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Commentary

The Yin and Yang of vitamin D receptor (VDR) signaling in neoplastic progression: Operational networks and tissue-specific growth control

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ABSTRACT

Substantive evidence implicates vitamin D receptor (VDR) or its natural ligand $1\alpha,25\text{-}(OH)_2\ D_3$ in modulation of tumor growth. However, both human and animal studies indicate tissue-specificity of effect. Epidemiological studies show both inverse and direct relationships between serum 25(OH)D levels and common solid cancers. VDR ablation affects carcinogen-induced tumorigenesis in a tissue-specific manner in model systems. Better understanding of the tissue-specificity of vitamin D-dependent molecular networks may provide insight into selective growth control by the seco-steroid, $1\alpha,25\text{-}(OH)_2\ D_3$. This commentary considers complex factors that may influence the cell- or tissue-specificity of $1\alpha,25\text{-}(OH)_2\ D_3$/VDR growth effects, including local synthesis, metabolism and transport of vitamin D and its metabolites, vitamin D receptor (VDR) expression and ligand-interactions, $1\alpha,25\text{-}(OH)_2\ D_3$ genomic and non-genomic actions, Ca^{2+} flux, kinase activation, VDR interactions with activating and inhibitory vitamin D responsive elements (VDREs) within target gene promoters, VDR coregulator recruitment and differential effects on key downstream growth regulatory genes. We highlight some differences of VDR growth control relevant to colonic, esophageal, prostate, pancreatic and other cancers and assess the potential for development of selective prevention or treatment strategies.

Keypoints

- Complex factors influence the cell- or tissue-specificity of vitamin D biological and growth effects, including local synthesis, metabolism and transport of vitamin D and its metabolites, vitamin D receptor (VDR) expression and ligand-interactions, $1\alpha,25\text{-}(OH)_2\ D_3$ genomic and non-genomic actions, $1\alpha,25\text{-}(OH)_2\ D_3$-mediated Ca^{2+} flux, kinase activation, VDR interactions with specific vitamin D responsive elements within target gene promoters, VDR coregulator recruitment and differential effects on key downstream target genes.
- Animal and in vitro studies show cell- or tissue-restricted vitamin D growth control.
- Epidemiological studies indicate vitamin D tissue-specific effects on neoplastic progression.
- E-cadherin and osteopontin (OPN) are functionally antagonistic VDR target genes that orchestrate the growth response to $1\alpha,25\text{-}(OH)_2\ D_3$ in diverse tumor types.
- Consideration of $1\alpha,25\text{-}(OH)_2\ D_3$-dependent signaling networks in a cell-lineage or tissue-specific context may shed light on its disparate growth regulatory effects and help exploit the promising therapeutic potential of VDR ligands, for selected cancers.

1. Introduction

1.1. The vitamin D endocrine system

Groundbreaking discoveries of the early 20th century elucidated vitamin D's essential role in calcium and phosphate homeostasis, bone mineralization and enabled major public health advances. The capacity of a novel fat-soluble vitamin that was distinct from vitamins A, B or C, for prevention of experimental

Abbreviations: $1\alpha,25\text{-}(OH)_2\ D_3$, one alpha, 25 dihydroxyvitamin D3; APC, adenomatous polyposis coli; CRC, colorectal cancer; DMBA, dimethylbenzanthracene; DR3-type, directly repeated arrangement of the hexameric binding sites with three spacing nucleotides; DRIP, Vitamin D receptor-interacting protein; ERK, extracellular signal-regulated kinase; GSK3β, glycogen synthase kinase beta; HDAC, histone deacetylator co-repressor complex; MAPK, mitogen-activated protein kinase; NCoR, nuclear receptor co-repressor; NHL, non-Hodgkins lymphoma; OPN, osteopontin; RAC3, receptor activated coactivators 3; ROCK, Rho-associated coiled kinase; RXR, retinoid X receptor; SRC-1, steroid receptor coactivators-1; Tcf, T cell factor; TIF2, transcriptional intermediary factor 2; TPA, 12-O-tetradecanoylphorbol-13-acetate; VDRE, vitamin D response element; VDR, vitamin D receptor; WINAC, Williams syndrome transcription factor (WSTF) including nucleosome assembly complex.

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Rickets was shown in a seminal study by Mellanby [1]. Subsequently, Chick et al. demonstrated that clinical Rickets could be cured by dietary cod liver oil supplementation or sunlight exposure [2]. The Nobel prize in Chemistry was awarded to Dr Adolf Windaus in 1928, in recognition of his achievement in isolation of vitamin D and demonstration of its steroid structure [3]. In the 1930s, fortification of milk with vitamin D virtually eradicated Rickets from the United States, although it had previously been a highly prevalent crippling disease of childhood [4].

The mammalian form of vitamin D is a fat-soluble prohormone cholecalciferol (vitamin D_3) that may be generated endogenously by ultraviolet light-mediated metabolism of the precursor sterol 7-dehydrocholesterol, in the skin. Alternatively, vitamin D_3 may be obtained from dietary sources [5]. This prohormone (cholecalciferol) is hydroxylated to 25-hydroxycholecalciferol ($25(OH)D_3$) by hepatocyte 25-hydroxylase. Further hydroxylation by 1α-hydroxylase (CYP27B1), into the main biologically active hormone, 1α 25-dihydroxycholecalciferol (1α,25-$(OH)_2$ D_3 or calcitriol) occurs in the proximal renal tubule in a tightly regulated fashion [6]. 1α,25-$(OH)_2$ D_3 then acts as a steroid chemical messenger in a diverse target tissues, in what is known as the vitamin D endocrine system [7]. To meet needs of bone mineralization, 1α,25-$(OH)_2$ D_3 stimulates intestinal calcium and phosphate absorption, bone calcium and phosphate metabolism as well as renal calcium and phosphate reabsorption, by differential effects on osteoblasts, chondrocytes, renal and intestinal epithelia [8]. Furthermore, discovery of VDR expression in diverse normal human tissues including B and T lymphocytes, the hair follicle, muscle, adipose tissue, bone marrow and in cancer cells has widened the perceived scope of the vitamin D endocrine system, beyond bone homeostasis [7].

1.2. 1α,25-$(OH)_2$ D_3 chemical structure and conformational relationships

1α,25-$(OH)_2$ D_3, the active form of vitamin D, is a highly flexible molecule with a steroid carbon skeleton, involving 4 fused cyclopentanoperhydro-phenanthrene rings, A–D. Unlike other steroids, the 9–10 carbon bond is broken, thus creating a conformationally flexible molecule in which the "A" ring may rotate (Fig. 1). The molecule is technically classified as a seco-steroid. The spatial arrangements of principal functional components of the 1α,25-$(OH)_2$ D_3 molecule comprise a hugely important determinant of its biological activities. *Cis–trans* isomerism influences stability and reactivity. The unusual degree of flexibility within 1α,25-$(OH)_2$ D_3 enables synthesis of structural analogs (Fig. 1b) that elicit well-defined subsets of the vitamin D response (see below) [9,10].

1.3. Vitamin D transport

Normally, only 0.04% of 25(OH)D and 0.4% of 1α,25-$(OH)_2$ D_3 are free in plasma, the remainder being tightly bound to either a vitamin D transporter protein (DBP) (85–88%; high affinity; dissociation constant [K_d] ~ 1 nM) [11] or albumin (12–15%; low affinity) [12]. Only free unbound vitamin D sterols are considered to be biologically active, since only the free form and not DBP-bound 1α,25-$(OH)_2$ D_3 induces metabolic responses in target cells [13]. In addition to transport, DBP functions to maintain stable serum stores of vitamin D metabolites, modulate bioavailability and influence responsiveness of some end-organs [14]. 1α,25-$(OH)_2$ D_3 binds to its "nuclear" receptor (VDR) with high affinity (dissociation constant value of [K_d] ~ 1 nM or lower) [15].

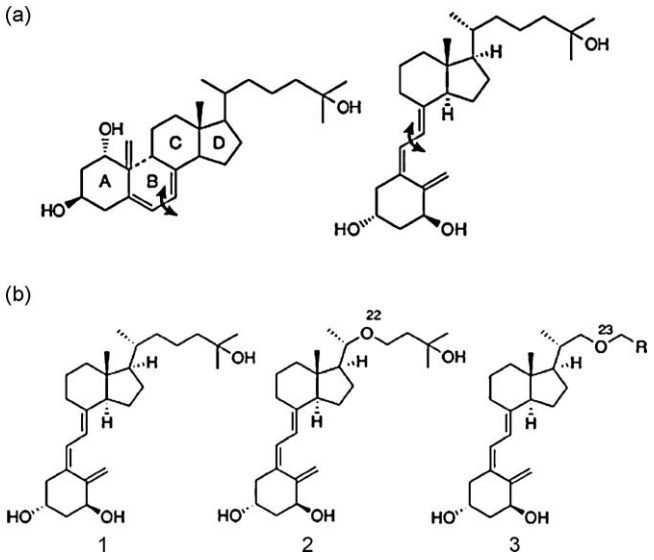

Fig. 1. Chemistry of 1α,25-$(OH)_2$ D_3. 1α,25-$(OH)_2$ D_3 is derived from the 4 cyclopentanoperhydro-phenanthrene ring structure (A, B, C, and D rings) for steroids. In 1α,25-$(OH)_2$ D_3, the 9,10 carbon–carbon bond of ring B is broken between ring A and rings C and D (arrow, a) and the molecule is technically classified as a seco-steroid. The molecule may then rotate along the bond between ring A and rings C and D (arrow), to provide the structure of 1α,25-$(OH)_2$ D_3 (a). Stepwise modification of the molecule, involving location of a oxygen atom at position 23 on the C and D ring side chain or removal of the terminal –OH group can have important biological effects (b).

1.4. The vitamin D receptor (VDR)

Free 1α,25-$(OH)_2$ D_3 enters the cell and binds the vitamin D receptor (VDR) (Fig. 2a), that may be present in the cytoplasm, nucleus or partitioned between the cytoplasm and nucleus [16]. VDR is an endocrine member of the nuclear receptor superfamily [8] with high structural and ligand-binding homology across various species [6]. Ligands for VDR include bile acid metabolites as well as 1α,25-$(OH)_2$ D_3 [17]. VDR has the same modular structure as other members of the nuclear receptor superfamily, including an N-terminal A/B region, a conserved DNA-binding domain, a flexible hinge region and a moderately conserved ligand-binding pocket that contains a dimerization interface and a ligand-dependent transcriptional activation domain, AF-2 [18] (Fig. 2a and b). Ligand binding induces a conformational change of the AF-2 region that allows dissociation of accessory proteins, exposure of the DNA-binding pocket and recruitment of coactivators [19]. Specific mutations that cause deletions, frameshift mutations, premature stop codons or splice site abnormalities that impede VDR expression or binding activity, effectively suppress key VDR actions [20].

1.5. 1α,25-$(OH)_2$ D_3/VDR mediated genomic responses

The 1α,25-$(OH)_2$ D_3/VDR complex functions to regulate gene transcription through heterodimerization with any of three retinoid X receptor (RXR) isoforms and binds to cognate vitamin D responsive elements (VDREs) in the promoter region of target genes. VDRE structures within promoter regions of primary 1α,25-$(OH)_2$ D_3 regulated genes can vary [21]. However, the majority of known VDREs show a DR3-type structure comprising a directly repeated arrangement of hexameric binding sites with 3 spacing nucleotides [22]. This arrangement provides the most efficient interface for VDR/RXR heterodimer binding to core VDREs. Subclasses of DR3 VDREs show some sequence variation but their in vivo functionality is proportional to their in vitro binding affinity