion channels, like mitochondrial, are encoded by the same genes as plasma membrane channels. Therefore, the comprehensive genomic regulation of the channels from these two different cellular compartments we analyzed using a bioinformatic approach. The second theory explores non-genomic pathways of vitamin D_3 activities. It was shown, that $1,25(OH)_2D_3$ indirectly regulates enzymes that impact ion channels, change membrane physical properties, or directly bind to channel proteins. In this article, the involvement of genomic and non-genomic pathways regulated by $1,25(OH)_2D_3$ in the modulation of the levels and activity of plasma membrane and mitochondrial ion channels was investigated by an extensive review of the literature and analysis of the transcriptomic data using bioinformatics.

1. Introduction

An active form of vitamin D_3 ($1,25(OH)_2D_3$), is a naturally occurring hormone with pleiotropic activities and the key regulator of mineral homeostasis. In addition to the long-known important role in regulating the level of calcium in the body, $1,25(OH)_2D_3$ is implicated in the modulation of cell differentiation, and proliferation and also in the prevention of cancer (Slominski et al., 2020b); (Slominski et al., 2017); (Slominski et al., 2020a); (Chen et al., 2020); (Muñoz and Grant, 2022). The major stable circulating form of vitamin D_3 in the blood is $25(OH)D_3$. Vitamin D_3 is naturally produced from 7-dehydrocholesterol (7DHC) in the skin, in a nonenzymatic reaction driven by the ultraviolet B (UVB) fraction of sunlight (Holick, 2020). For its activation, it requires hydroxylation at the C-25 position (carbon number 25) by cytochrome P450 family 2 subfamily R member 1 (Cyp2R1) in the liver. Then the active form of vitamin D_3 is produced in the kidney via hydroxylation in the C-1 (carbon number 1) by cytochrome P450 Family 27 subfamily B member 1 (CYP27B1) (Żmijewski, 2022). However, $25(OH)D_3$ and $1,25(OH)_2D_3$ also can be produced locally in the skin keratinocytes. $1,25(OH)_2D_3$ exerts steroid-like effects by directly interaction with heterodimers composed of nuclear vitamin D receptor (VDR) and retinoid-X-receptor (RXR), thereby affecting the expression of many genes (Koll et al., 2023). The binding of $1,25(OH)_2D_3$ to the VDR: RXR complex or VDR homodimer to the vitamin D response element (VDRE) could repress or enhance the transcription of many genes through modification of the target gene promoter activity (Żmijewski, 2022) (Zmijewski and Carlsberg 2020). VDR-independent non-genomic vitamin D_3 signalling mainly occurs via membrane-bound proteins, such as protein disulfide isomerase family A member 3 (PDIA3), also known as endoplasmic reticulum resident protein 57 (ERp57) and membrane-associated rapid response to steroid ($1,25D_3$-MARRS) (Gaucci et al., 2016). The existence of alternative receptors for vitamin D_3 derivatives is worth emphasizing. For example, the tachysterol hydroxyderivatives were found to regulate aryl hydrocarbon receptor (AhR), liver X receptor (LXR), or PPARgamma receptor (Slominski et al., 2022). Retinoic acid-related orphan receptors (RORs) activity were shown to be modulate by the 20-hydroxyvitamin D_3 and 20,23-dihydroxyvitamin D_3 (Slominski et al., 2014). The LXR might be also regualted by the derivatives of lumisterol and vitamin D_3 (Slominski et al., 2021) while AhR by the 20,23-dihydroxyvitamin D_3 (Slominski et al., 2018).

Alternatively, $1,25(OH)_2D_3$ can act in a non-genomic way by regulating plasma membrane ion channels (Long et al., 2021). In addition to the nuclear and plasma membrane effects of $1,25(OH)_2D_3$/VDR, recently a new mitochondria regulatory mechanism of VDR has been suggested. The active form of vitamin D_3 is also strongly linked with mitochondria. First, key enzymes for vitamin D_3 metabolism, such as cytochrome P450 subfamily members A, B, and R, are located in the mitochondria. Secondly, VDR is translocated into the mitochondria of some cell types (Silvagno et al., 2013). It seems that the interaction of this pluripotent secosteroid with mitochondria is complex and vitamin D_3 and its metabolites have a significant direct or indirect impact on mitochondria. Here we will focus on the effect of the active form of vitamin D_3 on ion channels, mitochondrial biogenesis, and bioenergetics.

The concept of how $1,25(OH)_2D_3$ can regulate ion channels is based on the classic long-time dependent action of the ligated VDR receptor in the nucleus and the fast non-genomic action of $1,25(OH)_2D_3$ or ligated VDR in the plasma membrane and cytoplasm (Fig. 1**A**). In a non-classical, non-genomic way, $1,25(OH)_2D_3$ after forming a complex with the cytoplasmatic or membrane form of VDR, can influence kinases and phosphatases that regulate the gating properties of ion channels. Another possibility is to change the properties of the lipid bilayer in which the channels are located. Such membrane changes (fluidity), affect conductivity and the probability of channel openings. Because vitamin D_3 is metabolized to many intermediate products (Tuckey et al., 2019), the impact of these metabolites on ion channels should also be considered. The last possible regulation of ion channels is by direct binding to the channel protein, independent of the VDR (Fig. 1**A, B**).

2. Genomic action of the active form of vitamin D_3 on ion channels

Activation of the classic genomic pathway of response to $1,25(OH)_2D_3$ results in time-dependent modulation of expression of the genes under control of VDR: RXRA responding elements (JASPAR matrix MA0074.1; also called DR3-type) in their promoters and regulatory sequences. However, there is a very large group of genes with only VDRE motive, thus presumably their expression depends on VDR homodimer alone (JASPAR matrix MA0693.2). Moreover, at early time points of the genome's response to $1,25(OH)_2D_3$, an increase in the expression of genes encoding transcription factors and chromatin modifiers is observed. Such observations indicate that there is a so-called genomic response hierarchy (Warwick et al., 2021), based on primary targeted genes, which is followed by secondary or even ternary responses activated by transcription factors and modifiers initially activated by $1,25(OH)_2D_3$. The genomic effect of $1,25(OH)_2D_3$ on ion channels has not been investigated in detail so far. Based on the transcriptomic data of our research group and published by others (only data collected for a similar $1,25(OH)_2D_3$ concentration and incubation time were included), we extracted genes encoding channel proteins with differential expression under the influence of $1,25(OH)_2D_3$ (Fig. 2**A**). So far, transcriptomic studies using $1,25(OH)_2D_3$ have been carried out on colonic organoids (Li et al., 2021), normal keratinocytes (Slominski et al., 2018), squamous carcinoma cells (Olszewska et al., 2024b), human monocytic cells (THP-1) (Warwick et al., 2021), peripheral blood mononuclear cells (Fernandez et al., 2022), breast cancer cell line (MCF-7) (Murray et al., 2017), asthmatic bronchial epithelial cells (Boutaoui et al., 2019), human breast cancer tissue (Sheng et al., 2016), colorectal cancer cells (Guo et al., 2023), airway smooth muscle cells (Himes et al., 2015), immortalized human oral keratinocytes (Menzel et al., 2019).

Depending on the cell type, the ratio of up-and down-regulated genes encoding channel proteins was different (Fig. 2**A**). However, our analysis revealed commonly regulated genes including transient receptor potential cation channel subfamily V (gene: *TRPV*) channels, two-pore domain potassium channels (gene: *KCNK*), calcium-regulated potassium channels (genes: *KCNN* and *KCNMA*), or chloride intracellular channels (genes: *CLIC*).

The best-known channels regulated by $1,25(OH)_2D_3$ belong to the TRPV channels class (TRPV5, TRPV6) that act as signal transducers by altering membrane potential or intracellular calcium (Long et al., 2021). *TRPV5* is expressed mainly in the kidney and *TRPV6* is expressed in a range of epithelial tissues such as the intestine, kidney, placenta, epididymis, and exocrine glands such as the pancreas, prostate, salivary, sweat, and mammary glands (Khattar et al., 2022). These channels play a special role in carcinogenesis by affecting proliferation, differentiation (Marini et al., 2023), and metastasis of the cells (Bai et al., 2023). In renal cell carcinoma, the expression of the *TRPV5* gene was decreased in comparison to normal renal tissue, and the expression of *TRPV5* is strongly dependent on the intake of vitamin D_3. VDR knockdown increases *TRPV5* expression and VDR overexpression decreases *TRPV5* expression in such cells, and this suggests that VDR is involved in the development and progression of renal carcinoma via regulating the transcription of *TRPV5* (Chen et al., 2018). Moreover, the human *TRPV5* promoter contains several consensus VDREs (Van Cromphaut et al., 2001). The TRPV6 channels are mainly presented in the intestinal epithelial cell membranes and are responsible for $1,25(OH)_2D_3$-regulated calcium entry into the cell and epithelial-mesenchymal transition (Kärki et al., 2020). *In silico* analysis and ChiP assay revealed five putative VDR elements in promoter sequences encoding TRPV6 channels and mutagenesis of three of them abrogated response to $1,25(OH)_2D_3$ (Meyer et al., 2006). Additionally, studies on the hypercalciuric stone-forming (GHS) rat model demonstrated that VDR binds to three

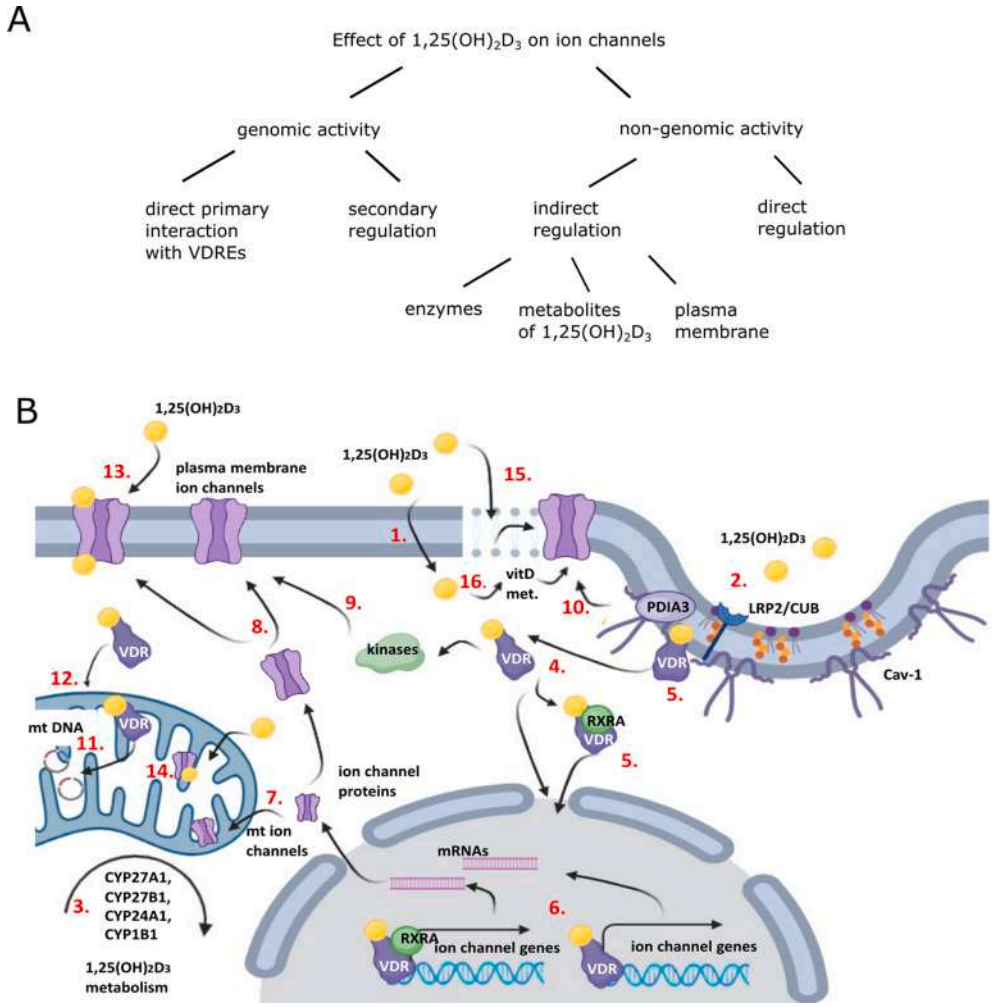

Fig. 1. Proposed mechanism of action of active form of vitamin D_3 on ion channels from plasma membranes and mitochondria. (A) Different genomic and non-genomic ways of regulation of ion channels by $1,25(OH)_2D_3$. **(B)** In genomic or non-genomic action, non-hydroxylated vitamin D_3 and $1,25(OH)_2D_3$ can enter the cell directly through the plasma membrane (1) or can be imported via receptor-mediated endocytosis by the protein megalin/cubilin complexes (LRP2/CUBN) in caveolin 1 (Cav-1)-rich membranes (2). In mitochondria non-hydroxylated vitamin D_3 can be metabolized into $1,25(OH)_2D_3$ (3). $1,25(OH)_2D_3$ binds vitamin D receptor (VDR) in cytoplasm (4) or near plasma membranes (5). In genomic action $1,25(OH)_2D_3$ as a complex with VDR or additionally retinoid X receptor alpha (RXRA) co-receptor is transported to the nucleus and impacts the expression level of genes encoding ion channels (6). Translated ion channel proteins can be imported into the mitochondrial membranes (7) or plasma membranes (8). In non-genomic action $1,25(OH)_2D_3$-VDR complex can impact ion channels via a kinases-dependent manner (9) or via protein disulfide isomerase family member 3 (PDIA3)-dependent manner (10). VDR receptor can also be transported to the mitochondria influencing mtDNA (11) or bioenergetics (12). According to one concept $1,25(OH)_2D_3$ can directly regulate ion channels in the plasma membrane (13) or mitochondria (14) or may affect the properties of the membrane and thus indirectly affect the activity of channels (15). The last of the non-genomic indirect ways of regulation is the effect on channels via vitamin D metabolites (16). Abbreviations: CYP1B1 cytochrome P450 family 1 subfamily B member 1; CYP24A1 cytochrome P450 family 24 subfamily A member 1; CYP27A1 cytochrome P450 family 27 subfamilies A member 1; CYP27B1 cytochrome P450 Family 27 Subfamily B Member 1; LRP2/CUBN megalin/cubilin; VDR vitamin D receptor; RXRA retinoid X receptor alpha; CAV1 caveolin-1; vitD met. vitamin D metabolites.

enhancers in the *Trpv6* promoter followed by histone acetylation in the same regions (Guo et al., 2022).

Our detailed analyses of transcriptional data revealed that majority of affected genes by 1,25$(OH)_2D_3$ belong to the potassium channel family: voltage-activated potassium channels, calcium-activated potassium channels, and two-pore domain potassium channels (Fig. 2**A**). All the found genes encoding ion channels were analyzed by us in the CiiiDER program (Gearing et al., 2019) for the presence or absence of binding sites for VDR: RXRA (Jaspar matrix MA0074.1) or VDR alone (Jaspar matrix MA0693.2) in the promoter sequences. The *CLCN2* (chloride voltage-gated channel 2), *KCTD14* (potassium channel tetramerization domain containing 14, that share sequence similarity with the cytoplasmic domain of voltage-gated K^+ channels), *KCNMA1* (large conductance calcium-regulated potassium channel), *KCNMB4* (potassium calcium-activated channel subfamily M regulatory beta subunit 4) and *TRPV5*, *TRPV6* genes had the most VDR: RXRA binding sites (100 kbp upstream and downstream to transcription start site) (Fig. 2**B**). In a case of VDR binding sites, genes *KCNMB4, CLIC4* had the most of them. Additionally, we performed a similar analysis, but using data from the publicly available ChIP-Atlas database (Oki, 2015). Most sites binding the VDR were found in sequences occurring in close proximity to *KCNMA1*, *KCNMB4, TRPV5,* and *TRPV6* genes. The lack of binding site motifs for both analyzed transcription factors does not mean that a given gene is not a target for 1,25$(OH)_2D_3$ but may mean that it can belong to the second group of the genomic response to 1,25$(OH)_2D_3$, the so-called indirect genomic targets. If genes encoding channel proteins appear in RNAseq or qPCR data and VDR binding sites appear in Chip-seq experiments or *in silico* analyses, it may be suggested that a given gene is directly regulated by 1,25$(OH)_2D_3$ within 4 h after administration.

Transcriptomic results described above were also supported by qPCR, Chip-seq experiments, and luciferase reporter gene assay (Warwick et al., 2021); (Slominski et al., 2018); (Olszewska et al., 2024b). Our transcriptomic data on squamous cell carcinoma treated with 1,25$(OH)_2D_3$ for 24 h revealed that the majority of deregulated ion channel genes belong to the potassium channel family. Fig. 3**A** shows a heat map of genes coding for potassium channels deregulated after incubation with 1,25$(OH)_2D_3$ for 24 h. Although there were differences between individual replicates for some genes, the modulatory effects of 1,25$(OH)_2D_3$ were confirmed by qPCR (Fig. 3**B**). The expression level of *KCNMA1*, *KCNMA1 STREX* (potassium calcium-activated channel subfamily M alpha 1 with stress-axis regulated exon), *KCNK9* (two-pore domain potassium channel) and *KCNJ11* (ATP-sensitive potassium channel) in skin squamous cell carcinoma was decreased after treatment (Fig. 3**B**) (primers from: (Olszewska et al., 2022). Interestingly, in

A

squamous cell carcinoma (A431) (Olszewska et al. 2024)		human epidermal keratinocytes neonatal (HEKn) (Slominski et al. 2018)		colonic organoids (Li et al. 2021)		breast cancer tissue (Shen et al. 2016)		keratinocytes cells (OKF6/TERT1) (Menzel et al. 2019)	
DOWN	UP	DOWN	UP	DOWN	UP	DOWN	UP	DOWN	UP
CLCN4	*CLCN5*	*KCNIP3*	*TRPV6*	*SCNN1G*	*TRPV6*		*KCNK3*		*KCNK3*
KCNH3	*TRPV4*	*KCTD14*	*TRPV4*	*SCNN1B*	*TRPV5*		*SCNN1B*		*TRPV6*
CLIC3	*CNGB1C*	*VDAC2*	*SCNN1G*	*KCNE3*	*KCNJ3*		*SCNN1A*		*KCNMA1*
	LCN1	*KCTD5*	*SCNN1A*	*CNGA1*	*KCNE4*		*TMC4*		*KCNB2*
	KCNS3	*CLIC4*	*CLIC1*	*KCNH6*	*KCNV1*		*CACNG4*		*TRPC6*
	CLCA4	*MCOLN1*	*SCNN1B*	*PIEZO1*	*KCNJ13*		*KCNC4*		*KCNN4*
	ANO-1	*KCNG1*	*TRPM4*	*KCNJ2*	*KCNMB4*				
		RRAD	*SCNM1*	*CLIC4*	*KCTD17*				
			PKD1	*CLCA4*	*CLCN5*				
			KCTD9	*CLCN2*	*CACNA2D3*				
			KCNK1	*CACNB1*	*TMC6*				
			CLCN3	*KCNK1*	*CRACR2B*				
			KCTD10	*SCN5A*	*KCNMA1*				
			KCNN4	*TRPM6*	*MCOLN2*				
			HCN3	*SCNN1A*	*TRPM4*				
			KCTD15	*CRACR2A*					
			SCNN1D	*TRPV3*					
			VDAC3	*KCTD5*					
				KCNK6					
				TMC5					
				KCTD3					
				KCTD2					
				KCNK5					
				VDAC1					

B

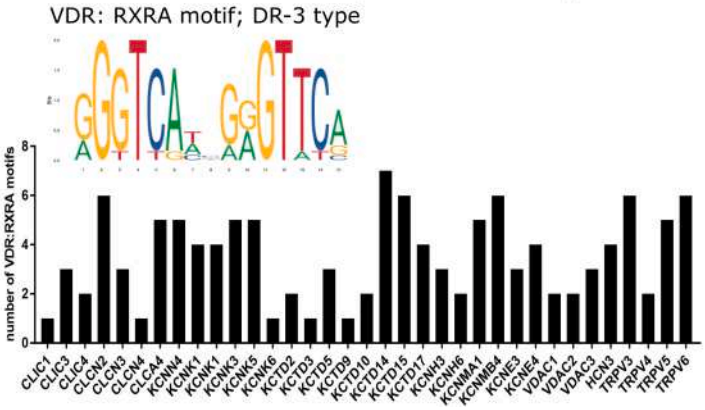

Fig. 2. Genomic action of the active form of vitamin D_3 on genes encoding ion channels based on transcriptomic data from selected publications. (A) Differentially expressed ion channel genes after 24 h 1,25$(OH)_2D_3$ treatment in different cell models (results from selected RNAseq experiments). Genes encoding channels that are also found in mitochondria are written in red. **(B)** Number of predicted VDR:RXRA binding sites (JASPAR matrix MA0074.1) in the ion channel genes by the CiiiDER program (100 kbp upstream of TSS, 100 kbp upstream of Abbreviations: TSS transcription start site.

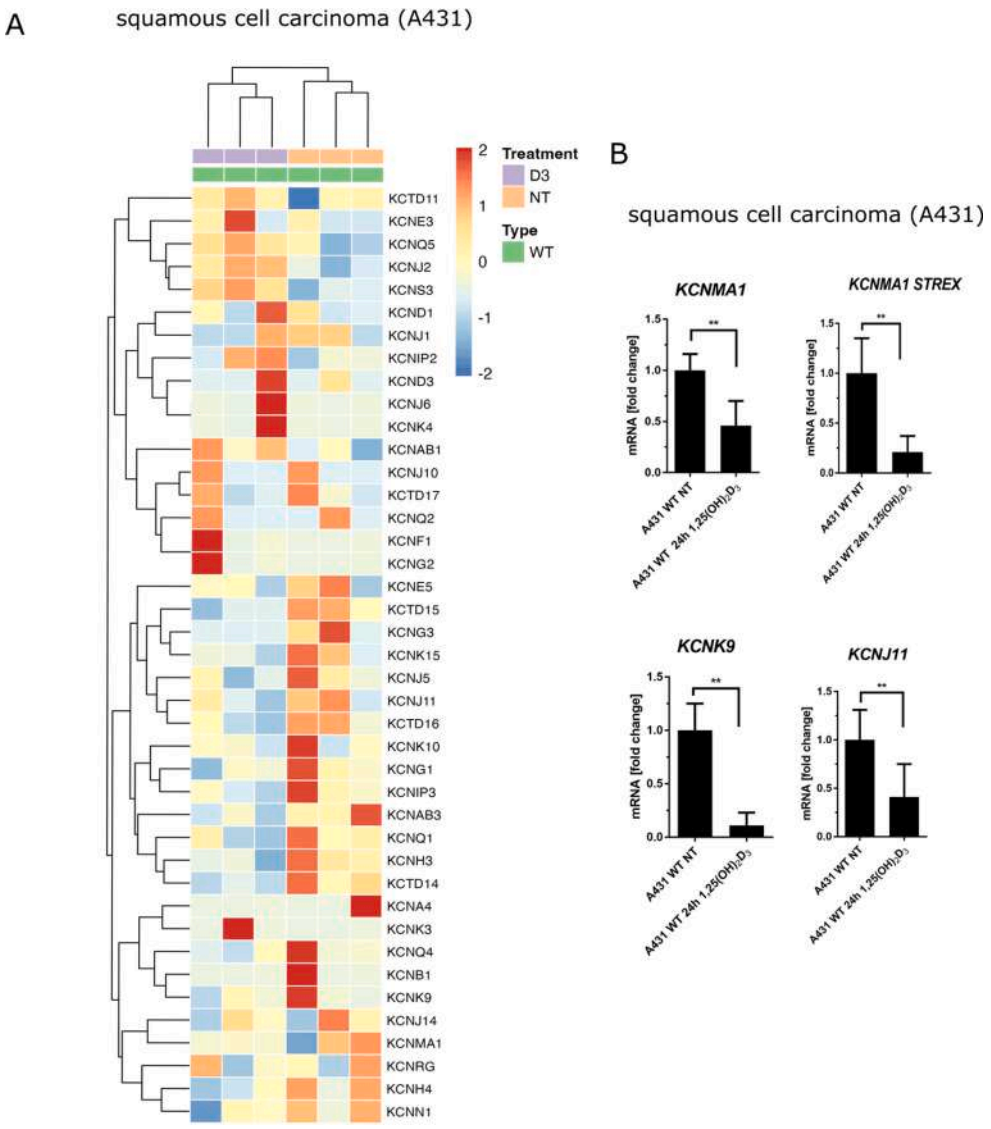

Fig. 3. Genomic action of the active form of vitamin D_3 on genes encoding ion channels based on transcriptomic data from squamous carcinoma cell line A431. (A) Heatmap of RNA-seq expression data from A431 showing the potassium ion channels genes that were differentially regulated following treatment with $1,25(OH)_2D_3$ for 24 h. The color of cells represents the Z-score of normalized gene expression values. **(B)** The expression level of the *KCNMA1, KCNMA1 STREX, KCNK9,* and *KCNJ11* genes encoding also mitochondrial potassium channels in A431 cells treated with $1,25(OH)_2D_3$ for 24 h. Data are expressed as mean ± SEM. $^{**}P < 0.01$. Abbreviations: A431 squamous cell carcinoma cells; KCNMA1 potassium calcium-activated channel subfamily M alpha 1; *KCNMA1* STREX potassium calcium-activated channel subfamily M alpha 1 with stress-axis regulated exon; KCNK9 two-pore domain potassium channels type 9; KCNJ11 potassium inwardly rectifying channel subfamily J member 11.

normal keratinocytes (HaCaT) after short stimulation (2–4 h) of $1,25(OH)_2D_3$ (100 nM) an increase in the expression of the *KCNN1* (small conductance calcium-regulated potassium channel member 1) and *KCNN2* (small conductance calcium-regulated potassium channel member 2) was observed. In a case of longer stimulations, the increase in expression for the *KCNN3* (small conductance calcium-regulated potassium channel member 3), *KCNMA1*, and *KCNK9* genes was visible (Olszewska et al., 2022). The expression of the *KCNMA1* channel coding gene in the breast cancer cells treated with 1 μM $1,25(OH)_2D_3$ for 72 h was more than 90 % lower than in the control and corresponded with the decline in protein level (Khatun et al., 2016). Interestingly, it was proposed that such regulation was not only a direct genomic effect but also the partial contribution of histone deacetylases (HDACs), whose protein level was decreased after $1,25(OH)_2D_3$ treatment (Khatun et al., 2016). A similar result was obtained in the case of the *KCNH1* (EAG1) gene encoding human ether à-go-go-1 a voltage-gated K^+ channel. The ERG channels were downregulated by 100 nM $1,25(OH)_2D_3$ (24 h incubation) in cancer cells from the breast, cervix, prostate, and mammary gland resulting in a decrease in EAG1 protein levels at various incubation times (Avila et al., 2010). $1,25(OH)_2D_3$ effect on *KCNH1* expression was VDR-dependent and it was suggested that such mRNA repression by $1,25(OH)_2D_3$ involves E-box type VDRE which is a functional negative vitamin response element in the hEAG1 promoter (Cázares-Ordoñez et al., 2015). The ether à-go-go-1 potassium channel became a promising therapeutic target due to its association with oncogenesis. The use of vitamin D_3 analogs in parallel with channel inhibitors enhanced the desired anti-cancer effect on two levels – genomic and non-genomic (García-Quiroz et al., 2014).

Another gene with VDRE in the promoter sequence is the *KCNE4* encoding voltage-gated potassium channel auxiliary subunit β, responsible for the suppression of Kv7 channels. Kv7 channels are regulators of vascular tone and increased *KCNE4* expression resulted in higher Kv7 conductance of the channel. Four VDR: RXRA elements were found in the human *KCNE4* gene, but only one of them (AGTTCAGGGAGTTGA)

was conserved between humans and mice and VDR-VDRE interaction was confirmed by 3D-footprint software analyses. Additionally, *KCNE4* expression was increased in $Vdr^{-/-}$ mice, demonstrating that this subunit is regulated by VDR (Olivencia et al., 2023), and mice lacking VDR did not exhibit pulmonary arterial hypertension. Our current knowledge concerning the genomic effects on channels is summarized in Table 1.

3. Non-genomic action of the active form of vitamin D_3 on ion channels

Although the classical $1,25(OH)_2D_3$ – VDR signaling axis explains the long-term changes induced by vitamin D_3, it still cannot fully explain the phenomenon of rapid cell response to this hormone (Zmijewski and Carlberg, 2020). The classical axis includes changes in gene transcription that last several hours (Carlberg, 2022) (Carlberg et al., 2023). In contrast, changes observed, for example, in the stimulation of rapid transport of calcium ions in muscle cells and intestinal epithelium, require only a few minutes (Christakos et al., 2011) (Fleet, 2022). Such observations initiated the concept that $1,25(OH)_2D_3$ affects membrane proteins, including ion channels in a non-genomic manner, directly or indirectly. This concept is supported by three main observations: (1) vitamin D_3 deficiency induces ionic remodeling in cardiac tissue (Barsan et al., 2022), brain (Kasatkina et al., 2020) and bones (Zanello and Norman, 2006); (2) VDR itself was detected in the cell membrane of many cell lines and colocalized with the plasma membrane proteins (co-immunoprecipitation or co-immunofluorescence studies) like caveolin-1 (CAV1) (Huhtakangas et al., 2004), caveolin-3 (CAV3) (Zhao and Simpson, 2010), A Disintegrin And Metalloproteinase Domain 10 (ADAM10) (Dursun and Gezen-Ak, 2017), Protein Disulfide Isomerase Family A Member 3 (PDIA3) (Chen et al., 2013; Khanal and Nemere, 2007), megalin/cubilin (LRP2/CUBN) (Rowling et al., 2006); amyloid precursor protein (APP) (Dursun and Gezen-Ak, 2017); Nicastrin (Dursun and Gezen-Ak, 2017); (3) $1,25(OH)_2D_3$ regulate membrane-based signaling pathways like Wnt (Tapia et al., 2020) (Yu et al., 2023) (Zhang et al., 2023), sonic hedgehog signaling (SHH) (Oak et al., 2020) (Moisejenko-Golubovič et al., 2022), transforming growth factor-β (TGFβ) (Lozano-Ros et al., 2023) (Shah et al., 2023), activated plasma membrane rapid responses like PDIA3-dependent activation of Phospholipase A2 (PLA_2) (Larriba et al., 2014) and phosphatidylinositol 3-kinase PI3K/Akt/mTOR pathway (Suares et al., 2019); (4) electrophysiological techniques indicates that $1,25(OH)_2D_3$ added to the patch-clamp measured pipette can influence the conductance of calcium, chloride and potassium channels; (5) vitamin D_3 can modulate lipid composition of the membranes (Payet et al., 2023) (Conte et al., 2021).

The first studies indicating the involvement of vitamin D_3 in the regulation of ion channels concern calcium channels, as $1,25(OH)_2D_3$ itself is a master regulator of calcium-phosphate homeostasis. It was shown that vitamin D_3-dependent calcium transport channel proteins in the intestine include TRPV channels, or L-type Ca^{2+} channels (Cav1.3). TRPV channels are best described in the context of $1,25(OH)_2D_3$ regulation also due to their contribution to cell proliferation (Zhong et al., 2022) and pain therapy (Szallasi, 2024). In the case of electrophysiological experiments, $1,25(OH)_2D_3$ at nanomolar concentrations (100 nM) acts as a mild agonist of transient receptor potential cation channel TRPV1, but at higher concentrations of TRPV1-specific agonist capsaicin, acts as an inhibitor of the channel in HEK293T cells expressing human TRPV1 (Long et al., 2020); (Tripathy and Majhi, 2020). TRPV1-vitamin D_3 interaction is relevant in the therapy of pathological pain and pharmacological or genetic inhibition of TRPV1 prevents the secretion of pro-inflammatory cytokines and vitamin D_3 supplementation inhibits the hyperactive TRPV1 channels (Tripathy and Majhi, 2020). Also, 1,25

Table 1
Genomic impact of the active form of vitamin D_3 on different ion channels. Abbreviations: CaV2.3 voltage-gated calcium 2.3; Eag1 ether-à-go-go voltage-gated potassium channel; HERG human ether-a-go-go-related; K2P3.1 two pore domain potassium ion channel TASK-1; KCa1.1 (BK) large conductance calcium-regulated potassium channel; KCa2.1 small-conductance calcium-activated potassium channel 2.1; KCa2.2 small-conductance calcium-activated potassium channel 2.2; KCa2.3 small-conductance calcium-activated potassium channel 2.3; KCa3.1 intermediate-conductance calcium-activated potassium channel 2.1; Kir3.1 inward rectifier potassium channel; KV7 voltage-gated potassium channel; KVLQT1 potassium voltage-gated channel, KQT-like subfamily, member 1; TASK-3 two-pore domain potassium channel; WB western-blot.

Cellular model	$1,25(OH)_2D_3$ concentration	Channels regulated by $1,25(OH)_2D_3$	Main experimental methods	Publications
mice pulmonary arteries smooth muscle cells (PASMCs)	1 nM	K_V7	qPCRs WB	(Olivencia et al., 2023)
human and mouse pancreatic islets	2 nM or 20 nM	$Ca_V2.3$	glucose-stimulated calcium uptake	(Kjalarsdottir et al., 2019)
squamous cell carcinoma line (A431)	100 nM	KCa2.1 KCa2.2 KCa2.3 KCa3.1 KCa1.1 TASK-3	qPCRs	(Olszewska et al., 2022)
9 to 10-week-old male rats		Kir3.1 HERG K_VLQT1	qPCRs WB	(Luo et al., 2022)
kidney from VDR-null ($Vdr^{(-/-)}$) mice and wild-type mice ($Vdr^{(+/+)}$)C57BL/6J	15 or 50 nmol/kg	TRPV5 TRPV6	qPCRs	(Ishizawa et al., 2018)
human breast cancer cells (MDA-MB-453)	1 μM	KCa1.1	qPCR WB	(Khatun et al., 2016)
human pulmonary artery smooth muscle cells (PASMCs)	1 μM	K2P3.1	qPCR WB	(Callejo et al., 2020)
hypercalciuric stone-forming rat model (GHS)	200 ng/kg BW	TRPV6	ChiP-seq qPCR	(Guo et al., 2022)
epithelial cells from colorectal adenocarcinoma (Caco2, LS180)	10^{-10} to 10^{-7} M	TRPV6	ChiP-seq luciferase assay qPCR	(Guo et al., 2022; Meyer et al., 2006)
breast cancer cells	1×10^{-9} M	Eag1	qPCR WB	(García-Becerra et al., 2010)
human syncytiotrophoblast cells breast cancer cell line (MCF7); uterus/cervix cancer cell line (SiHa, HeLa); prostate cancer cell line (PC-3);	1×10^{-7} M	Eag1	qPCR WB	(Avila et al., 2010)

$(OH)_2D_3$ at 50–200 nM concentration modulates naïve T-cells through direct inhibition of TRPV1 in a VDR-independent manner. Such action is important in the regulation of type 1 diabetes risk by dampening naïve T-cell activation and inflammatory response (Long et al., 2021). To our knowledge, there are no electrophysiological studies to date demonstrating the involvement of vitamin D_3 in the regulation of the TRPV6 channel. In the case of the effect of $1,25(OH)_2D_3$ on the activity of L-type voltage-gated channels (L-type VDCC), most studies are based on $^{45}Ca^{2+}$ influx measurements, and only one study is based on somatic nucleated patch recordings in single-cell resolution (Gooch et al., 2019). In the prefrontal cortex neurons, the L-type VDCC channel rapidly responded to 0.1 nM $1,25(OH)_2D_3$ by enhancing activity-dependent Ca^{2+} $\Delta F/F$. Authors suggested that vitamin D_3 deficiency may produce a transient channelopathy-like state, in that the activity of L-type VDCC is altered during critical periods of neurodevelopment (Gooch et al., 2019). A stimulatory effect of $1,25(OH)_2D_3$ on $^{45}Ca^{2+}$ influx which involves the activation of L-type VDCC, K^+-ATP, K^+-Ca^{2+}, and Kv channels was shown on isolated rat pancreatic islets model. Such regulation augments cytosolic calcium and prevents insulin resistance via coordination of insulin secretion (Mendes et al., 2022). In zebrafish intestines, $1,25(OH)_2D_3$ was shown to stimulate calcium influx via L-type VDCC channels but not TRPV1 channels. Additionally, $1,25(OH)_2D_3$ inhibits SERCA (sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase) activation similarly to thapsigargin results in maintaining of high level of free Ca^{2+} in the cytosol (Dambrós et al., 2023).

Several electrophysiological studies indicated a non-genomic influence of $1,25(OH)_2D_3$ on the activity of potassium channels. Using the patch-clamp technique, restoration of $1,25(OH)_2D_3$ levels was shown to improve TASK-like-current in pulmonary artery smooth muscle cells (PASMC). As a result, amelioration of pathophysiological features of pulmonary arterial hypertension was observed (Callejo et al., 2021). $1,25(OH)_2D_3$ (1 nM) also increases outward K^+ current in ventricular myocytes via Akt signaling, which may contribute to the protective effect of vitamin D_3 on the heart (Tamayo et al., 2017) (Tamayo et al., 2018). Myocytes treated with $1,25(OH)_2D_3$ showed higher values of total K^+ currents (I_{total}) than those treated with vehicle. $1,25(OH)_2D_3$ increases fast transient outward current and ultrarapid delayed rectifier K^+ current and such effect was lost in myocytes isolated from VDR-knockout mice and myocytes pretreated with Akt inhibition, which means that channel regulation requires active VDR receptor and Akt kinase. (Tamayo et al., 2018) Interestingly action of $1,25(OH)_2D_3$ on these K^+ currents did not change action potential duration, and such observation was explained by the fact that calcitriol increases L-type calcium current and this might counterbalance the effect of increased outward K^+ currents in calcitriol-treated myocytes. Such L-type calcium channels are further examples of channels regulated by $1,25(OH)_2D_3$ in an indirect, non-genomic manner, in this case through the active PKA kinase (Tamayo et al., 2017).

Not only vitamin D_3 itself but also its metabolites or analogs can influence the activity of ion channels. Application of 100 nM $25(OH)D_3$ (calcidiol) on HEK293T cells in cell-attached *patch-clamp* mode increased the time spent in the open state, the frequency of single-channel opening, and the open probability of the channel (Long et al., 2020). Application of 100 nM $25(OH)_2D_3$ in a single-channel patch-clamp mode, increases the time spent in the open state of the channel resulting in a significant increase in open probability. Molecular docking studies have shown that $25(OH)_2D_3$ interacts directly with the channel protein by binding to the valinoid binding pocket as capsaicin and capsazepine and interacting with Y511 and S512 residues (Long et al., 2020).

Although our electrophysiological results indicate of a direct effect of $1,25(OH)_2D_3$ on the channel (Olszewska et al., 2022), we cannot completely exclude the effect of $1,25(OH)_2D_3$ on the cell membrane, whose changing properties also affect the channel itself. Most of the research from the 1980 s was focused on the effects of $1,25(OH)_2D_3$ on the physicochemical properties of membranes. It was shown that administration of $1,25(OH)_2D_3$ leads to an increase in the *de novo* synthesis of phosphatidylcholine (PC) and the total PC content. It also increases the turnover of fatty acids into PC, which increases the content of polyunsaturated fatty acids in the PC fraction. Thus, it was postulated that $1,25(OH)_2D_3$ regulates membrane fluidity, and increases the calcium transport rate through the calcium channel) (Rasmussen et al., 1982). For example, membrane fluidity measured by fluorescence anisotropy of 1,6-diphenyl-1,3,5-hexatriene was shown to be significantly increased in rat intestinal brush border membranes treated with $1,25(OH)_2D_3$ (Deliconstantinos et al., 1986). In chondrocytes, $1,25(OH)_2D_3$ treatment results in rapid changes in arachidonic acid release, its re-incorporation, alterations in membrane fluidity, and Ca^{2+} reflux (Boyan et al., 1999). Other data suggest that $1,25(OH)_2D_3$ specifically modulates fatty acids composition in adipose tissue through direct regulation of Elovl3, an enzyme that functions in the synthesis of C20 −C24 saturated and mono-unsaturated long-chain fatty acids (Ji et al., 2016). According to the literature, all non-genomic effects on channels are summarized in Table 2.

4. Effect of the active form of vitamin D_3 on mitochondria

Many experimental studies indicate a strong link between $1,25(OH)_2D_3$ and mitochondria. In the inner mitochondrial membrane, there are heme-containing enzymes involved in the metabolism of vitamin D_3 belonging to the cytochrome P450 family, including cytochrome P450 family 1 subfamily B member 1 (CYP1B1) (Lin et al., 2023), cytochrome P450 family 27 subfamilies A member 1 (CYP27A1) (Cali and Russell, 1991), cytochrome P450 family 27 subfamily B member 1 (CYP27B1) (Srikuea et al., 2012), cytochrome P450 family 24 subfamily A member 1 (CYP24A1) (Annalora et al., 2010), and cytochrome P450 family 11 subfamily A member 1 (CYP11A1) (Rosal et al., 2022). The last of the mentioned cytochromes CYP11A1 initiates a novel pathways of vitamin D_3 metabolism. The placenta (Slominski et al., 2012), adrenal glands (Slominski et al., 2005), and epidermal keratinocytes (Slominski et al., 2012) (Slominski et al., 2015) have been shown to metabolize vitamin D_3 via this CYP11A1-mediated pathway that is modified by the activity of CYP27B1. Moreover, it is well established that, steroid hormone receptors, like glucocorticoid or estrogenic are present in mitochondria and interact with mitochondrial DNA (mtDNA) (Psarra and Sekeris, 2011, 2008). A few previous studies with the used of (BODIPY)-calcitriol suggested the extra-nuclear cytoplasmatic distribution of VDR (Barsony et al., 1997). VDR receptors, as steroid receptors, in addition to their classic locations: in the nucleus and cytoplasm, have also been found in mitochondria of human platelets (Psarra and Sekeris, 2008), megakaryocytes (Silvagno et al., 2010), keratinocytes (Silvagno et al., 2013), fibroblasts (Barsony et al., 1997), primary neurons and SH-SY5Y cells (Gezen-Ak et al., 2023) but no in mitochondria from in skeletal muscle cells (Ryan et al., 2016) or squamous cell carcinoma mitochondria (Olszewska et al., 2024a). The colocalization of VDR and mitochondria was also detected by confocal laser scanning microscopy in human kidney proximal tubular cells (HK-2) (Chen et al., 2024). The VDR overexpression from plasmid followed by $1,25(OH)_2D_3$ treatment for 72 h was shown to promote mitochondrial localization of VDR (Chen et al., 2024). Based on studies on human keratinocytes, a model has been proposed according to which the VDR does not have an obvious N-terminal mitochondrial import sequence, and the receptor is not transported by the translocase of the outer and inner mitochondrial membrane (TOM/TIM translocase), but rather by a permeability transition pore (PTP)-dependent pathway (Silvagno et al., 2013). Interestingly, VDR does not have an obvious N-terminal mitochondrial import sequence, and the receptor is not transported by the translocase of the outer and inner mitochondrial membrane (TOM/TIM translocase). Thus, the import of VDR by a PTP-dependent pathway was suggested based on studies on human keratinocytes (Silvagno et al., 2013).

Interestingly, it seems that mitochondrial localization of VDR seems to be a common feature of proliferating cancer cell lines, rather than

Table 2
Non-genomic impact of the active form of vitamin D_3 on different ion channels. Abbreviations: GsMTx4 spider venom peptide; K^+-ATP potassium channel regulated by ATP; K^+-Ca^{2+} potassium channel regulated by Ca^{2+}; $K_{Ca}3.1$ calciu-regulated intermediate conductance potassium channel; Kv potassium channel regulated by voltage; L-type VDCC L-Type Voltage-Dependent Calcium Channel; L-VGCCs L-type voltage-gated calcium ion channels; ORCC outwardly rectifying chloride channel; Piezo1 piezo-type mechanosensitive ion channel component 1; SERCA sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase; TASK-Like K^+ two-pore domain potassium channel; TEA tetraethylammonium; TRPC transient receptor potential canonical ion channels; TRPC6 transient receptor potential canonical ion channels type 6.

cellular model	$1,25(OH)_2D_3$ concentration/and additional drugs	channels regulated by $1,25(OH)_2D_3$	type of electrophysiological experiments and other experiments	publications
isolated rat pancreatic islets	$1,25(OH)_2D_3$ 1 nM TEA 20 nM diazoxide 25 μM apamine 1 μM	L-type VDCC K^+-ATP K^+-Ca^{2+} Kv	$^{45}Ca^{2+}$ influx	(Mendes et al., 2022)
HEK293T cells	$1,25(OH)_2D_3$ 100 nM $25OHD_3$ 100 nM capsaicin 1 μM	TRPV1	patch-clamp cell-attached, whole-cell currents *in silico* modeling and docking of 25OHD to human TRPV1	(Long et al., 2020)
chronic vitamin D_3 deficiency mice	TRPC6 antagonist GsMTx4 (2 mg/kg)	mechanosensitive cation channel transient receptor potential C cation channels (TRPC and TRPC6)	measurement of intraventricular pressure	(Stratford et al., 2021)
ten-week-old male C57BL/6J mice	vitamin D_3 group mice (20 mg/kg/d), vitamin D + Piezo1 agonist, Yoda1 (2.6 mg/kg/d), vitamin D + Piezo1 inhibitor,GsMTx4 (0.8 mg/kg/d)	Piezo1	cells co-culture model calcium staining flow cytometry	(Liu et al., 2023)
pulmonary artery smooth muscle cells (PASMC)	rodent standard diet vitamin D_3 1500 IU/Kg	TASK-Like K^+	whole-cell patch-clamp	(Callejo et al., 2021)
balb/c mice prefrontal cortex	$1,25(OH)_2D_3$ 0.1 nM L-VGCC agonist-Bay K8644 2.5 μM cadmium 1 μM	L-type voltage-gated calcium channels (L-VGCCs)	somatic nucleated patch recordings calcium imaging	(Gooch et al., 2019)
zebrafish	$1,25(OH)_2D_3$ 1 nM nifedipine 1 μM thapsigargin 1 μM	L-VDCC channels; SERCA	$^{45}Ca^{2+}$ influx histological stainings	(Dambrós et al., 2023)
mouse preosteoblast cells (MC3T3-E1)	$1,25(OH)_2D_3$ 100 nM TRAM-34 1 μM DCEBIO 10 μM	intermediate-conductance Ca^{2+}-activated K^+ channels ($K_{Ca}3.1$)	whole-cell patch-clamp	(Kito et al., 2020)
thoracic aorta rings from $BK^{+/+}$ or $BK^{-/-}$ mice	$1,25(OH)_2D_3$ 500,000 IU/kg body weight NS1619 20 μM paxilline 10 μM BMS191011 10 mg· kg^{-1} ·d^{-1}	large-conductance calcium-activated potassium (BK) channel	whole-cell patch-clamp	(Ning et al., 2022)
monkey kidney cells (COS-1), Sertoli cell line (TM4)	$1,25(OH)_2D_3$ 1 nM-10 nM DIDS 200 μM	outwardly rectifying chloride channel (ORCC)	whole-cell patch-clamp	(Menegaz et al., 2011)

differentiated (Consiglio et al., 2014). Nevertheless, the potential role of mitochondrial localization of VDR is still under debate. *In silico* analysis showed that two VDRE sites can be located in the displacement loop (D-loop) of the mtDNA with high affinity (89 % and 82 % of the maximum score) and a total of 40 VDRE sites with low-affinity scores (>60 % of the maximum) clustered in a few regions (Gezen-Ak et al., 2023); (Consiglio et al., 2014). Recent results based on mtDNA-ChIP assays and the electrophoretic mobility shift assay indicate that VDR is significantly associated with mtDNA D-loop site in several locations and interacts with mitochondrial transcription factor A (TFAM) (Demonacos et al., 1996); (Gezen-Ak et al., 2023). Other data based on mammalian two-hybrid assays, coimmunoprecipitation analyses, and biochemical coactivator recruitment assays demonstrated an interaction between VDR and peroxisome proliferator-activated receptor gamma coactivator-1alpha (PGC-1α) a transcriptional coactivator that plays a role in mitochondrial biogenesis. PGC-1α augments ligand-dependent VDR transcription (Savkur et al., 2005).

To demonstrate that $1,25(OH)_2D_3$ is involved in the regulation of the expression of mitochondrial genes RNAseq datasets published previously from human epidermal keratinocytes neonatal (HEKn), squamous cell carcinoma (A431) and ChiP atlas and MitoCarta3.0 was used (Fig. 4. **A**). Among differentially expressed genes (DEGs) (FDR (false discovery rate) =<0,05) from A431 cells, 136 mitoDEGs (mitochondrial differentially expressed genes) were found in the MitoCarta3.0 database. Additionally, it was shown previously that *VDR* knockout in A431 cells completely inhibits the expression of $1,25(OH)_2D_3$-dependent genes after 24 h $1,25(OH)_2D_3$ incubation (Olszewska et al., 2024b). Among DEGs from HEKn cells, 264 mitoDEGs were found in the MitoCarta3.0 database. Interestingly, among VDR-regulated genes from the ChiP atlas, 85 mitochondrial were found in the MitoCarta3.0 database. This combination indicates that indeed vitamin D_3 affects mitochondrial gene expression, and the common genes in the above list included CYP24A1, IDH2 (isocitrate dehydrogenase), PCK2 (phosphoenolpyruvate carboxykinase 2), TXNRD1 (thioredoxin reductase 1) and ACOT11 (acyl-CoA thioesterase 11). Our ontology analyzes using genes from MitoCarta 3.0 (marked in red boxes) of the pathway network and gene-set enrichment analysis (PANGEA web tool; version 1.1, https://www.flyrnai.org/tools/pangea/web/home/7227) showed that the most significantly enriched category was “mitochondrion organization” and “mitochondrial transport” (Fig. 4**B**) (supplementary Table 1.).

Despite ongoing debate on VDR involvement in regulation of expression of gene coded by mtDNA, it seems that of VDR-mediated modulation of expression of key regulators of biogenesis and mitochondrial activity is prevailing mechanism of $1,25(OH)_2D_3$ action on mitochondria. Treatment of cortical neurons with $1,25(OH)_2D_3$ resulted in significantly increased of mRNA levels of respiratory chain proteins: mitochondrially encoded NADH:ubiquinone oxidoreductase core subunit 3 (MT-ND3), NADH:ubiquinone oxidoreductase core subunit 4 (MT-ND4), NADH:ubiquinone oxidoreductase core subunit 5 (MT-ND5), mitochondrially encoded cytochrome C oxidase I (MTCO1) and mitochondrially encoded ATP synthase membrane subunit 8 (MT-ATP8). In human macrophages, $1,25(OH)_2D_3$ increases the mRNA level of cytochrome *c* oxidase subunit II (*COXII*) and mitochondrially encoded ATP synthase membrane subunit 8 (*MT-ATP6*) (Bergandi et al., 2021). The

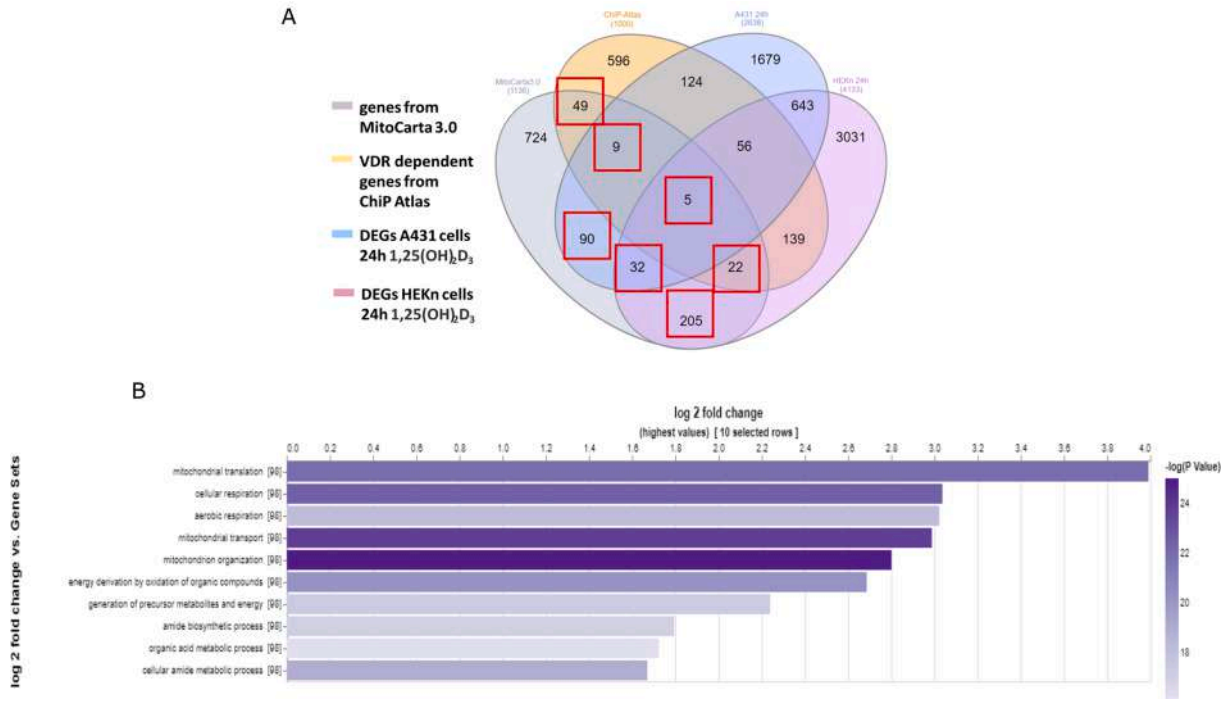

Fig. 4. The effect of the active form of vitamin D_3 on genes encoding mitochondrial proteins. (A) Venn diagram showing the distribution of the differentially expressed genes between MitoCarta3.0, A431, HEKn treated with $1,25(OH)_2D_3$ for 24 h and ChiP-Atlas data demonstrating the impact of $1,25(OH)_2D_3$ on genes encoding mitochondrial proteins (red frames). (**B**) The ontology analyses of the genes encoded mitochondrial proteins (red frames) extracted from ChiP Altas data, DEGs from A431 and HEKn 24 h $1,25(OH)_2D_3$ treated cells. Abbreviations: A431 squamous cell carcinoma cells; HEKn human epidermal keratinocytes neonatal; DEGs differentially expressed genes.

mRNA levels of cytochrome *c* oxidase subunit IV (*COXIV*), a subunit of the mitochondrial cytochrome *c* oxidase; *CPT1b*, a key enzyme of fatty acid oxidation; and *UCP3*, a mitochondrial uncoupling transmembrane protein, were also strongly decreased in plantar muscles of vitamin D_3-depleted rats in comparison with control rats (Salles et al., 2022).

Many studies indicate the influence of $1,25(OH)_2D_3$ on mitochondrial respiration and expression level of the oxidative phosphorylation (OXPHOS) subunits. Three months of vitamin D-restricted diet in C57BL/6 J mice reflected in lowered mitochondrial respiration and maximal electron transport chain (ETC) capacity in skeletal muscles (Ashcroft et al., 2021). Consequently, it was reported that a treatment of human primary muscle cells with $1,25(OH)_2D_3$, at 10 nM concertation, for 48 h increased mitochondrial oxygen consumption rate (Ryan et al., 2016). Enhanced mitochondrial respiratory capacity was also observed in human hepatocyte-like stem cells subjected to $1,25(OH)_2D_3$ at 50 nM concentration for 4–8 days (Yuan et al., 2021) and C2C12 myotubes treated with $1,25(OH)_2D_3$ at 100 nM concentration for 24 h (Schnell et al., 2019). Interestingly, studies on transgenic mice with tamoxifen-inducible deficiency demonstrated that vitamin D_3 supplementation improved muscle mass and strength (Salles et al., 2022). Also, mitochondrial respiration was increased by $1,25(OH)_2D_3$ treatment in trophoblasts isolated from obese women (Phillips et al., 2022). Interestingly, the effect was specific to $1,25(OH)_2D_3$ but not for vitamin D_3 analogs. This observation is consistent with the high binding affinity of $1,25(OH)_2D_3$ for the VDR compared to the lower affinities of the other analogs especially lacking hydroxyls groups (Salles et al., 2022).

Several studies also point out the involvement of $1,25(OH)_2D_3$ in the regulation of mitochondrial fusion/fission machinery. It was shown, that vitamin D_3 supplementation improved the mitochondrial cristae shape in simvastatin-induced myopathy mice model by regulating the expression of mitofusin-1/2 (*MFN1/2*), optic atrophy 1 (*OPA1*) and dynamin-related protein 1 (*DRP1*) (Ren et al., 2020). An increase in *OPA1* expression was also observed after vitamin D_3 supplementation in vitamin D_3 deficient mice with statin-induced myopathy (Ren et al., 2020), as well as in human skeletal muscle cells treated with $1,25(OH)_2D_3$ (Ryan et al., 2016). Interestingly, these results oppose the effect of $1,25(OH)_2D_3$ on *OPA1* in squamous cell carcinoma (Olszewska et al., 2024a). A decrease in *OPA1* and *MFN2* expression and an increase in *FIS1* (mitochondrial fission 1 protein) expression, without changes in *MFN1* expression, was observed in A431 cells, after $1,25(OH)_2D_3$ administration (Olszewska et al., 2024a). A similar effect was observed in osteosarcoma cells MG-63, where vitamin D_3 promoted mitochondrial fission, but via deregulation of *OPA3* and *MFN1* genes (Quigley et al., 2022). However, recent publications indicate also the involvement of non-genomic pathways in the regulation of mitochondrial activity. In streptozotocin-induced diabetic rats co-immunoprecipitation (CO-IP) analysis performed in renal tissue demonstrated that the anti-VDR antibody pulled down both VDR and Mfn2 proteins, but not Mfn1, Drp1 or Fis1. In addition in resent studies on muscle cells, mRNA levels for the proteins involved in mitochondrial fusion, i.e., MFN1 and MFN2, were significantly downregulated in the vitamin D-depleted group while gene expression of *FIS1*, a protein involved in mitochondrial fission, was unaffected (Salles et al., 2022).

5. The action of the active form of vitamin D_3 on mitochondrial channels

Multiple ion channels were identified in the mitochondrial membranes, and a majority of them belong to the potassium channels family. To date, eleven different potassium channels have been identified in the inner mitochondrial membrane: (1) small conductance calcium-regulated potassium channel (mitoSK$_{Ca}$; encoded by *KCNN1-3*) (Dolga et al., 2013); (2) intermediate conductance calcium-regulated potassium channel (mitoIK$_{Ca}$; encoded by *KCNN4*) (De Marchi et al., 2009); (3) large conductance calcium-regulated potassium channel (mitoBK$_{Ca}$; encoded by *KCNMA1*) (Siemen et al., 1999); (4) large conductance potassium channel DEC isoform (mitoBK$_{Ca}$-DEC; encoded by *KCNMA1*) (Gałecka et al., 2021); (5) two-pore domain potassium channel

(mitoTASK-3; encoded by *KCNK9*) (Toczyłowska-Mamińska et al., 2014); (6) ATP-sensitive potassium channel (mitoK$_{ATP}$; encoded by *KCNJ11, CCDC51*) (Bednarczyk et al., 2018); (7) 1.3 voltage-gated potassium channel (mitoKv1.3; encoded by *KCNA3*) (Szabò et al., 2005); (8) 1.5 voltage-gated potassium channel (mitoKv1.5; encoded by *KCNA5*) (Leanza et al., 2012); (9) 7.4 voltage-gated potassium channel (mitoKv7.4; encoded by *KCNQ4*) (Testai et al., 2016); (10) mitochondrial hyperpolarization-activated cyclic nucleotide-gated channel (mitoHCN; encoded by *HCN1-4*) (León-Aparicio et al., 2019); (11) mitochondrial sodium-activated potassium channel (mitoSLO2; encoded by *KCNT2*). Among anion-selective channels, in the outer mitochondrial membranes was discovered chloride intracellular channel type 4 (CLIC4; encoded by *CLIC4*) (Ponnalagu et al., 2016) and voltage-dependent anion channel (VDAC; encoded by *VDAC1-3*) (Najbauer et al., 2021). In the inner mitochondrial membrane chloride intracellular channel type 5 (CLIC5; encoded by *CLIC5*) (Ponnalagu and Singh, 2017) and calcium-activated chloride channel transmembrane protein 16A (TMEM16A, encoded by *ANO1*) (Allawzi et al., 2018). In the inner mitochondrial membrane was also found mitochondrial calcium uniporter (MCU; encoded by *MCU*) (Chaudhuri et al., 2013). Interestingly, the expression of the above-mentioned channel proteins was tissue specific.

The proper functioning of mitochondria is related to maintaining the potential of the inner mitochondrial membrane (−180 mV, pH 7.8), membrane integrity, ATP production, reactive oxygen species (ROS) production, and the storage of calcium ions. There is growing evidence that mitochondrial channels play a significant role in mitochondria homeostasis and cell-protective strategies. Most importantly, modulation of activity these channels showed cytoprotective effects on cardiac and nervous tissue after hypoxia, or induction of cell death in cancer cells., suggesting potential clinical implications (Szabo and Szewczyk, 2023); (Wrzosek et al., 2020); (Kulawiak et al., 2021). It was documented that tissue preconditioning with potassium channel modulators results in cytoprotection through the regulation of mitochondrial channels (Kulawiak et al., 2021); (Su et al., 2021); (Boovarahan and Kurian, 2021). Furthermore, the transport of potassium ions into mitochondria via mitochondrial potassium channels causes changes in the volume of the mitochondrial matrix (Dos Santos et al., 2002); (Bednarczyk et al., 2008); mitochondrial respiration, due to structural coupling with the respiratory chain (Bednarczyk et al., 2013); inner membrane potential (Debska et al., 2001); rate of generation of reactive oxygen species, redox signaling (Kulawiak et al., 2008); and calcium influx (Facundo et al., 2006); (Sato et al., 2005). It seems that all these changes occur to protect the cell from death (Szewczyk et al., 2009).

MitoBK$_{Ca}$ and mitoKv channels are the best-described channels of the inner mitochondrial membrane in the context of cytoprotection (Kampa et al., 2022) (Kicinska et al., 2020) (Lukowski et al., 2022) (Kampa et al., 2021) and cancer therapy (Leanza et al., 2015) (Zuccolini et al., 2022) (Dupuy et al., 2023).

The role of 1,25(OH)$_2$D$_3$ in the regulation of BK$_{Ca}$ channel has also been studied in the context of vascular calcification in cardiovascular disease (Ning et al., 2022), chronic kidney disease (Hanna-Mitchell et al., 2016), and breast cancer (Khatun et al., 2016). *KCNMA1* genes encoding BK$_{Ca}$ channels were downregulated in vascular smooth muscle cells after induction of calcification *in vitro* and *in vivo* and such a result was confirmed on protein level and functionally by *patch-clamp* recordings. BK$_{Ca}$ channel agonist NS1619 (20 μM) significantly alleviated vascular calcification by decreasing calcium content and alkaline phosphatase activity, while BK$_{Ca}$ channel inhibitor paxilline (10 μM) caused the opposite effects. Additionally, BK$_{Ca}$ channel activation by BMS191011 (10 mg/kg) ameliorates vitamin D$_3$-induced calcification in mice (Ning et al., 2022). In breast cancer cells, the expression of BK$_{Ca}$ channel was markedly higher than in control tissue, while after incubation with paxilline (10 μM) viability of cancer cells was significantly suppressed. Interestingly down-regulation of the BK$_{Ca}$ protein by the treatment with VDR agonists was almost completely prevented by the treatment with proteasome inhibitor MG132. Thus, the proposed mechanism of the VDR agonists includes transcriptional repression of the channel gene and degradation of the channel protein (Khatun et al., 2016). Transcription of the *KCNMA1* gene of the BK$_{Ca}$ channel and its splicing is regulated by several hormones. Some *KCNMA1* transcripts possess stress-axis regulated exon (STREX) regulated by progesterone and estradiol (Zhu et al., 2005). Sex steroid hormones: estrogen, progesterone, or androgen via binding to corresponding receptors regulate transcription of BK$_{Ca}$ channel auxiliary subunit *KCNMB1*. Two estrogen receptor binding sites were identified in promoter of *KCNMB1* and the existence of such sites was proved by ChiP assays, site-direct mutagenesis, and dual-luciferase reporter assay (Wen et al., 2023). It was also shown that estradiol and progesterone binds directly to the auxiliary beta1 subunit of the plasmalemma BK$_{Ca}$ channel, namely with hydrophobic residues in the second transmembrane domain and activated channel in smooth muscle cells and mice myocytes (Granados et al., 2019) (North et al., 2023). In the case of the mitochondrial BK$_{Ca}$ channel estradiol effect is quite the same, estradiol increased the open probability of the mitochondrial BK$_{Ca}$ channel in U87-MG cells during the first minutes after application, and closing the PTP channel, which may be protective for the cell, by preventing the cell from apoptosis (Thiede et al., 2012). Since much data indicates that sex hormones influence BK$_{Ca}$ channel activity both genomically and non-genomically, this would suggest that vitamin D$_3$ may act similarly.

As yet, the regulation of the mitochondrial membrane BK$_{Ca}$ channel by 1,25(OH)$_2$D$_3$ was studied on the human astrocytoma cell line model (U87-MG) (Olszewska et al., 2022). Using patch-clamp technique on isolated mitochondria, 1,25(OH)$_2$D$_3$ (100–300 nM) was shown to lower or increase the probability of opening the mitochondrial BK$_{Ca}$ channel and the effect was dependent on calcium ions concentration. Under high calcium concentration (100 μM) open probability of the channel decreased, but in low calcium concentration c (10 μM) effect was the opposite. Such experiments were carried out in patch-clamp inside-out mode which means that 1,25(OH)$_2$D$_3$ was applied from the mitochondrial matrix site in the presence and absence of calcium ions. Observed changes in open probability of the channel on mitoplasts are quite fast (1 min) which provides evidence of direct effects of 1,25(OH)$_2$D$_3$ on mitochondrial function excluding involvement of VDR-driven genomic pathway. The potential binding site of 1,25(OH)$_2$D$_3$ with the BK$_{Ca}$ channel was simulated *in silico* use of the AutoDock program. Interestingly, two 1,25(OH)$_2$D$_3$ binding sites (binding energies: −9.26 kcal/mol and −9.21 kcal/mol) for the Ca^{2+}-bound BK$_{Ca}$ channel were detected. The predicted binding sites were located in segments S7-S11 of the cytoplasmic domain of the Ca^{2+}-bound BK$_{Ca}$ channel. On the other hand, the global and local ligand docking indicated a large variety of low-energy binding sites Ca^{2+}-free BK$_{Ca}$ channel, indicating weak interaction (Olszewska et al., 2022).

A structural similarity of vitamin D$_3$ to cholate lithocholic acid has been recently speculated (Nehring et al., 2007). that which activates BK$_{Ca}$ channels makes BK$_{Ca}$ channel activation highly probable under the influence of vitamin D$_3$ (Dopico and Bukiya, 2014). In the case of the widely studied cholesterol, both direct and indirect regulation BK$_{Ca}$ channels have been described (Granados et al., 2021; Singh et al., 2012; Barbera et al., 2019). Cholesterol molecules can directly interact with the channel or with the auxiliary subunit of the channel (Singh et al., 2012) (Bukiya and Dopico, 2021). Comparing the binding sites for 1,25 (OH)$_2$D$_3$ and cholesterol in the BK$_{Ca}$ channel structure, only one common side was found within the cholesterol binding motif (CRAC1), including fragment covering amino acids 1010–1018 of the channel (Kim et al., 2020) (Olszewska et al., 2022).

It was postulated that an increase in the activity of the mitoBK$_{Ca}$ channel in the inner mitochondrial membrane reduces the activity of the permeability transition pore (PTP) (Cheng 2008). Consequently, the decrease in the activity of the mitoBK$_{Ca}$ channel would cause hyperpolarization of the mitochondrial potential, followed by increased ROS and cytochrome release. Thus, the observed reduction of the activity of the

mitoBK$_{Ca}$ channel after treatment with 1,25(OH)$_2$D$_3$ explains some of its anti-cancer properties.

The patch-clamp results indicated a direct impact of 1,25(OH)$_2$D$_3$ on the BK$_{Ca}$ channel, however, the structural similarity of vitamin D$_3$ and cholesterol suggest also direct interaction of vitamin D with the cell membrane. Potential binding of vitamin D$_3$ to the cell membrane may change its properties, thus also affecting the activity of the ion channels. Most research on the influence of 1,25(OH)$_2$D$_3$ on the physicochemical properties of membranes comes from the 1980 s. Administration of 1,25 (OH)$_2$D$_3$ leads to an increase in the *de novo* synthesis of phosphatidylcholine (PC) and an increase in the total PC content. It also increases the turnover of fatty acids into PC, which increases the content of polyunsaturated fatty acids in the PC fraction. 1,25(OH)$_2$D$_3$ regulates PC membrane content, increases membrane fluidity, and increases in calcium transport rate through the calcium channel regulated by 1,25 (OH)$_2$D$_3$ (Rasmussen et al., 1982). Membrane fluidity measured by fluorescence anisotropy of 1,6-diphenyl-1,3,5-hexatriene, was significantly greater in rat intestinal brush border membranes treated with 1,25(OH)$_2$D$_3$ (Deliconstantinos et al., 1986). In chondrocytes, 1,25 (OH)$_2$D$_3$ action results in rapid changes in arachidonic acid release and re-incorporation, alterations in membrane fluidity, and Ca^{2+} ion flux (Boyan et al., 1999). Other data suggest that 1,25(OH)$_2$D$_3$ specifically modulates fatty acids composition in adipose tissue through direct regulation of Elovl3, an enzyme that functions in the synthesis of C20 −C24 saturated and mono-unsaturated long-chain fatty acids (Ji et al., 2016).

In the case of mitochondrial membrane, there are some reports that the fluorescence anisotropy in the mitochondria from vitamin D$_3$-treated chicks is significantly lower than that from the vitamin D$_3$-deficient animals. The fluorescence studies performed in mitochondrial subfractions revealed that 25(OH)D$_3$ treatment resulted in a decrease in lipid order parameters of the mitochondrial inner membrane (Tolosa De Talamoni et al., 1989).

To sum up, many studies indicate that 1,25(OH)$_2$D$_3$ is involved in the regulation of the biological activity of mitochondria in cells, but it is not yet clear what mechanisms of action of 1,25(OH)$_2$D$_3$ are behind these effects. However it seems, this effect is pleiotropic. In the future, it would be interesting to investigate, the factors which are responsible for mitochondrial localization of VDR and its physiological consequences.

6. Conclusions

In summary, here we review the evidence indicating that mitochondrial channels represent a new link between 1,25(OH)$_2$D$_3$ and mitochondria. In addition to well-established, genomic effects of 1,25 (OH)$_2$D$_3$, many studies point to non-genomic, direct effects of 1,25 (OH)$_2$D$_3$ on ion channels. However, there is still limited data concerning the effects of the 1,25(OH)$_2$D$_3$ on intracellular ion channels, including mitochondria. Electrophysiological studies would be very helpful in this aspect. After careful examination of the potential impact of 1,25(OH)$_2$D$_3$ towards a specific mitochondrial potassium channel, new therapeutic perspectives are opening for 1,25(OH)$_2$D$_3$ and its analogs. Moreover, it should be emphasized that 1,25(OH)$_2$D$_3$ itself, by increasing the expression of genes encoding channel proteins can enhance the therapeutic effects of classic ion channel modulators.

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CRediT authorship contribution statement

A.M. Olszewska: Conceptualization, Funding acquistion, Writing – original draft, Writing – review & editing, Visualization. **M.A. Zmijewski:** Conceptualization, Writing – review & editing, Supervision.

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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mito.2024.101891.

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