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REVIEW

Impact of vitamin D metabolism on clinical epigenetics

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Abstract The bioactive vitamin D (VD) metabolite, 1,25-dihydroxyvitamin D_3 regulates essential pathways of cellular metabolism and differentiation via its nuclear receptor (VDR). Molecular mechanisms which are known to play key roles in aging and cancer are mediated by complex processes involving epigenetic mechanisms contributing to efficiency of VD-activating CYP27A1 and CYP27B1 or inactivating CYP24 enzymes as well as VDR which binds to specific genomic sequences (VD response elements or VDREs). Activity of VDR can be modulated epigenetically by histone acetylation. It co-operates with other nuclear receptors which are influenced by histone acetyl transferases (HATs) as well as several types of histone deacetylases (HDACs). HDAC inhibitors (HDACi) and/or demethylating drugs may contribute to normalization of VD metabolism. Studies link VD signaling through the VDR directly to distinct molecular mechanisms of both HAT activity and the sirtuin class of HDACs (SIRT1) as well as the forkhead transcription factors thus contributing to elucidate complex epigenetic mechanisms for cancer preventive actions of VD.

Keywords Vitamin D · Epigenetics · Cancer

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Introduction

Apart from its original definition as a regulator of calcium homeostasis, vitamin D (VD) is now known to have a broad spectrum of actions as illustrated by a large number of diseases resulting from an insufficient VD supply or VD metabolism (Fig. 1). Interest in the role of epigenetics in VD metabolism is nourished by the fact that it influences many metabolic factors promoting a series of epigenetic mechanisms which are dysregulated in the etiology of numerous diseases. VD may be termed as a hormone because endogenous production of its essential precursor is UVB-stimulated photoconversion of 7-dehydrocholesterol in skin, in addition to a few dietary sources (Lin and White 2004), followed by processing via liver and kidney (Fig. 2). Several animal models of cancer have demonstrated the essential role of VD as a chemopreventive agent, mainly because it induces cell cycle arrest and influences cellular differentiation (Dace et al. 1997; Gurlek et al. 2002; Lin et al. 2002; Palmer et al. 2003). As early as 1986, it was postulated that calcitriol (the active form of VD) and a variety of VD analogs affect proliferation and differentiation of normal and leukemic cells of the myeloid line (Munker et al. 1986) and solid cancers (Peterlik et al. 2009).

Although previously termed as an inactive prohormone, it has been found that both calcidiol and calcitriol are active hormones and act together. Calcidiol uptake is mediated by megalin-mediated endocytosis of the VD binding protein calcidiol complex. This would determine the biological output of VD action (Tuohimaa 2009) and has the potential to reflect the clinical situation better than calcitriol. However, both calcidiol and calcitriol are active hormones and cofactors in hematopoiesis, thus explaining observations indicating a differentiating effect of VD on hematopoietic and

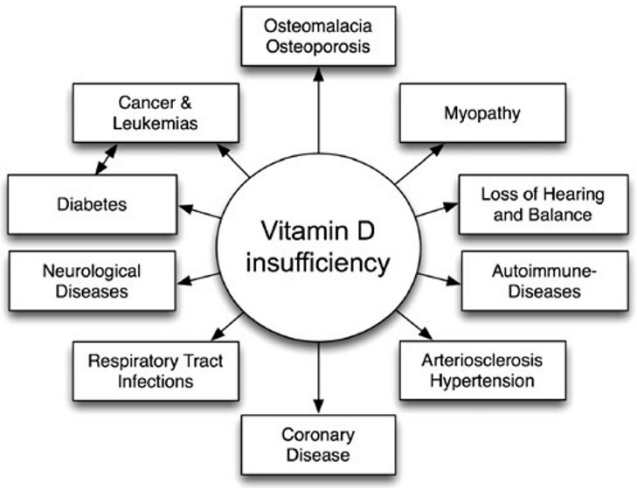

Fig. 1 Impact of vitamin D insufficiency in disease etiology. Insufficient uptake or metabolism of vitamin D appears to play a key role in the development of a multitude of diseases affecting the central nervous system, the skeleton and various organs where metabolic disturbances may contribute to the generation of malignancies

leukemic cells (Collins 1987; Sim et al. 2010), which may be enhanced through synergistic action with a demethylating drug (Koschmieder et al. 2007) that reduces epigenetic DNA methylation. Other than nutrients and vitamins such as folic acid (vitamin B_{12}), which act directly as donors of methylgroups involved in DNA promoter methylation or as inhibitors of this process (e.g., resveratrol) (Meeran et al. 2010), epigenetic activity of VD is mainly mediated through interaction with its receptor VDR. This may also be associated with expression of key enzymes CYP27A1 and CYP27B1 which are involved in conversion of vitamin D_3 to (pre-)hormones calcidiol and calcitriol and the inactivating enzyme CYP24A1 (Fig. 2) (Deeb et al. 2007; Diesel et al. 2005; Johnson et al. 2010).

Thus, both calcidiol and calcitriol mediate VD signaling to the VDR. VDR belongs to a large family of nuclear receptors binding small hydrophobic molecules like steroids, thyroid hormones and retinoids, and VD. It usually forms dimers, often with retinoid X receptors (RXR) (Nishikawa et al. 1994) and binds to specific genomic sequences (VD response elements or VDREs) which influence gene transcription. To regulate transcription, the VDR/RXR dimer interacts with histone acetyltransferases (HATs), which are known as transcriptional activators. HATs introduce acetyl groups into the nucleosomes, partially equalizing the basic capacity of histones, opening the chromatin and by this making it more accessible to transcription factors (Fujiki et al. 2005). Binding of the VDR/RXR complex to negative VDREs recruiting transcriptional co-repressors like NCOR1 and SMRT leading to histone deacetylation promotes transcriptional inactivation. Regulation of additional select aspects of metabolic functions involves co-repressors. An important co-repressor involved in metabolic regulation is receptor-interacting protein140 (RIP140). RIP140 is a transcriptional co-repressor of nuclear receptors such as the VDR. Thus, depletion of RIP140 in RIP140 null mice enhances the activity of VDR and contributes to the insulin-sensitive and lean phenotype of these animals (Christian et al. 2006; Lin et al. 2002).

Considering observations indicating that epigenetic effects of calcitriol are primarily observed as histone modifications, especially acetylation, the observation of demethylating effects of VD on the promoter DNA of osteocalcin (Haslberger et al. 2006) may be interpreted as a consequence of the above-mentioned chromatin modifications. In addition to (epi)genomic actions, a non-genomic activity of VDR is discussed as well, although, both effects seem to converge (Andraos et al. 2010; Ordonez-Moran and Munoz 2009). However, to the best of our knowledge, it has not yet been convincingly documented that VDR is subject of cytogenetic rearrangements or that mutations of the VDR directly associate with tumor development. Although a number of polymorphic variations of the VDR protein were associated variously with cancer incidence, degree of aggressiveness and metastasis (Peterlik et al. 2009), it becomes increasingly

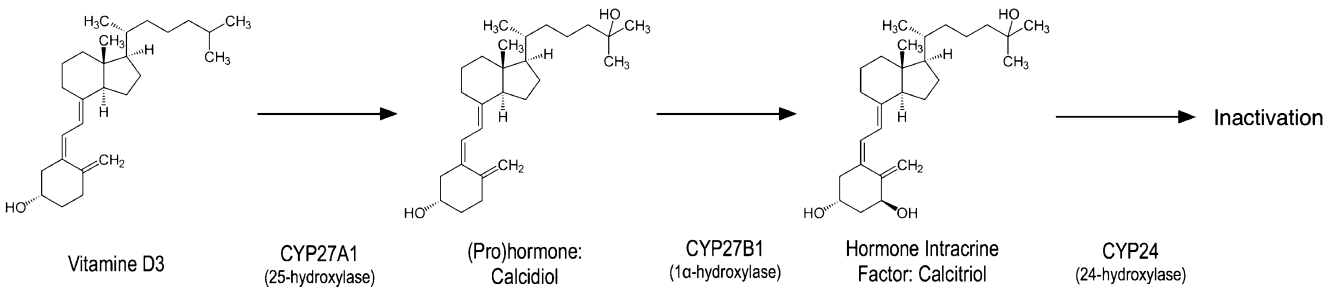

Fig. 2 Synthesis and catabolism of calcitriol. In a multistep process vitamin D3 (cholecalciferol) is hydroxylated by liver mitochondrial and microsomal 25-hydroxylase (25-OHase) CYP27A1. The resultant pre-hormone 25-hydroxycholecalciferol, named in this figure as calcidiol is 1α hydroxylated in the kidney by CYP27B1 (a mitochondrial 1α-hydroxylase). This yields the hormonally active secosteroid 1α $25(OH)_2D_3$ (calcitriol). 24-hydroxylation of $25(OH)D_3$ and 1α $25(OH)_2D_3$ by the cytochrome P450 enzyme25-hydroxyvitamin D24-hydroxylase CYP24A1 is the rate-limiting step for calcitriol catabolism

clear that epigenetic mechanisms play a key role in regulating transcriptional responsiveness of VDR.

Vitamin D receptor co-operates with other epigenetically regulated nuclear receptors mediating response to lipophilic nutrients and metabolism

Nuclear receptors sensitive for a magnitude of primary or secondary metabolites interact either directly or indirectly with VDR in regulating gene expression. Such interactions are known to recruit histone-modifying enzymes that are either organized into transcription-inactivating, or in the majority of cases, -activating protein complexes (Fig. 3).

The patterns of *VDR*-associated co-activators appear to be unique for regulation of different genes: *RUNX2*, *EP300*, and *SCR1* are associated with *VDR* in the osteocalcin promoter, whereas *MYBB1A* (also described as P160/SRC) together with other mediators such as *MED1* (also described as DRIP) co-activate *VDR* in the *SPP1* (osteopontin) promoter (Montecino et al. 2007). Interestingly, cancer-related ectopic expression of the bone-related transcription factor *RUNX2* in non-osseous metastatic tumor cells is linked to metastatic cell proliferation and motility (Leong et al. 2010), which may also induce production of osteocalcin in metastases of solid tumors (Gao et al. 2010; Ou et al. 2003) as well as leukemias (Wihlidal et al. 2006; Wihlidal et al. 2008). This is in contrast to effects *of RUNX2* on osteoblasts, where it attenuates proliferation and stimulates maturation, but underlines the crucial role of *VDR/RUNX2* association in regulating essential features of cellular physiology.

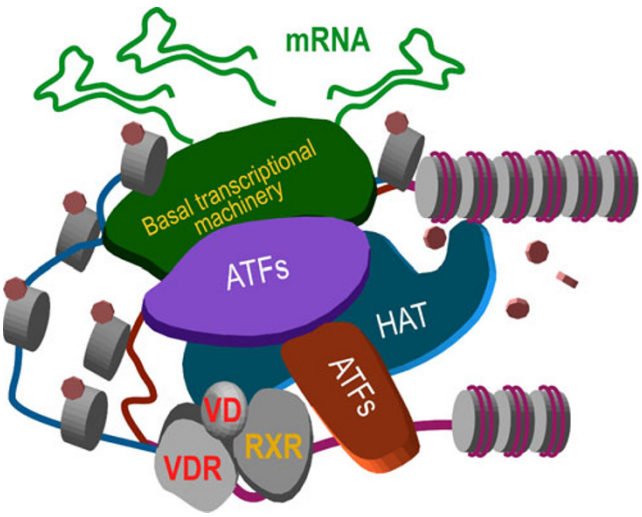

Fig. 3 Schematic illustration of epigenetic activity mediated by vitamin D_3 (VD). VD exerts its activity in association with its receptor (VDR) and other nuclear receptors such as the RXR and HAT, which transfers acetyl groups to histones and consequently loosens DNA structure resulting in activation of gene expression (probably including DNA demethylation). The chromatin of a previously inactive gene becomes relaxed upon binding of transcription factors to DNA recognition sequences. This process may be counteracted by recruitment of CBFA partner proteins such as TLE that interact with factors having HDAC activity

Figure 4 illustrates observations of cooperativity between VDR and other nuclear receptors. These may be localized more or less proximal or distal of VDR, with distances of up to several hundreds of base pairs, which can be overcome by loop domains of the transcriptional complex as recently shown by extensive structural studies on the assembly of the hematopoietic transcription factor complex (El Omari et al. 2010). Endogenous compounds such as bile acids, retinoids, steroid hormones, and thyroid hormones, which interact with liver X receptors, farnesoid X receptor, pregnane X receptor, retinoic receptors (RAR and RXR) and thyroid hormone receptors (TR) cooperate with VDR. Some of these ligands like bile salts activate multiple receptors (Makishima et al. 2002). Furthermore, lipids (Correale et al. 2010) are endogenous ligands for the peroxisome proliferator-activated receptors (PPARs) linking them directly to metabolism. An association of PPARs with the VDR signaling pathway was recently suggested (Sertznig et al. 2009).

Last but not least, sex steroid hormone receptors such as the estrogen (ESR1 and ESR2), progesterone and androgen receptors, whose expression may be epigenetically downregulated in malignancies also bind ligands with high affinity (Nicolaiew et al. 2009; Sasaki et al. 2002; Walton et al. 2008; Yao et al. 2009). The functional synergy between estradiol and calcitriol is based on co-operative epigenetic activities of their nuclear receptors (Carlberg and Seuter 2010). Clinical results indicate that estrogen promotes calcitriol metabolism, suggesting a greater protective effect of calcitriol-based therapeutic strategies against multiple sclerosis in women (Correale et al. 2010) as well as successful integration of calcitriol in combined treatment strategies against osteoporosis for post-menopausal females (Miller and Derman 2010). Beyond the endogenous ligands, nutritional as well as synthetic components exist that regulate the above-mentioned receptors, frequently involving described epigenetic mechanisms (Berner et al. 2010).

Epigenetic inactivation of VDR impairs activity of VD

Research on epigenetic resistance intends to explore epigenetic mechanisms, inhibiting VDR signaling. For example, it has been proposed that apparent calcitriol insensitivity is not determined solely by a linear relationship between the levels of calcitriol and the VDR, but rather epigenetic events such as methylation of VDR promoter (Marik et al. 2010), VDR-governed epigenetic control of other tumor suppressor genes (Thorne et al. 2010) or VDR microRNA (Essa et al. 2010) regulate the responsiveness of

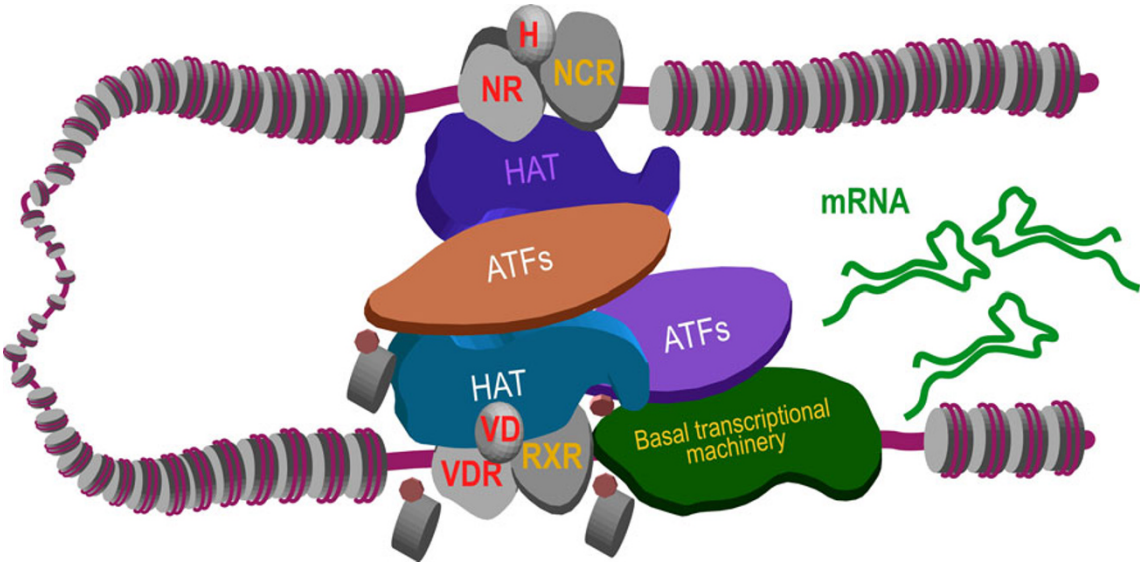

Fig. 4 Cooperativity between VDR and other nuclear receptors (NFRs) and linking to the basal transcriptional machinery. Accessory transcription factors (ATFs) may be localized more or less proximal or distal of VDR, with distances of up to several hundreds of base pairs, which can be overcome by loop domains of the transcriptional complex

target gene promoters. Epigenetically active drugs have the potential to reverse calcitriol insensitivity as evidenced by gene expression studies. Enhancement of VD efficiency for monocytic differentiation by DAC (5-aza-2-desoxycytidine, decitabine) indicates a synergistic role of demethylation in VD metabolism (Koschmieder et al. 2007). Microarray studies demonstrated that VDR reactivation induced by the histone deacetylase (HDAC) inhibitor trichostatin A (TSA) plus calcitriol uniquely upregulated a group of "repressed" gene targets associated with the control of proliferation and induction of apoptosis (Khanim et al. 2004; Rashid et al. 2001).

An association between HDAC regulation and energy metabolism was further confirmed by a recent study which demonstrated the downregulating effect of an HDAC-inhibiting drug (vorinostat) on energy metabolism of leukemic cells (Karlic et al. 2010). The leukemic differentiation block is attributed to deregulated transcription, which may be caused by leukemic fusion proteins aberrantly recruiting HDAC activity. One essential differentiation pathway blocked by the leukemic fusion proteins is calcitriol signaling. Puccetti and co-workers (Puccetti et al. 2002) investigated the mechanisms by which the leukemic fusion proteins interfere with calcitriol-induced differentiation. The VDR is, like the retinoid receptors RAR, RXR, and the TR, a ligand-inducible transcription factor. In the absence of ligand, the transcriptional activity of TR and RAR is silenced by recruitment of HDAC activity through binding to co-repressors. In the presence of ligand, TR and RAR activate transcription by releasing HDAC activity and by recruiting HAT activity (Martens et al. 2010; Zelent et al. 2005). VDR binds co-repressors in a ligand-dependent manner and inhibition of HDAC activity increases calcitriol sensitivity of HL-60 cells. It has been shown that the expression of the translocation products PML/RARalpha and PLZF/RARalpha impair the localization of VDR in the nucleus by binding to VDR.

Considering breast cancer, a similar spectrum of reduced calcitriol responsiveness between non-malignant breast epithelial cells and cancer cell lines has been shown in parallel studies (Abedin et al. 2006). Again, this was not determined solely by a linear relationship between the levels of calcitriol and *VDR* mRNA expression. Rather elevated mRNA levels from co-repressors notably *NCOR1*, in breast cancer cell lines were observed and determined sensitivity towards calcitriol (Banwell et al. 2004). By exploring elevated co-repressor levels in both cancer cell lines and primary cultures (Abedin et al. 2006), it was reasoned that this could be targeted by co-treatment of calcitriol plus the HDAC inhibitor TSA. Supportively, it was demonstrated that calcitriol response of androgen-independent PC-3 cells was restored to levels indistinguishable from control normal prostate epithelial cells, by co-treatment with low doses of TSA (Banwell et al. 2004). Treatment with calcitriol plus TSA appears to coordinately regulate the *CDKN1A* (=P21) mRNA expression; notably upregulating the target in a unique manner in breast cancer cells (MDA-MB-231) (Banwell et al. 2004). Such data compliment a number of parallel studies, indicating cooperativity between calcitriol and butyrate compounds, such as sodium butyrate (NaB) (Costa and Feldman 1987; Daniel et al. 2004; Gaschott et al. 2001a; Gaschott et al.

2001b; Gaschott and Stein 2003; Newmark and Young 1995; Tanaka et al. 1989). These studies further underscore the importance of the dietary derived milieu to regulate epithelial proliferation and differentiation beyond classic sites of action in the gut (Hippe et al. 2010).

The interaction of un-liganded VDR with co-repressors recruiting multiprotein complexes containing HDACs appears to be responsible for anti-proliferative effects of HDAC inhibitors and calcitriol together with induction of genes of the cyclin-dependent kinase inhibitor (CDKI) family (i.e., *CDKN2B*=P15 or *CDKN2A*=P16). Results of chromatin immunoprecipitation and RNA inhibition assays showed that the co-repressor NCOR1 and some HDAC family members complexed un-liganded VDR and repressed the basal level of CDKI genes, but their roles in regulating CDKI gene expression by TSA and calcitriol were contrary. *HDAC3* and *HDAC7* attenuated calcitriol-dependent induction of the *CDKN1A* gene, for which *NCOR1* is essential. In contrast, TSA-mediated induction of the *CDKN2C* (=P18) gene was dependent on *HDAC3* and *HDAC4*, but was opposed by *NCOR1* and un-liganded VDR. This indicates that the attenuation of the response to TSA by *NCOR1* or to calcitriol by HDACs can be overcome by their combined application achieving maximal induction of anti-proliferative target genes (Malinen et al. 2008).

Histone deacetylase inhibitors TSA and NaB and the methylation inhibitor DAC have the potential to promote VD-induced apoptosis through *PTEN* upregulation (Pan et al. 2010). Results suggest potential benefits of VD in gastric cancer therapies in association with the use of TSA/NaB and DAC. Targeted co-treatments of calcitriol plus HDAC inhibitors (TSA, NaB) resulted in re-expression of anti-proliferative target genes (e.g. *GADD45alpha*, *CDKN1A*) and synergistic inhibition of proliferation. These data suggest that VDR actions in solid tumors are retained, but may be skewed by epigenetic mechanisms to suppress selectively anti-proliferative target gene promoter responses. This molecular lesion provides a novel chemotherapy target for acceptable doses of calcitriol plus HDAC inhibitors (Abedin et al. 2006). Many HDAC inhibitors are short-chain fatty acids (Chen et al. 2003), thus playing a key role in regulating the activity of VDR.

The association of VDR and transcriptional regulation was confirmed and analyzed in detail in a recent study (An et al. 2010). Forkhead box O (FOXO) regulation can be modulated by VDR. Calcitriol-mediated activation of VDR stimulates attachment of FOXO3A and FOXO4 to promoters of their target genes. In addition to FOXO proteins, VDR also binds to additional epigenetic regulators such as sirtuin (SIRT1). Thus, sirtuin HDACs may act as cancer suppressors while under other circumstances they may promote cellular malignancy (Voelter-Mahlknecht and Mahlknecht 2010). Age- and diet-related metabolic disturbances are associated with loss of *SIRT* activity and corresponding defects in glucose metabolism and mitochondrial function. Under conditions of restricted caloric intake which may be favored by VD (Lynch 2010, Shahar et al. 2010), *SIRT1* activity is enhanced in various tissues along with improvements in metabolic function and longevity (Lonard et al. 2007). *SIRT4* directly targets mitochondria. *SIRT6* is involved in the nuclear regulation of genes playing a role in metabolic physiology; it also contributes to genomic stability, and its loss leads to an aging-like phenotype. Given the significant structural differences in the sirtuin class of HDACs and their distinctly different enzymatic mechanism from non-sirtuin HDACs, this class of proteins represents promising targets for the design of new drugs (Lonard et al. 2007). These studies link calcitriol signaling through the VDR directly to the sirtuin class of HDACs and provide a molecular basis for the cancer chemopreventive actions of calcitriol (Voelter-Mahlknecht and Mahlknecht 2010).

Conclusion

The efficiency of VD in prevention and treatment of cancer is highly dependent on epigenetic modifications of its receptor and the resulting signaling cascade. Combination of either VDR or other nuclear receptor ligands with potent HDAC inhibitors and possibly also demethylating drugs has the potential to deliver more focused and sustained treatment regimes for a range of solid tumors and leukemias. Additionally, VD/VDR regulates epigenetic DNA methylation and modulates gene expression. However, considering the heterogeneity of factors interacting with VD metabolism, observations of “in vitro” and “in vivo” studies should be carefully interpreted.

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Conflict of interest Authors indicate that they do not have any potential conflicts of interest.

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