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Letter to the Editor

The Vitamin D/VDR Axis: An Emerging Epigenetic and Immunometabolic Brake on the Cancer–Inflammation Interplay

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Dear Editors,

In a recent review of the cancer–inflammation interplay, the NF-κB pathway, the STAT3 pathway, and the NLRP3 inflammasome are mapped as central molecular engines of malignant progression, with emphasis on their translational relevance in shaping the tumor microenvironment and response to therapy.[1] However, the review only briefly touches on the vitamin D/vitamin D receptor (VDR) axis and does not explore its potential as a modifiable counter-regulatory system intersecting with each of these pathways or as a candidate biomarker for immunotherapy stratification. Current evidence positions $1,25(OH)_2D_3$ not merely a micronutrient but a pleiotropic hormone whose nuclear receptor—VDR—orchestrates transcriptional programs antagonizing key oncogenic cascades, while also exerting context-dependent immunoregulatory effects.[2]

At the molecular level, $1,25(OH)_2D_3$-activated VDR suppresses the NF-κB pathway through direct physical interaction with IκB kinase β (IKKβ). This VDR–IKKβ binding disrupts the IKK complex, abrogates IKKβ phosphorylation at Ser-177/Ser-181, and arrests tumor necrosis factor-alpha (TNF-α)-induced p65 nuclear translocation and NF-κB transcriptional activity in a VDR-dependent manner, suppressing downstream pro-inflammatory mediators including interleukin-6 (IL-6), TNF-α, and cyclooxygenase-2, the latter being a key driver of prostaglandin-mediated immunosuppression in the tumor microenvironment.[2,3] Simultaneously, the VDR axis targets the STAT3 pathway by inducing the tyrosine phosphatase SHP-1, which dephosphorylates and inactivates STAT3. In a validated experimental inflammatory model, $1,25(OH)_2D_3$ significantly upregulated SHP-1 while downregulating phospho-STAT3 and reducing TNF-α, IL-6, transforming growth factor beta 1, and monocyte chemoattractant protein-1 (all $P < 0.05$), effects fully abrogated upon SHP-1 inhibition.[4] In the absence of adequate VDR signaling, the tumor microenvironment remains chronically primed, facilitating the epithelial–mesenchymal transition and early oncogenesis.[2]

Within the NLRP3 inflammasome pathway, VDR physically engages the NLRP3 leucine-rich repeat domain and inhibits its BRCC3-mediated deubiquitination by preserving K63-linked ubiquitination—a key anti-assembly modification—thereby preventing ASC speck formation, caspase-1 activation, maturation of IL-1β and IL-18, and the excessive pyroptosis that amplifies the pro-tumorigenic milieu.[5]

Within the tumor immune microenvironment, VDR messenger RNA (mRNA) levels are approximately 20-fold higher in tumor-infiltrating myeloid-derived suppressor cells (MDSCs) than in their bone marrow counterparts, with monocytic MDSCs expressing approximately 4-fold higher VDR mRNA than granulocytic MDSCs. $1,25(OH)_2D_3$ treatment significantly inhibited MDSC T-cell-suppressive function ($P < 0.05$) by downregulating arginase-1 and indoleamine 2,3-dioxygenase (IDO)—enzymes that deplete arginine and tryptophan from the tumor microenvironment and thereby deprive effector T cells of essential metabolic substrates.[2,6] The VDR axis further sustains the cancer–immunity cycle by downregulating programmed cell death-ligand 1 expression on tumor cells and promoting tumor-infiltrating $CD8^+$ T cells toward an activated effector-memory phenotype, while maintaining gut barrier integrity via E-cadherin/VDR interactions—thereby preventing systemic lipopolysaccharide (LPS) translocation that chronically fuels the cancer–inflammation axis.[2,7,8] It must be acknowledged, however, that $1,25(OH)_2D_3$ simultaneously promotes $CD4^+CD25^+FOXP3^+$ regulatory T cell (Treg) differentiation by binding vitamin D response elements within the FOXP3 gene, which may paradoxically attenuate effector anti-tumor immunity in certain tumor microenvironments and underscores the context-dependent nature of VDR-targeted interventions.[9]

Epigenetically, the ligand-activated VDR recruits coregulatory complexes—including CREB-binding protein/p300, the steroid receptor coactivator family, and the SWItch/Sucrose Non-Fermentable chromatin-remodeling complex—reshaping chromatin accessibility at tumor-suppressor loci including BRCA1 and p21, with calcitriol inducing an approximately 6-fold increase in BRCA1 protein in breast cancer cells.[10] Genome-wide ChIP-seq analyses identify 1,000–13,000 VDR-specific binding sites; VDR-bound distal regulatory elements are marked preferentially by H3K4me1—a signature of poised enhancers—whereas transcriptionally active promoters display H3K4me3 enrichment, establishing a cell-type-specific combinatorial histone code that determines context-dependent VDR gene activation.[10] Chronic vitamin D deficiency

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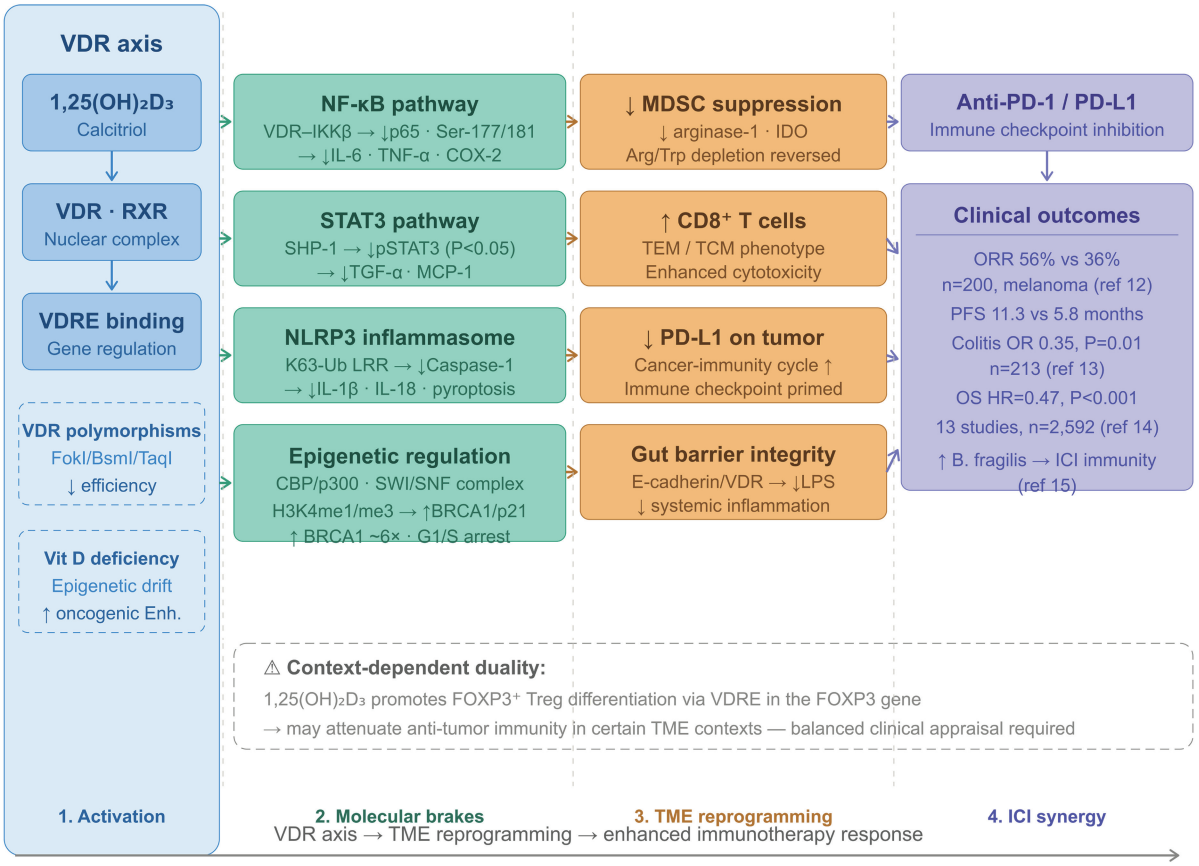

Fig. 1. The vitamin D/VDR axis as a multi-tiered immunometabolic brake on the tumor microenvironment: Molecular mechanisms and ICI synergy. BRCA1, breast cancer 1 susceptibility protein; CBP, CREB-binding protein; COX-2, cyclooxygenase-2; Enh., enhancer; HR, hazard ratio; ICI, immune checkpoint inhibitor; IDO, indoleamine 2,3-dioxygenase; IKKβ, IκB kinase β; IL, interleukin; LPS, lipopolysaccharide; LRR, leucine-rich repeat; MDSC, myeloid-derived suppressor cell; OR, odds ratio; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; SNF, Sucrose Non-Fermentable ; SWI, SWItch; TCM, central memory T cell; TEM, effector memory T cell; TNF-α, tumor necrosis factor alpha; Treg, regulatory T cell; VDR, vitamin D receptor; VDRE, vitamin D response element.

promotes epigenetic drift toward silencing of tumor-suppressor networks, a vulnerability further amplified by common VDR polymorphisms—particularly FokI (rs2228570), BsmI (rs1544410), and TaqI (rs731236)—which alter receptor conformational stability and transcriptional efficiency and may partly explain interindividual variation in vitamin D responsiveness in oncologic settings.[2] Critically, VDR and BRCA1 physically co-occupy vitamin D response elements at the p21 promoter, enhancing histone H3/H4 acetylation and inducing G1/S growth arrest in breast cancer cells—an effect abolished upon BRCA1 knockdown—demonstrating that the epigenetic competency of the VDR axis can translate into functionally relevant tumor-suppressive outcomes.[11]

The vitamin D/VDR axis demonstrates clinically meaningful synergy with immune checkpoint inhibitors (ICIs). In a prospective analysis of 200 patients with advanced melanoma receiving anti-programmed cell death protein 1 therapy (nivolumab or pembrolizumab), vitamin D sufficiency was associated with a superior objective response rate (ORR: 56.0% vs. 36.2%) and longer progression-free survival (PFS: 11.25 vs. 5.75 months). While these associations are compelling, they remain hypothesis-generating and may reflect residual confounding by performance status, nutritional state, and comorbidities in the absence of dedicated randomized controlled trials.[12] Vitamin D further mitigates immune-related adverse events. In a multicenter retrospective cohort of 213 melanoma patients receiving ICIs, pre-treatment vitamin D intake (n = 66/213; 31% of patients) independently conferred significantly reduced odds of ICI-induced colitis in multivariable regression analysis (odds ratio (OR) 0.35, 95% confidence interval (CI) 0.1–0.9, $P = 0.01$), findings externally validated in an independent cohort of 169 patients (OR 0.46, 95% CI 0.2–0.9, $P = 0.03$).[13] A systematic review and meta-analysis of 13 studies (n = 2,592 cancer patients receiving immunotherapy) further reported that higher vitamin D concentrations were independently associated with significantly improved overall survival (hazard ratio = 0.47, 95% CI 0.39–0.58, $P < 0.001$), PFS, and ORR. These effects are partly mediated by vitamin D-driven expansion of Bacteroides fragilis in the gut microbiome, amplifying ICI-dependent antitumor immunity.[14,15] Collectively, these data support vitamin D status as a potentially informative prognostic and predictive biomarker reflecting global host fitness but do not yet justify assuming that supplementation alone will improve immunotherapy response without adequately powered, prospective interventional trials.

Thus, the vitamin D/VDR axis constitutes a multi-tiered, druggable regulatory system operating at molecular, inflammasome, immunometabolic, epigenetic, and clinical levels (Fig. 1). The convergent mechanistic and clinical evidence justifies systematic

integration of vitamin D status assessment—and, where feasible, VDR or epigenomic profiling—into translational oncologic strategies, while acknowledging that context-dependent immunomodulation, residual host-related confounding, and the current absence of randomized immunotherapy-specific trial data necessitate cautious interpretation. Adequate interventional studies targeting defined 25(OH)D thresholds in ICI-treated populations represent the critical step toward establishing this axis as a validated therapeutic co-target.

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Conflict of interest

The authors declare no competing interests in relation to this work.

Author contributions

Contributed to study concept and design (HR), data acquisition (HR), data analysis (HR), drafting of the manuscript (HR), critical revision of the manuscript (HR, NB), and supervision (NB). Both authors have made significant contributions to this study and have approved the final manuscript.

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