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REVIEW

Vitamin D Receptor in Cancer: Biological Functions, Mechanistic Insights, and Clinical Relevance

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Abstract: Vitamin D (VD) has been the focus of extensive clinical research, yet conclusions regarding its biological roles remain inconsistent. VD exerts its functions through the vitamin D receptor (VDR), a nuclear transcription factor that regulates the expression of VD3-responsive target genes. Notably, divergent findings across studies have been reported regarding VDR expression patterns and functional roles, underscoring the complexity of VDR in cancer biology. Whether this complexity interferes with VD's biological activity-thereby contributing to the variable impacts of VD3 on cancer prevention and treatment-remains unclear. This review systematically addresses: (1) the association between VDR expression (assessed by immunohistochemistry) and cancer prognosis; (2) the roles and mechanisms of VDR in cancer; (3) the multi-level regulatory networks governing VDR expression and activity; and (4) the translational implications of VDR in cancer therapy. Elucidating the precise roles and mechanisms of VDR is critical for optimizing cancer treatment strategies and resolving conflicting clinical evidence.

Keywords: vitamin D receptor, cancer, prognosis, function and mechanism, therapy

Introduction

Compelling experimental data confirm the significant anti-tumor efficacy of vitamin D (VD).[1] Despite inconsistent findings from observational and cohort studies,[2] the potential of VD in cancer prevention and treatment remains highly promising, fueling ongoing investigations into combination therapeutic strategies. The vitamin D receptor (VDR) serves as the principal mediator of VD signaling, binding to its bioactive ligand, 1,25-dihydroxyvitamin D3 [1,25$(OH)_2D_3$]. Recent research has unveiled complexities in VDR expression patterns and functional roles, which may represent critical determinants of VD's biological activity. This review employs a problem-oriented approach to address the paradoxical role of VDR in cancer. Utilizing a systematic "expression-function-regulation-therapy" framework, it synthesizes current evidence on VDR's expression patterns, prognostic significance, context-dependent functions in malignant and stromal cells, multi-level regulatory mechanisms, and clinical therapeutic applications. Based on a focused literature search in PubMed using key terms such as "vitamin D receptor," "cancer," and "VDR signaling," priority was given to original studies offering mechanistic insights or clinical correlations, while reviews were incorporated for contextual framing. The review aims to provide actionable guidance for advancing personalized vitamin D-based therapeutic strategies.

The Structure and Biological Function of VDR

In 1969, VDR was first identified in chicken intestinal mucosa as a receptor for 1,25$(OH)_2D_3$.[3] Subsequent studies confirmed that the VDR gene, located on the long arm of chromosome 12, consists of 9 exons.[4] The full-length VDR

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protein contains four functional domains essential for its activity (Figure 1). As a member of the nuclear hormone receptor superfamily, binding of $1,25(OH)_2D_3$ to VDR triggers its nuclear translocation, thereby regulating transcription of VD_3-responsive target genes. To date, over 1000 VDR target genes have been identified.[5] Additionally, cytoplasmic VDR may regulate enzymes and signaling cascades, primarily by mediating rapid responses that ultimately influence target gene expression.[6] In tumor cells, VDR is also activated via this canonical signaling pathway. However, it recruits different coregulator complexes, which can lead to divergent biological outcomes.[7]

The Expression of VDR and Its Prognostic Significance in Cancer

Expression of VDR in Cancer Based on IHC Detection and Its Prognostic Significance

VDR has been found to aberrantly express in multiple cancer types. This review synthesizes evidence from retrospective cohort studies that employed immunohistochemistry (IHC) to explore the VDR-prognosis relationship, in order to assess the association between in situ VDR expression and patient prognosis (Table 1). These studies have reported inconsistent conclusions regarding VDR expression levels and their clinical significance, even within the same cancer type. Taking breast cancer-a relatively well-studied model-as an example, Nina et al reported a 92.7% VDR positivity in breast cancer, with about 60% of patients showing high IHC scores.[8] Notably, patients with high IHC-based VDR expression exhibited superior progression-free survival (PFS) and overall survival (OS) compared to those with moderate/low expression.[8] Conversely, Jamila et al found that most breast tumors showed moderate-to-strong VDR expression but there was no association between VDR expression and patient survival outcomes.[9] Such discrepancies in VDR expression profiles and clinical relevance are universal in various cancers and have hindered the development of VDR-targeted therapeutics.

Factors Underlying Inconsistent Findings on VDR Expression and Prognostic Significance

We analyzed potential factors influencing conclusions about VDR expression and prognostic significance. First, most current studies focus solely on nuclear VDR while neglecting cytoplasmic expression-despite evidence that VDR localizes to both nuclei and cytoplasm in cancer cells. Considering VDR subcellular localization reveals complex

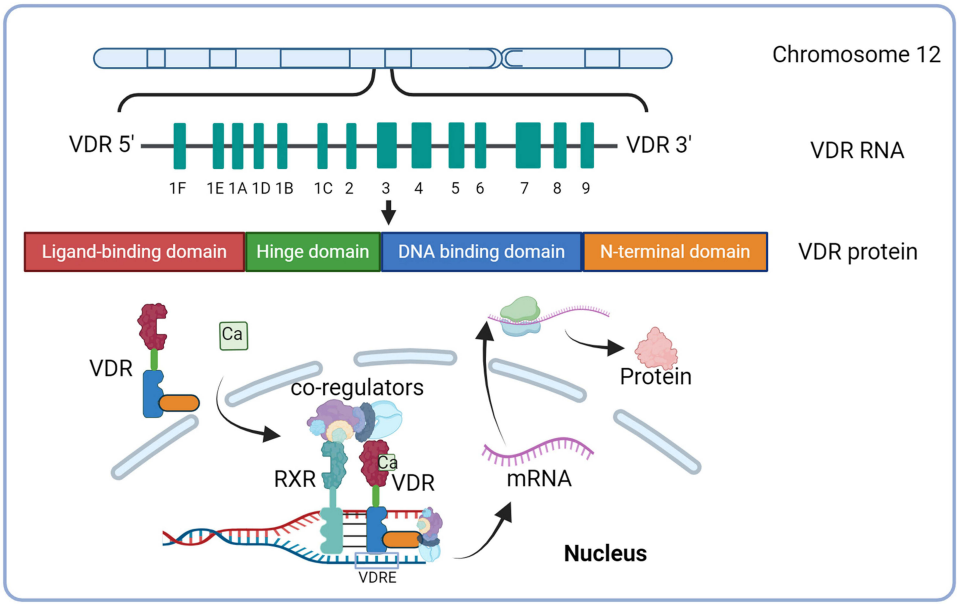

Figure 1 The VDR protein comprises four functional domains. The *VDR* gene, located on the long arm of chromosome 12, comprises nine exons. Its protein product features several functional domains: The C-terminal ligand-binding domain (LBD) is responsible for ligand binding and interacts with coactivators and corepressors. The highly conserved DNA-binding domain (DBD), which contains two zinc finger motifs, facilitates binding to specific vitamin D response elements (VDREs) in target genes and enables heterodimerization with the retinoid X receptor (RXR). The formation of the VDR/RXR heterodimer significantly enhances the affinity for VDREs and regulates transcriptional activity through the recruitment of coregulatory complexes. A flexible hinge region connects the LBD and DBD, while the N-terminal domain (NTD) is involved in binding coregulators that modulate transcription.

Table 1 Summary of the Association Between VDR in situ Expression by IHC Assay and Cancer Patient Prognosis Based on Clinical Retrospective Cohort Studies

Cancer (Cohort Size)	Location	Antibody (CAT#)	Findings	Logrank Test χ^2	HR (95% CI)	P	Reference (PMID)
BC (75)	Nucleus	AbD Serotec (MCA 3543Z)	Higher VDR, as the dependent variable, is associated with better PFS and OS.		DFS (uv): 0.83 (0.73–0.94) DFS (mv): 0.67 (0.24–1.9) OS (uv): 0.35 (0.15–0.81) OS (mv): 0.39 (0.14–1.04)	0.046 0.436 0.014 0.060	22108646
BC (1114)	Nucleus	Thermo Fisher (MA1-710)	VDR expression (moderate/ strong) showed no association with OS, PFS, or CSS.		Strong-OS (uv): 1.04 (0.78–1.39) Strong-PFS (uv): 1.14 (0.87–1.50) Strong-CSS (uv): 1.06 (0.70–1.61) Moderate-OS (uv): 1.02 (0.77–1.36) Moderate-PFS (uv): 1.09 (0.84–1.43) Moderate-CSS (uv): 0.87 (0.57–1.33)	>0.05 >0.05 >0.05 >0.05 >0.05 >0.05	27407090
BC (136)	Nucleus	Provided by M. R. Haussler	Patients with higher VDR have a longer DFS	OS: χ^2=1.81 DFS: χ^2=4.01		>0.1 0.045	1846309
BC (320) Unifocal:173 Multifocal: 147	Nucleus	Vector Laboratories	VDR expression is an independent factor for OS in the multifocal BC.		Uni-OS (mv): 1.086 (0.921–1.280) Multi-OS (mv): 0.804 (0.671–0.964)	0.327 0.019	31731733
BC Nucleus:678 Cytoplasm:679	Nucleus Cytoplasm	Santa Cruz (sc-13133)	Patients with higher nuclear VDR have a better CSS.		Nucl-CSS (uv):0.46 (0.31–0.69) Cyto-CSS (uv): 0.47 (0.28–0.79) Nucl-CSS (mv): 0.56 (0.34–0.91) Cyto-CSS (mv): 0.59 (0.30–1.16)	<0.05 <0.05 <0.001 >0.05	31358030
IDC (68)	Nucleus	Thermo Fisher (MA1-710)	Patients with higher VDR are associated with improved OS.	OS: χ^2=11.677	OS (mv): 0.118 (0.3–0.466)	0.001 0.002	33906311
BC (117) BRCA1^{mut}(38) Sporadic (79)	Nucleus	AbD Serotec	VDR predicts favorable OS in BRCA1-mutated cases.	Not Provided	Not Provided	0.004 0.047	28427429
CRC (98)	Membrane Cytoplasm	Santa Cruz (sc-13133)	Low VDR expression marks poor prognosis.		OS (uv): 0.447 (0.210–0.949) OS (mv): 0.720 (0.314–1.647)	0.036 0.436	32355523
CRC (419)	Nucleus Cytoplasm	Abcam (ab3508)	Patients with low VDR have shorter OS.	Not Provided		<0.01	32900990
NSCLC (73)	Nucleus Cytoplasm	Thermo Scientific	High level of nuclear VDR was associated with improved OS.		Nucl-OS (uv): 0.52 (0.25–1.09) Nucl-OS (mv): 0.36 (0.17–0.79) Cyto-OS (uv):0.99 (0.54–1.81) Cyto-OS (mv):1.28 (0.65–2.49)	0.085 0.011 0.963 0.478	20955794
OC (156)	Nucleus Cytoplasm	AbD Serotec (MCA3543Z)	High cytoplasmic VDR is associated with impaired OS.		Cyto-OS (mv): 2.218 (1.106–4.448)	0.025	32572587

(*Continued*)

Table 1 (Continued).

Cancer (Cohort Size)	Location	Antibody (CAT#)	Findings	Logrank Test χ^2	HR (95% CI)	P	Reference (PMID)
PADC (61)	Cytoplasm	Santa Cruz (sc-1008)	High VDR, a non-independent factor, is associated with longer OS.	Not Provided	Not Provided	0.037 0.069	25641222
PDAC (127)	Nucleus (stromal)	Abcam (ab8756)	High VDR expression was associated with improved OS in localized disease.		OS (mv): 0.35 (0.16–0.74)	0.006	33109584
PCa (841)	Cytoplasm Membrane	Santa Cruz (sc-1008)	The highest VDR expression reduced risk of lethal PCa.		OS (uv): 0.17 (0.07–0.41) OS (mv): 0.37 (0.14–0.94)	<0.001 <0.036	21537045
SKCM (69)	Nucleus Cytoplasm	Abcam (clone 97A)	Both nuclear and cytoplasmic VDR contributed to a better prognosis in the patients without ulceration.	Cyto-OS: χ^2=6.125 Nucl-OS: χ^2=8.632		0.0468 0.0134	24922634
BLCA (71)	Nucleus Cytoplasm	Abcam (clone 97A)	Both reduced cytoplasmic and nuclear VDR, identified as dependent factors, are associated with longer OS.		Nucl-OS (uv): 2.47 (0.85–7.22) Cyto-OS (uv): 1.92 (0.53–4.00) Nucl-OS (mv): 0.45 (0.17–1.17) Cyto-OS (mv): 0.59 (0.28–1.25)	0.02 0.04 0.11 0.17	26501255
EAC (116)	Membrane Cytoplasm	Santa Cruz	VDR is not associated with OS.	Not Provided		0.99	24951052
GBM (61)	Nucleus Cytoplasm	Santa Cruz	Pooled VDR is positive associated with longer OS.	Not Provided		0.046	24584679

Notes: The included studies employed Log rank tests and/or Cox proportional hazards models, reporting p-values; however, several failed to provide complementary statistics such as hazard ratios or confidence intervals, despite declaring the analytical methods used. A p-value of less than 0.05 was considered statistically significant.

Abbreviations: OS, overall survival; DFS, disease-free survival; CSS, cancer-specific survival; PFS, progression-free survival; HR, Hazard ratio; CI, Confidence interval; IDC, invasive duct carcinoma; BC, breast cancer; CRC, colorectal cancer; NSCLC, non-small cell lung carcinoma; LUAC, lung adenocarcinoma; OC, ovarian cancer; PDAC, pancreatic ductal adenocarcinoma; PCa, prostatic cancer; SKCM, Skin Cutaneous Melanoma; BLCA, Bladder Urothelial Carcinoma; EAC, esophageal adenocarcinoma; GBM, glioblastoma multiforme; uv, Univariate analysis; mv, Multivariate analysis; Nucl, Nucleus; Cyto, Cytoplasm.

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expression patterns and prognostic roles. Francis et al showed nuclear VDR associated with low-grade breast tumors, whereas cytoplasmic VDR correlated with lymph node metastasis.[10] Xu et al conducted a meta-analysis and found overall VDR expression (not nuclear VDR alone) linked to improved OS in breast cancer.[11] Šutalo et al observed VDR in both nuclei and cytoplasm of colon cancer: nuclear expression peaked in normal mucosa/hyperplastic polyps, declined in adenomas, and vanished in CRC, while cytoplasmic VDR showed the opposite trend.[12] VDR localization likely influences its function, explaining divergent clinical significance. Current questions remain: Does differential localization relate to nuclear localization signal changes, antibody selection, VDR isoforms, or vitamin D levels? Further research is needed to address these mechanisms.

Second, specific genetic alterations may modulate VDR expression and clinical significance. Sabine et al found VDR levels were significantly higher in BRCA1-mutated breast cancers than in sporadic cases, with VDR conferring a favorable prognosis exclusively in BRCA1-mutated tumors.[13] Mechanistically, VDR activates BRCA1 transcription in $1,25(OH)_2D_3$-sensitive breast cancer cells,[14] indicating regulatory crosstalk between BRCA1 and VDR in breast carcinogenesis. In CRC, Shoko et al reported 38% VDR positivity, with expression correlated to PIK3CA/KRAS mutations but not survival outcomes (CSS/OS).[15] Breast cancer molecular subtypes also show differential VDR expression,[16] highlighting how genetic backgrounds (eg, BRCA1 status, oncogenic mutations) influence VDR patterns and prognostic relevance in tumors.

Third, VD levels may influence VDR expression and function. Studies show unliganded VDRs can translocate to the nucleus, exerting basal transcriptional activity via co-repressors or co-activators.[17–19] In VD deficiency, unliganded VDR dominates, promoting breast cancer cell proliferation while inhibiting apoptosis. Conversely, VD supplementation restores ligand-bound VDR's tumor-suppressive activity.[20]

Additionally, histological subtypes and crosstalk between the VD axis and other signaling pathways may modulate VDR expression and function in cancer. For instance, VDR positivity rates differ significantly between small-cell lung cancer (26%) and non-small cell lung cancer (NSCLC, 57%).[21] Cross-talk between VDR and the androgen receptor has also been documented: VDR knockdown-mediated promotion of prostate cancer cell growth is abrogated by testosterone supplementation.[22] Furthermore, heterogeneity across studies, such as variations in sample size and statistical approaches, may also contribute to divergent conclusions regarding the prognostic value of VDR.

Collectively, these findings indicate that multiple factors modulate VDR function. Understanding these dynamics is critical for developing patient-tailored VDR-targeted therapies.

The Biological Function and Mechanism of VDR in Cancer Cells

Lots of studies have shown that VDR involved into various biological processes in cancer mainly functioning as a transcription factor (TF). Here, we systemically reviewed the targets of VDR and their biological effects as summarized in Figure 2. On this basis, we focus on the recent advances in the roles of VDR in tumor cell metabolism and gut microbiota regulation with the aim of achieving a more profound and comprehensive understanding of VDR.

VDR Regulates the Metabolism of Cancer Cells

Reprogramming of energy metabolism is a hallmark of cancer, enabling tumor cells to adapt to nutrient-limited environments. Silvagno et al first identified the mitochondrial localization of VDR in human HaCaT keratinocyte cells.[23] Subsequent studies revealed that VDR disrupts the respiratory chain and redirects acetyl-CoA metabolism from the energy-generating tricarboxylic acid (TCA) cycle to biosynthetic pathways, fueling cancer cell proliferation.[24] In colon cancer, the tumor suppressor p53 inhibits growth through a VDR-dependent mechanism. p53 directly binds to the VDR gene promoter, upregulating VDR expression and promoting peroxisomal fatty acid β-oxidation (FAO) while suppressing purine synthesis.[25] Conversely, VDR silencing enhances respiratory activity, triggering excessive reactive oxygen species (ROS) production that damages healthy cells and drives tumorigenic phenotypes.[26] In addition, VD-activated VDR upregulates the long non-coding RNA MEG3 in colon cancer cells. MEG3 restricts glycolysis by initiating c-Myc ubiquitination and degradation, subsequently suppressing c-Myc target genes involved in the glycolytic pathway, thereby reducing glycolytic capacity and lactate production.[27]

Notably, recent research shows that in acute kidney injury, VDR activation by VD improves LPS-induced glucose dysregulation via the AMPK-PDHA1 axis, highlighting VDR's role in metabolic reprogramming beyond cancer.[28] These findings underscore VDR's multifaceted functions in regulating metabolism across physiological and pathological contexts.

Collectively, VDR is an important regulator of metabolic reprogramming, functioning across levels from mitochondrial activity to epigenetic modulation.

VDR Deficiency Alters the Gut Microbiota to Promote Cancer Development

A genome-wide association study (GWAS) has shown that genetic variation at the VDR locus significantly influences gut microbial composition and the gut-liver axis.[29] Intestinal epithelial VDR deficiency drastically alters bacterial profiles, increasing *E. coli* and *Bacteroides* while reducing butyrate-producing bacteria (eg, Butyrivibrio).[30] Such VDR-altered microbiota promotes carcinogenic susceptibility. For instance, AOM/DSS-treated VDR−/− mice developed larger and more colonic tumors than wild-type controls, a phenotype partially driven by dysbiotic gut flora.[31] One proposed mechanism involves VDR improving intestinal permeability by upregulating tight junction protein Claudin-5.[31] Zhang et al recently showed that VDR deletion promotes bacterial translocation and impairs colon tumorigenesis barriers, a process linked to reduced Claudin 10 expression.[32] Additionally, VDR deficiency enhances Jak2/STAT3 signaling in colon tumors by directly upregulating Jak2, with fecal transfers from VDR−/− mice stimulating STAT3 activation in human/mouse colonoids.[33]

Notably, VDR-mediated microbiota remodeling promotes extraintestinal carcinogenesis: Zhang et al found VDR deficiency increases breast cancer risk.[34] Conversely, gut microbes modulate VDR activity via multiple pathways. For

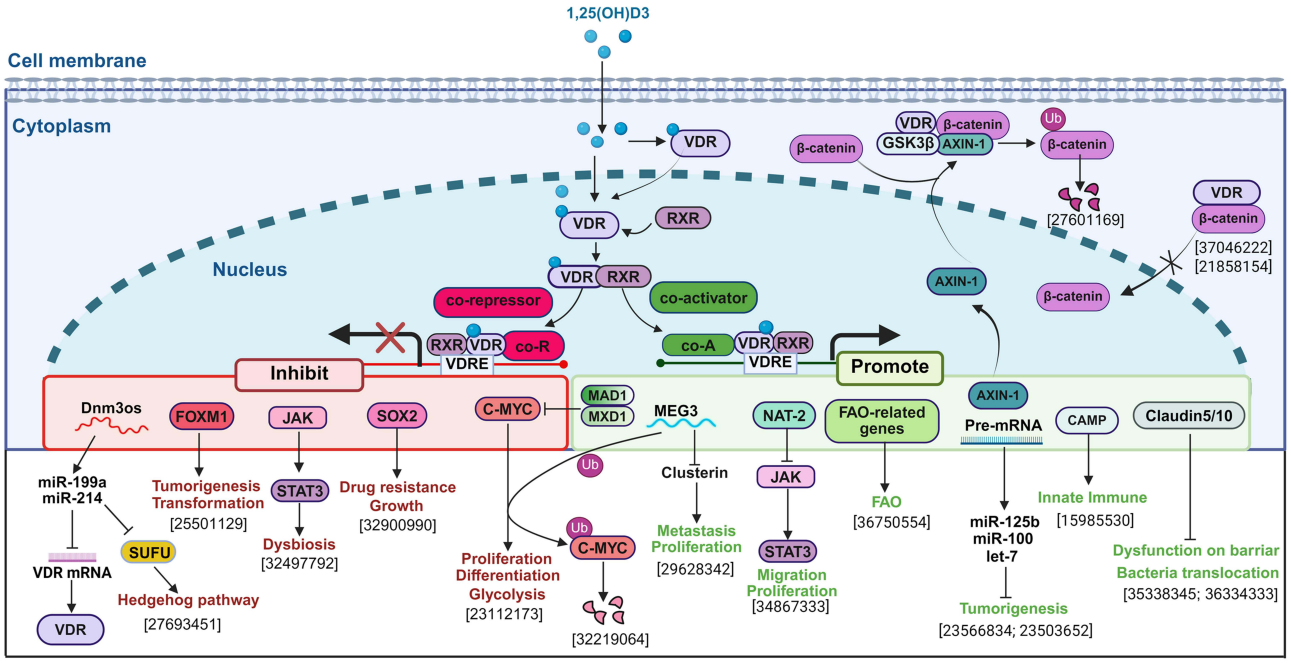

Figure 2 The targets of VDR and their biological effects. This figure summarizes the transcriptional regulatory network mediated by VDR and its biological outcomes. Target genes upregulated or downregulated by VDR are indicated in green (right) and red (left), respectively, along with their corresponding effects on tumor cells. VDR transcriptionally activates several protein-coding genes, including NAT2 (inhibiting JAK-STAT signaling), Claudin-5/10 (enhancing intestinal barrier function), CAMP (promoting innate immunity), and peroxisomal FAO-related genes (modulating metabolism). It also induces the transcriptional repressor MAD1/MXD1, which suppresses c-MYC. In addition, VDR upregulates non-coding RNAs such as MEG3—which suppresses Clusterin and promotes methyl-dependent degradation of c-MYC, thereby inhibiting proliferation, metastasis, and glycolysis—as well as microRNAs including let-7, miR-125b, and miR-100 (collectively inhibiting tumorigenesis). Conversely, VDR represses several oncogenic factors, including SOX2, FOXM1, c-MYC, JAK, and the miR-199a/214 cluster (via inhibition of Dnm3os). Suppression of miR-214 not only forms a positive feedback loop that reinforces VDR expression but also leads to SUFU-mediated inhibition of the Hedgehog pathway. A key mechanism involves multi-level suppression of Wnt/β-catenin signaling by VDR, through blockade of its nuclear translocation and promotion of Axin1-mediated degradation. These actions collectively contribute to inhibited tumor invasion/proliferation and enhanced apoptosis/differentiation.

Abbreviations: CAMP, cathelicidin antimicrobial peptide; DNM3OS, dynamin-3 opposite strand; FAO, fatty acid β-oxidation; FOXM1, forkhead box M1; MEG3, maternally expressed gene 3; NAT2, N-acetyltransferase 2; SOX2, SRY-box transcription factor 2; SUFU, suppressor of fused homolog; MAD1, mitotic arrest deficient-like 1; MXD1, MAX dimerization protein 1.

example, gut-colonizing *C. maltaromaticum* collaborates with other microbes to enhance intestinal VD synthesis in an estrogen-dependent manner, activating host VDR and inhibiting colon cancer in female mice.[35] Butyrate, a bacterial metabolite, also potentiates colonic epithelial VDR activity.[30] A lard-based high-fat diet protects against DSS-induced colitis and cancer by activating VDR through microbiota-bile acid metabolite interactions.[36]

In summary, VDR acts as a key host factor maintaining gut microbiota homeostasis. VDR deficiency drives dysbiosis to promote cancer initiation and progression.

The Biological Function and Mechanism of VDR in Cancer Stromal Cells

Pancreatic ductal adenocarcinoma (PDAC) is a highly desmoplastic tumor dominated by pancreatic stellate cells (PSCs). Activated PSCs secrete abundant extracellular matrix (ECM), impairing PDAC responsiveness to immunotherapy and chemotherapy. VDR activation quiesces PSCs and remodels the tumor microenvironment, enhancing therapeutic efficacy.[37,38] Synergistic autophagy inhibition to deplete p62, combined with VDR signaling activation in PSCs, reprograms PSCs to reduce fibrosis, thereby potentiating the antitumor effects of PD-1 blockade and chemotherapy.[39] In hepatic stellate cells (HSCs), p62 directly interacts with VDR and RXR to promote heterodimerization, suppressing fibrosis/inflammation and limiting hepatocellular carcinoma (HCC) progression.[40] In CRC, high VDR expression in stromal fibroblasts correlates with better OS and PFS, independent of intratumoral VDR levels.[41] In gastric cancer, VDR expressed in cancer-associated fibroblasts (CAFs) mediates resistance to oxaliplatin: ligand-activated VDR (eg, calcipotriol) suppresses PI3K/Akt signaling, blocking CAF-derived IL-8 that confers drug resistance.[42] VDR activation in CAFs also reduces secretion of exosomal miR-10a-5p, diminishing its pro-tumorigenic effects on pancreatic cancer cells.[43]

VDR in macrophages modulates cancer progression: the extracellular domain of GcMAF (vitamin D binding protein-derived macrophage activating factor) interacts with the intracellular domain of VDR to activate macrophages, inducing apoptosis and phagocytosis of breast cancer cells.[44] Targeting VDR in tumor-associated macrophages of triple-negative breast cancer reshapes the cytokine milieu to promote anticancer immunity and hinder tumor growth.[45] Additionally, VDR rose in ovarian cancer patients' platelets, and a high VDR level was linked to a better prognosis.[46]

Stromal VDR alters tumor biology by remodeling the microenvironment or disrupting stromal-parenchymal crosstalk (Figure 3). These findings suggest VDR-targeted therapies may enhance anticancer efficacy by acting on both stromal and parenchymal compartments.

Regulatory Mechanisms of VDR Expression and Activity

With the growing recognition of VDR's critical role in cancer, the regulatory mechanisms of VDR expression and biological function have emerged as a research priority. Evidence indicates that VDR expression is modulated across multiple hierarchical stages, spanning from DNA-RNA transcriptional control to post-translational modifications (Figure 4).

DNA-Level Regulation

TCGA datasets demonstrate that VDR genomic loss correlates with tumor progression, with distant metastases exhibiting lower VDR copy numbers than regional lymph node metastases.[47] VDR promoter methylation is more prevalent in malignant cells compared to non-cancerous tissues,[48–50] showing an inverse correlation with VDR expression.[47] Methylation-induced VDR silencing decreases downstream effectors of the VDR pathway, contributing to calcitriol resistance in breast cancer,[51] putatively through activation of the PRC2 complex and elevation of H3K27me3 levels.[52]

Transcriptional Regulation

TGF-β signaling upregulates VDR via Smad phosphorylation, enhancing transcriptional activation.[53,54] In colon cancer, the acidic microenvironment inhibits VDR transcription by downregulating PPARD (a ligand-activated nuclear receptor TF) while promoting VDR nuclear export.[55] 17β-estradiol (E2) binding to caveolar estrogen receptors triggers Src-mediated tyrosine phosphorylation, activating the Ras-ERK pathway to upregulate VDR.[56] Downregulation of KLF4 (a VDR-specific TF) reduces VDR expression and promotes HCC cell proliferation.[57] The p38-MAPK pathway induces VDR transcription via c-Jun/AP-1 binding, mediating butyrate-induced differentiation in colon cancer cells.[58,59] Conversely, p38 suppresses VDR transcription in K-ras mutant colon cancer cells via AP-1-dependent trans-repression, leading to cell death.[60] In silico analysis

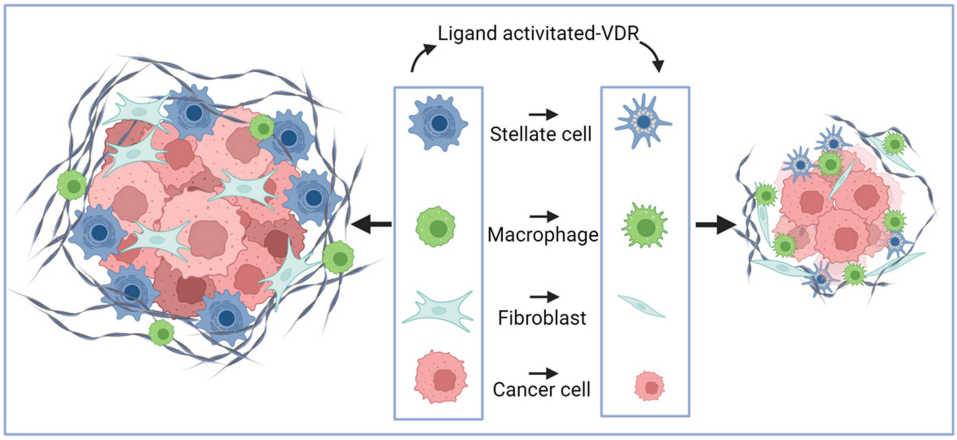

Figure 3 VDR activation in stromal cells exerts anti-tumor effects. TME comprises various stromal cells, including activated astrocytes and fibroblasts, which contribute to tumor progression and therapy resistance by promoting fibrosis and modifying the TME. Ligand-bound VDR activation can counteract these effects by reversing the activated state of these cells to a quiescent state, thereby reducing interstitial fibrosis and inhibiting tumor growth. Furthermore, VDR activation in macrophages promotes their anti-tumor activity, leading to increased tumor cell death.

shows p53 binds conserved VDR intronic regions to enhance transcription, reinforcing its tumor suppressive role,[61] whereas p63 directly targets the VDR promoter for specific upregulation.[62] Chronic intestinal inflammation-driven TNF-α increases Snail1/2 to suppress VDR expression.[63] EGFR upregulates Snail1 to downregulate VDR in colonic tumors, forming a bidirectional negative feedback loop with VDR-mediated EGFR inhibition.[64] SLUG (a SNAIL family member) recruits co-repressors CtBP1/HDAC1 to the VDR promoter, inhibiting expression via chromatin remodeling.[65] IRX4 functions as a tumor suppressor through putative transcriptional feedback with VDR.[66]

Thus, VDR expression is modulated by TFs and coregulators, including activatory and repressive mechanisms.

Post-Transcriptional Regulation

The Cross-Talk Between VDR mRNA and Non-Coding RNAs

miR-181a-5p targets VDR to enhance cisplatin sensitivity in breast cancer by activating autophagy.[67] TNF-α from inflamed tissues induces miR-346 in colonic epithelial cells, reducing VDR expression to promote colitis and carcinogenesis.[68] miR-125a-5p and miR-125b also regulate VDR.[69,70] VDR and lncRNA H19 form a negative feedback loop: VDR suppresses H19 by inhibiting c-Myc and promoting Mad-1 binding to the H19 promoter, while H19 overexpression reduces VDR via miR-675-5p (derived from H19).[71]

Alternative Splicing (AS) of VDR

AS is a key post-transcriptional mechanism underlying VDR functional heterogeneity in cancer. Ebihara et al identified a rat VDR isoform (rVDR1) generated by intron 8 retention, which lacks ligand-binding activity, cannot form RXR heterodimers, and inhibits vitamin D signaling.[72] Crofts et al showed that human VDR (hVDR) uses alternative promoters and AS to generate tissue-specific variants, including VDRB1—an N-terminally extended isoform that localizes to distinct nuclear foci with reduced transactivation activity.[73,74] In HCC, long-read RNA sequencing detected increased VDR AS variants (alternative 5′ splice sites and exon skipping) from normal liver to tumor tissue.[75] Functional studies reveal VDR isoform diversity: deletion of exon 3 (encoding the DNA-binding domain) impairs tumor suppressor activity, while loss of exon 8 (LBD) enhances ligand-independent signaling in cancer cells.[76] Collectively, AS enhances VDR structural and functional complexity in cancer. However, VDR AS remains understudied, with limited knowledge of isoform-specific expression and functions.

Translation Regulation

Lu et al identified two chicken VDR isoforms arising from distinct mRNA initiation sites during translation.[77] Normally, stop codons terminate translation, but ribosomes occasionally bypass them to translate the untranslated region (UTR),

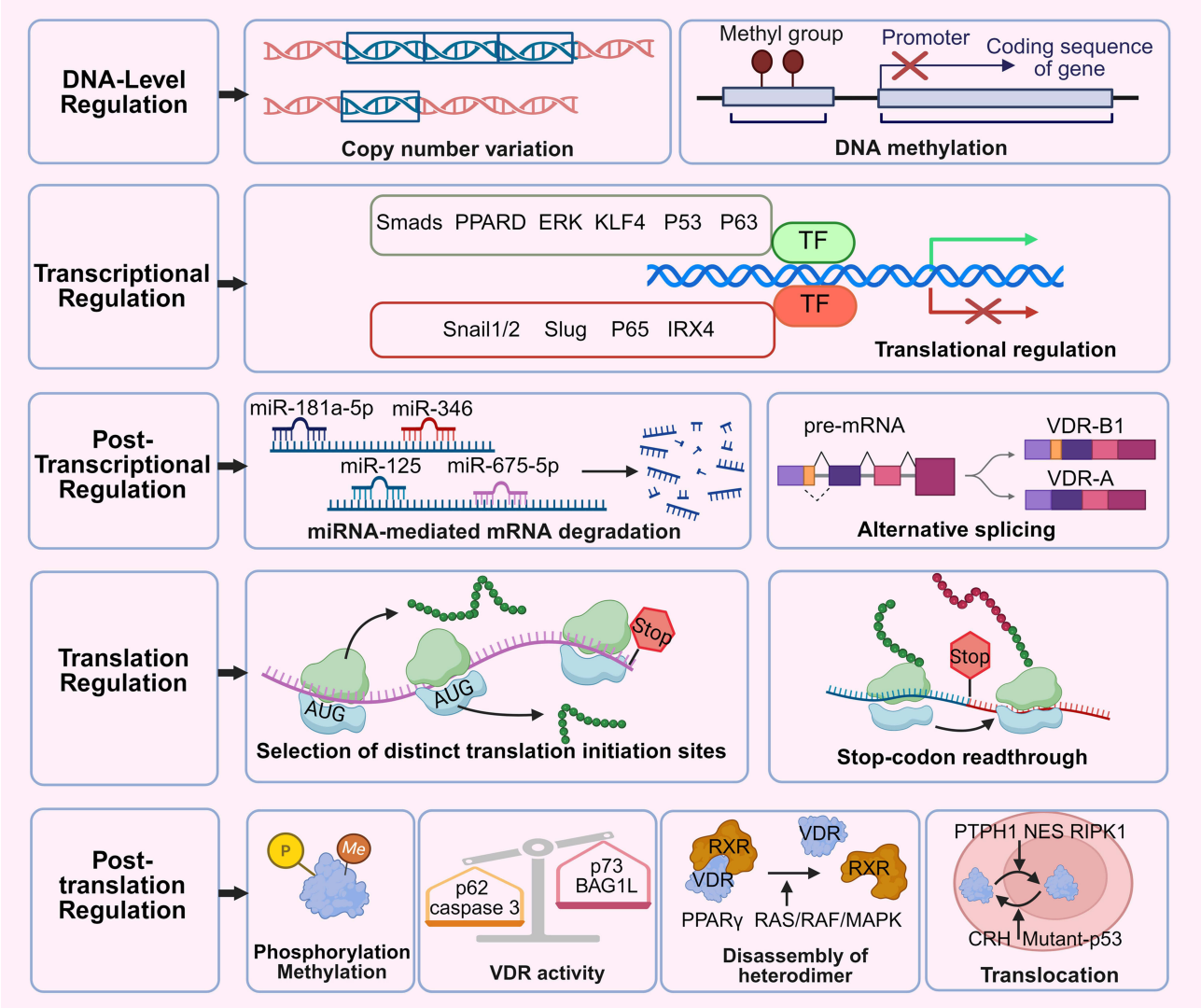

Figure 4 The mechanisms regulating VDR expression and activity. The expression and activity of VDR are regulated through multi-level mechanisms spanning from gene to functional protein. At the DNA level, VDR expression can be epigenetically suppressed by promoter methylation or reduced gene copy number. Transcription factors binding to the VDR promoter region further modulate its expression positively or negatively at the transcriptional level. Post-transcriptionally, VDR mRNA is subject to miRNA-mediated degradation, while alternative splicing generates diverse transcript variants encoding multiple protein isoforms. Translationally, the selection of alternative start codons or ribosomal readthrough of premature termination codons expands the variety of VDR protein products. Finally, at the post-translational level, modifications such as phosphorylation and methylation fine-tune VDR stability and activity, and protein-protein interactions-including those promoting dissociation from RXR heterodimers or regulating nucleocytoplasmic shuttling-collectively enable precise spatiotemporal control of VDR function.

Abbreviations: PPAR, peroxisome proliferator-activated receptor gamma; PTPH1, protein tyrosine phosphatase H1; RIPK1, receptor-interacting serine/threonine-protein kinase 1; CRH, corticotropin-releasing hormone; BAG1L, BAG family molecular chaperone regulator 1L; Smads, mothers against decapentaplegic homologs; KLF4, Krüppel-like factor 4; IRX4, Iroquois homeobox protein 4; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; RAS, rat sarcoma virus; RAF, rapidly accelerated fibrosarcoma; NES, nuclear export signal; AUG, translation start codon.

a process called stop-codon readthrough.[78] Loughran et al showed that readthrough generates VDRx, a 67-amino acid C-terminal extension of VDR, which exhibits reduced transcriptional responsiveness to active vitamin D.[79]

Post-Translational Regulation

Kinase-Mediated Modification

Inhibition of glycogen synthase kinase 3 (GSK3) induces VDR hyperphosphorylation, strengthening its interaction with coactivator SRC-3 to enhance transcriptional activity.[80] Ting et al showed that ATM, a DNA repair gene, phosphorylates VDR to activate its transactivation, while active VDR transcriptionally upregulates ATM, forming a positive feedback loop.[81]

Protein-Protein Interactions

Certain proteins modulate VDR transcriptional activity through direct interaction. BAG1L, a nuclear protein associated with Hsp70 chaperones, enhances VDR transactivation in a ligand-dependent manner[82] Mutant p53 interacts with VDR to augment its transcriptional activity,[83] while p73 (a p53 family member) regulates VDR activation during DNA damage and sensitizes cells to vitamin D therapy.[84] Lysine-specific demethylase 1A (LSD1) exhibits dual regulatory roles: it acts as a coactivator by recruiting VDR and DNMT1 to target gene promoters, and as a corepressor by modulating H3K4me2/H3K9Ac and DNA methylation.[85] Caspase-3 cleavage of VDR reduces its activity, linking apoptotic signaling to VDR inactivation.[86]

Heterodimer Dynamics

The formation of VDR-RXR heterodimers is critical for VDR function. PPARγ competes with VDR for RXRα binding, blocking VDR signaling.[87] The RAS-RAF-MAPK cascade phosphorylates RXRα at Ser260, disrupting VDR-RXR interaction and inhibiting signaling.[88] In prostate cancer, constitutive MAPK signaling reduces VDR-mediated transcription by phosphorylating RXR in VDR-RXR heterodimers, impairing coactivator recruitment to the transcription complex.[89]

VDR Subcellular Localization Regulation

Protein tyrosine phosphatase PTPH1 binds VDR to promote cytoplasmic retention independent of phosphatase activity.[90] Acidic microenvironments trigger VDR nuclear export via its NES,[55] while RIPK1 binding to the VDR LBD enhances cytoplasmic sequestration.[91] In MCF-7 cells, corticotropin-releasing hormone (CRH) upregulates VDR and facilitates nuclear translocation to induce apoptosis.[92] Mutant p53 interacts with VDR to stabilize nuclear VDR levels, upregulating p21 and suppressing CDK2 to inhibit gastric cancer cell growth.[93] These mechanisms collectively regulate VDR subcellular localization and functional output.

In summary, the expression and functional activity of VDR are orchestrated through a multi-level regulatory spectrum, extending from genomic control to post-translational modulation of the protein.

The Application Potential of VDR in Cancer Therapy

VDR expression and activation sensitize cancer cells to $1,25(OH)_2D_3$-induced growth inhibition.[59,94] Reintroducing VDR into VDR-knockout tumor cells restores responsiveness to activated vitamin D,[95] prompting trials of VDR agonists/$1,25(OH)_2D_3$ analogs. The first-generation VDR agonist EB1089 demonstrated potent anti-cancer activity in preclinical studies; however, its clinical application was limited by dose-limiting hypercalcemia.[96,97] This challenge prompted the development of low-calcemic, tissue-selective VDR agonists. A representative example is BXL-628, which retains anti-proliferative efficacy without inducing hypercalcemia.[98,99] Current research focuses on developing tissue-selective VDR modulators aimed at serving as effective adjuvants and sensitizing agents in combination cancer therapy.

VDR also modulates chemotherapy sensitivity. In cisplatin-resistant HNSCC, VD combined with cisplatin induces VDR/BIM-mediated apoptosis, suppressing PI3K/Akt/mTOR signaling.[100,101] Calcitriol enhances cisplatin's antiproliferative and anti-angiogenic effects in ovarian cancer.[102] In gemcitabine-resistant PDAC, calcitriol/calcipotriol sensitizes cells by reducing MUC1 expression,[103] while VDR knockdown enhances prostate cancer sensitivity to gemcitabine via γH2AX/Rad51 disruption.[104] Silibin restores $1,25(OH)_2D_3$ efficacy in colon cancer by reversing TNF-α-induced VDR repression.[105]

VDR links to immunotherapy, endocrinology, and traditional medicine. VD/VDR regulates PD-L1 in AML/MDS, with VDR antagonist MeTC7 reducing PD-L1 and boosting intratumoral CD8+ T cells.[106] Calcitriol restores antiestrogen sensitivity in ER-negative breast cancer by inducing ERα,[107] while VDR enhances tamoxifen efficacy in ER+ tumors via IRE1α-JNK suppression.[108] Chinese medicines activate VDR to inhibit Smad3/EMT and reduce angiogenesis/fibrosis.[109,110] Clinical trials are exploring VD/analog combinations for cancer therapy.

Collectively, targeting VDR holds therapeutic promise, potentially enhancing treatment efficacy when combined with other agents.

Conclusion and Perspective

Accumulating evidence has established VDR as a multifaceted regulator in cancer pathogenesis and progression. This review synthesizes evidence from clinical retrospective cohort studies using immunohistochemistry to evaluate the in situ

expression patterns of VDR across various cancers and their association with clinical outcomes. Although VDR expression levels and subcellular localization (eg, nuclear vs cytoplasmic) have been linked to patient survival, considerable inconsistencies persist across studies. These discrepancies may stem from factors such as genetic background, serum vitamin D levels, histological subtypes, and methodological variations-though the underlying mechanisms remain incompletely understood.

Functionally, VDR acts primarily as a ligand-activated transcription factor that binds to VDREs to regulate genes involved in cancer cell proliferation, invasion, and metastasis. Notably, the antitumor effects of VDR are not limited to malignant cells but also extend to components of the tumor microenvironment (TME). For instance, in pancreatic and liver cancers, VDR activation in stromal cells can inhibit their tumor-promoting functions. Moreover, VDR activity indirectly influences cancer progression via modulation of the gut microbiota. These findings highlight the dual-targeting potential of VDR-affecting both tumor parenchyma and stroma-which could inform the development of novel combination therapies.

VDR activity is subject to multi-level regulation, including transcriptional, post-transcriptional, and translational control, as well as mechanisms governing protein stability and subcellular localization. A particularly important regulatory layer is alternative splicing of the VDR gene, which generates several functionally distinct isoforms. This diversity may explain the context-dependent roles of VDR in cancer. Nonetheless, most studies to date have focused on the canonical VDRA isoform, leaving the expression patterns, functional profiles, and pathological relevance of other splice variants largely unexplored-a significant gap in current knowledge.

Future research should adopt an integrated approach to decipher the complexity of VDR signaling in cancer. Key directions include: (1) systematically characterizing the functional attributes of non-canonical VDR isoforms across different tumor types; (2) elucidating how VDR activity is modulated by tumor-intrinsic and microenvironmental factors, such as genetic mutations, metabolic signals, and stromal crosstalk; and (3) leveraging these insights to develop next-generation VDR-targeting agents capable of selectively engaging specific isoforms or stromal compartments. These efforts will be essential for advancing personalized, dual-targeting therapeutic strategies and accelerating the clinical translation of VDR-based anticancer approaches.

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Disclosure

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