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Vitamin D receptor, a tumor suppressor in skin[1]

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Abstract

Vitamin D and calcium are well-established regulators of keratinocyte proliferation and differentiation. Therefore, it was not a great surprise that deletion of the vitamin D receptor (VDR) should predispose the skin to tumor formation, and that the combination of deleting both the VDR and calcium sensing receptor (CaSR) should be especially pro-oncogenic. In this review I have examined 4 mechanisms that appear to underlie the means by which VDR acts as a tumor suppressor in skin. First, DNA damage repair is curtailed in the absence of the VDR, allowing mutations in DNA to accumulate. Second and third involve the increased activation of the hedgehog and β-catenin pathways in the epidermis in the absence of the VDR, leading to poorly regulated proliferation with reduced differentiation. Finally, VDR deletion leads to a shift in the expression of long noncoding RNAs toward a more oncogenic profile. How these different mechanisms interact and their relative importance in the predisposition of the VDR null epidermis to tumor formation remain under active investigation.

Résumé :

La vitamine D et le calcium sont des régulateurs bien établis de la prolifération et de la différenciation des kératinocytes. Ainsi, il n'est pas surprenant de constater que la délétion du récepteur de la vitamine D (VDR) prédispose à la formation de tumeurs cutanées, et que la combinaison de la délétion du VDR et du récepteur de détection de calcium (CaSR ; *Calcium sensing receptor*) soit particulièrement pro-oncogénique. Dans cet article de revue, l'auteur a examiné quatre mécanismes qui semblent sous-tendre les moyens par lesquels le VDR agit comme suppresseur de tumeurs cutanées. D'abord, la réparation du dommage à l'ADN est restreinte par l'absence du VDR, permettant aux mutations dans l'ADN de s'accumuler. Les deuxième et troisième mécanismes impliquent l'activation accrue des voies hedgehog et β-caténine dans l'épiderme en absence de VDR, conduisant à une prolifération faiblement régulée et une différenciation réduite. Finalement, la délétion du VDR mène à un changement de l'expression de longs ARN non codants vers un profil plus oncogénique. La recherche se poursuit activement afin de comprendre comment ces différents mécanismes interagissent, ainsi que leur relative importance dans la prédisposition de l'épiderme depourvu de VDR à la formation tumorale. [Traduit par la Rédaction]

Keywords

calcium; epidermis; DNA damage repair; hedgehog; catenin; LncRNA

Mots-clés

épiderme; réparation du dommage à l'ADN; caténine; long ARNnc

Introduction

Over 1 million skin cancers occur annually in the United States, 80% of which are basal cell carcinomas (BCC), 16% squamous cell carcinomas (SCC), and 4% melanomas, making skin cancer by far the most common cancer afflicting humankind (Greenlee et al. 2001). Ultraviolet radiation (UVR) from the sun is the major etiologic agent for these cancers. Of the solar radiation that does reach the earth, 95% is UVA and 5% is UVB. UVB (280–320 nm), although it does not penetrate past the epidermis, is absorbed by DNA in the epidermal cells creating characteristic mutations identified as cyclobutane pyrimidine dimers (CPDs) and pyrimidine(6-4)pyrimidone photoproducts (6-4PP), which if not repaired result in C to T or CC to TT mutations, the UVB "signature" lesion (Freeman et al. 1989; Hussein 2005). UV wavelengths between 320–400 nm (UVA) are capable of penetrating into the dermis, and do their DNA damage (e.g., 8 hydroxy $2'$ deoxyguanosine production) primarily by oxidative processes, although at high enough dose levels UVA can also produce CPDs (Besaratinia et al. 2005). On the other hand, UVB is required to convert 7-dehydrocholesterol levels in the skin to pre-vitamin D_3, which then isomerizes to vitamin D_3. The amount of UVB required to produce vitamin D in the skin is suberythemal (18 mJ/cm^2 in white males with class III pigmentation) (Matsuoka et al. 1989). Moreover, the skin is capable of converting vitamin D to its active metabolite $1,25(OH)_2D$ (Bikle et al. 1986), and this conversion is potentiated by UVR at least in part by cytokines such as tumor necrosis factor-α (TNFα)(Bikle et al. 1991), which are increased by UVR in the epidermis (Muthusamy and Piva 2009). Both melanocytes (Colston et al. 1982) and keratinocytes (Pillai et al. 1988) express the vitamin D receptor (VDR) and respond to $1,25(OH)_2D$ with reduced proliferation and increased differentiation (Colston et al. 1981; Bikle 2012). We have pursued the hypothesis that the $1,25(OH)_2D$ produced in the skin under the influence of UVB acting through its VDR, provides protection against UVB-induced tumors. Moreover, we have found that many of the actions of $1,25(OH)_2D$ in the skin are duplicated and (or) potentiated by calcium acting through its receptor, CaSR (Bikle et al. 2012). Most recently we found that mice lacking both the CaSR and the VDR in their skin develop tumors spontaneously, unlike mice lacking either the CaSR or VDR alone (Bikle et al. 2014). This article will review the mechanisms that we believe underlie the protection of VDR and CaSR for tumor development in the skin.

Calcium and 1,25(OH)₂D interact to regulate keratinocyte proliferation and differentiation

Calcium and 1,25(OH)$_2$D are critical for keratinocyte differentiation. If keratinocytes are grown at calcium concentrations below 0.07 mmol/L, they continue to proliferate but fail or are slow to develop intercellular contacts, stratify little if at all, and fail or are slow to form cornified envelopes. Acutely increasing the extracellular calcium concentration (Ca$_o$) above 0.1 mmol/L (calcium switch) leads to the rapid redistribution of a number of proteins from the cytosol to the membrane, where they participate in the formation of intercellular contacts. These include the calcium-sensing receptor (CaSR), phospholipase C-γ1 (PLCG1), Src family of tyrosine kinases, and the formation of the E-cadherin/catenin (CDH1/CTNN) complex with phosphatidyl inositol 3 kinase (PI3K), various catenins (CTNN) including β-catenin (CTNNB1), and phosphatidyl inositol 4-phosphate 5-kinase 1α (PIP5K1A), all of which play important roles in calcium-induced differentiation (Tu et al. 2001, 2005, 2008; Xie et al. 2005, 2009; Xie and Bikle 2007). Within hours of the calcium switch the keratinocytes begin making keratins KRT1 and KRT10 (Yuspa et al. 1989) followed by increased levels of profilaggrin (the precursor of filaggrin [FLG]), involucrin (IVL), loricrin (LOR), and other proteins that are cross-linked into the insoluble cornified envelope by the calcium induced transglutaminase 1 (TGM1) (Thacher and Rice 1985; Hohl 1990).

The CaSR is essential for these responses to calcium (Tu et al. 2004, 2008, 2011, 2012). Its role in the formation of the CDH1/CTNN complex and actin reorganization critical for the differentiation process is mediated through filamin (FLN)/RHOA (Tu et al. 2011). The CaSR is a 7-transmembrane domain, G-protein coupled receptor first identified in parathyroid cells (Brown et al. 1993) that we cloned from keratinocytes (Oda et al. 1998). We then developed a mouse in which the exon (exon 7) encoding the entire transmembrane domain and intracellular portion of the *Casr* is floxed, enabling its deletion in keratinocytes (and other cells) (Chang et al. 2008; Tu et al. 2008). We have used this model to demonstrate in vivo the role of CaSR in calcium signaling within the keratinocyte, and its importance in differentiation (Tu et al. 2008, 2012). In particular, mice lacking the CaSR fail to develop a normal permeability barrier, with decrements in the production of both the protein and lipid components, and demonstrate a defective innate immune response similar to what is seen in mice lacking the VDR or CYP27B1 (the enzyme producing 1,25(OH)$_2$D). These defects may be due in part to the reduction in expression of *Vdr* and *Cyp27b1* in these mice (Tu et al. 2012), indicating that as much as 1,25(OH)$_2$D/VDR induces *Casr* (see below), calcium/CaSR induces *Vdr* and *Cyp27b1*.

The expression of *Casr* is induced by 1,25(OH)$_2$D (Canaff and Hendy 2002), making the keratinocyte more sensitive to the prodifferentiating actions of calcium (Ratnam et al. 1999), just as calcium enhances the prodifferentiating actions of 1,25(OH)$_2$D (Su et al. 1994). All of the phospholipase C (*Plc*) family members are induced by 1,25(OH)$_2$D (Xie and Bikle 1997) as they are by calcium (Xie and Bikle 1999), and blocking phospholipase C-γ1 (*Plcg1*) expression prevents both 1,25(OH)$_2$D- and calcium-stimulated differentiation (Xie and Bikle 1999, 2001). Both calcium and 1,25(OH)$_2$D inhibit keratinocyte proliferation. The antiproliferative effects are accompanied by a reduction in the expression *Myc*

(Matsumoto et al. 1990) and *Ccnd1* (Bikle 2011) and an increase in the levels of cell cycle inhibitors CDKN1A (a.k.a., p21^{cip}) and CDKN1B (a.k.a., p27^{kip}). Like calcium/CaSR, 1,25(OH)$_2$D/VDR regulates the processing of the long chain glycosylceramides that are critical for permeability-barrier formation (Oda et al. 2009) and induce the receptors, Toll-like receptor 2 (TLR2) and its coreceptor CD14, which initiate the innate immune response in skin (Schauber et al. 2007). Activation of these receptors leads to the induction of CYP27B1, the product of which, 1,25(OH)$_2$D, induces cathelicidin (CAMP) production resulting in the killing of invasive organisms (Schauber et al. 2006, 2007). The roles of calcium/CaSR and 1,25(OH)$_2$D/VDR in immune regulation may contribute to their roles in protection of the skin against malignant transformation, although this has received little study.

Mechanisms by which VDR and CaSR provide cancer protection

The role of VDR as protection against epidermal tumor formation was demonstrated when Zinser et al. (2002) showed that 85% of *Vdr* null mice but none of the controls developed skin tumors within 2 months following 7,12 dimethylbenzanthracene (DMBA) administration. These were primarily papillomas. These results have been confirmed using topical administration of DMBA/TPA (Indra et al. 2007). However, although only papillomas were seen in the *Vdr* null mice, subsequently, Ellison et al. (2008) and our own group (Teichert et al. 2011) demonstrated that *Vdr* null mice were also more susceptible to tumor formation following UVB exposure, and many of the tumors were SCC. Our interest in the potential for calcium/CaSR providing additional protection against epidermal tumor formation was piqued when we discovered that the double knockout of *Vdr* and *Casr* in keratinocytes (^{epid}*Vdr*$^{-/-}$ / ^{epid}Casr$^{-/-}$, DKO) resulted in spontaneous tumor formation that we had not observed in mice in which either gene was deleted. The role of calcium/CaSR in the prevention of cancer is not unprecedented, as its involvement in colorectal cancer has been implicated in a number of studies with human colorectal cancer cell lines (Chakrabarty et al. 2003, 2005; Bhagavathula et al. 2007; Liu et al. 2010; Wang et al. 2010). In colorectal cancer, the major initiating lesion is a mutated *Apc* resulting in increased WNT/CTNNB1 signaling. Activating this pathway increases proliferation and reduces apoptosis, whereas inhibition of this pathway has the opposite effect in these cells (Varnat et al. 2009) or tumors in *Apc*^{tm1Mmt} mice (Arimura et al. 2009). Calcium via the CaSR blocks the transcriptional activity of CTNNB1 in part by increasing CDH1 translocation to the plasma membrane where it forms the CDH1/CTNN complex, much as it does in keratinocytes (Chakrabarty et al. 2003). As in the keratinocyte, the actions of calcium are synergistic with 1,25(OH)$_2$D. 1,25(OH)$_2$D induces the CaSR in colon cancer cells (Chakrabarty et al. 2005), and both calcium and 1,25(OH)$_2$D inhibit proliferation of these cells by increasing the cell cycle inhibitors CDKN1A and CDKN1B, while reducing the levels of MYC, CCND1, survivin (BIRC5), and thymidylate synthase (TYMS) (Bhagavathula et al. 2007; Liu et al. 2010). Moreover, 1,25(OH)$_2$D induces dickkopf 1 (DKK1), an inhibitor of WNT/CTNNB1 signaling (Pendas-Franco et al. 2008). When we (Rey et al. 2011) deleted *Casr* specifically in the intestinal epithelium, hyperproliferation was observed in these cells with increased localization of CTNNB1 in the nuclei. As in the skin, deletion of *Vdr* in the intestinal epithelium does not result in spontaneous tumors, but predisposes to tumor formation

following exposure to a carcinogen (Byers et al. 2011). DKO mice lacking both intestinal CaSR and VDR have not been tested. We now turn to 4 mechanisms in the epidermis that appear to underlie the role of VDR as a tumor suppressor in skin.

DNA damage repair

Part of the predisposition to tumor formation in the VDR null epidermis is due to a defective DNA damage repair process (Demetriou et al. 2012). UVB-induced DNA damage includes the formation of cyclobutane pyrimidine dimers (CPD) and pyrimidine (6-4)pyrimidone photoproducts (6-4PP). If these lesions are not repaired, C to T or CC to TT mutations result, the UVB "signature" lesion (Hussein 2005). Actinic keratoses, the precursor lesion to SCC, as well as SCC and BCC contain these mutations in genes such as p53 (Brash et al. 1991; Ziegler et al. 1993,1994; Bito et al. 1995; Daya-Grosjean and Sarasin 2005). Preventing UVB-induced DNA damage from producing DNA mutations is the role of DDR operating through mechanisms involving damage recognition, repair, and signal transduction. Nucleotide excision repair (NER) is the principal means by which UVB damage is repaired. By removing DNA damage before DNA replication begins, NER can eliminate DNA damage that would otherwise result in mutations that get incorporated into the DNA during replication (Chen et al. 1990; Wood 1999). The 2 major processes used by NER include transcription-coupled repair (TCR), involving the repair of genes undergoing active transcription, and global genomic repair (GGR) for the non-transcribed regions of the genome (Mellon et al. 1986; Hanawalt 1994; Wood et al. 2001). Heritable mutations in NER genes occur in several human diseases with increased susceptibility to UVB-induced epidermal malignancies, such as xeroderma pigmentosum (XP) and Cockayne syndrome (CS) (Wood et al. 2001). Identification of the genes mutated in these diseases has assisted substantially in identifying the genes and their protein products critical for DDR.

The epidermis of VDR null mice demonstrates a marked reduction in the clearance of CPDs and 6,4PPs following UVB, whether administered in vivo (Teichert et al. 2011) or in vitro (Demetriou et al. 2012). The Mason laboratory (Dixon et al. 2005; Gupta et al. 2007) has demonstrated that 1,25(OH)$_2$D, when topically applied, protects the skin from UVB-induced photodamage, including increased clearance of CPDs, decreased apoptosis, increased survival, and increased expression of p53. These effects do not appear to require genomic actions of VDR, as analogs of 1,25(OH)$_2$D that promote nongenomic actions of the VDR are equally effective. Moreover, using fibroblasts with mutations of the VDR that prevents its genomic actions but not its binding to 1,25(OH)$_2$D, this laboratory demonstrated photoprotective effects comparable with that in normal cells (Sequeira et al. 2012). VDR null cells did not show a protective effect, however (Sequeira et al. 2012). Whether these results will apply in vivo in the epidermis in keratinocytes is not known. On the other hand, Moll et al. (2007) found that 1,25(OH)$_2$D induced 2 genes important for DDR: XPC (xeroderma pigmentosum complementation group C) and DDB2 (damage-specific DNA binding protein 2, also known as XPE). Thus, 1,25(OH)$_2$D may have genomic and nongenomic actions to enhance DDR, although in all cases the VDR is required. Much remains to be investigated in terms of vitamin D signaling and DDR.

The hedgehog (HH) pathway in epidermal tumor formation

The appearance of BCC is characteristic of tumors formed when HH signaling is activated (Hahn et al. 1996), although UVR-induced SCC formation is also increased (Ping et al. 2001). Appreciation of the pivotal role of the HH signaling pathway in BCC development began with the identification of the *PTCH1* gene as the site of mutations underlying the rare autosomal dominant heritable basal cell nevus syndrome (BCNS) (Gorlin Syndrome), one of whose cardinal features is a high susceptibility to the development of BCCs (Hahn et al. 1996; Aszterbaum et al. 1998). The BCCs in these subjects frequently lose function of the inherited wildtype *PTCH1* allele, leaving the tumor cells functionally devoid of PTCH1. Subsequently it has become clear that essentially all BCCs, whether arising in patients with BCNS or sporadically, have mutations in *PTCH1* or other alterations in HH signaling (Aszterbaum et al. 1998). This appreciation has resulted in the development of the *Ptch1*^{tm1Mps} (Gorlin) mouse as the first practical model of mouse BCCs (Aszterbaum et al. 1999). UVR or ionizing radiation readily induces BCC as well as SCC in these mice.

PTCH1 is the membrane receptor for sonic hedgehog (SHH) in the skin. In the absence of SHH, PTCH1 inhibits the function of another membrane protein smoothened (SMO). SHH reverses this inhibition, freeing SMO to enable the activation of a family of transcription factors, GLI1, GLI2, and GLI3. GLI3 is primarily a repressor, whereas GLI1 is primarily an activator and GLI2 can either activate or repress transcription (Mimeault and Batra 2010). Suppressor of fused (SUFU) maintains these transcription factors in the cytoplasm and (or) limits their activity in the nucleus (Barnfield et al. 2005; Svard et al. 2006). GLI1 and 2 overexpression in keratinocytes can increase the expression of each other as well as PTCH1, the antiapoptotic factor BCL2, CCND1,2, E2F1, CDC45 (all of which promote proliferation) while suppressing genes associated with keratinocyte differentiation such as KRT1, KRT10, IVL, LOR, and VDR (Grachtchouk et al. 2000; Nilsson et al. 2000; Regl et al. 2002, 2004a, 2004b). Mice overexpressing GLI1, GLI2, or SHH in their basal keratinocytes (Oro et al. 1997; Grachtchouk et al. 2000; Nilsson et al. 2000) or grafted with human keratinocytes overexpressing SHH (Fan et al. 1997) develop BCC-like lesions. Furthermore, BCC show overexpression of PTCH1, SMO, GLI1, and GLI2 (Tojo et al. 1999; Bonifas et al. 2000).

We (Teichert et al. 2011) have found that the epidermis and epidermal portion (utricles) of the hair follicles of adult *Vdr* null animals overexpress elements of the HH signaling pathway, unlike the dermal portion of the hair follicle in which HH signaling is reduced (Teichert et al. 2010). These results suggest that one of the causes of the increased susceptibility of the epidermis to malignant transformation is due to a loss of VDR regulation of HH signaling in the epidermis. SHH, PTCH1, PTCH2, GLI1, and GLI2 have consensus sequences for vitamin D response elements (VDRE) in their promoters (Reddy et al. 2004; Wang et al. 2005; Palmer et al. 2008; Luderer et al. 2011), and we (Teichert et al. 2011) have found that 1,25(OH)$_2$D suppresses all elements of the HH pathway in a dose-dependent fashion that requires VDR (no repression in *Vdr* null epidermis). Of further interest is that vitamin D may regulate this pathway not only via the genomic actions of 1,25(OH)$_2$D, but also by direct inhibition by vitamin D of SMO (Bijlsma et al. 2006; Tang et al. 2011).

CTNNB1 signaling in epidermal tumor formation

Like the HH pathway, overexpression and (or) activating mutations in the CTNNB1 pathway lead to skin tumors, in this case pilomatricomas or trichofolliculomas (hair follicle tumors) (Gat et al. 1998; Chan et al. 1999; Xia et al. 2006). Palmer et al. (2008) evaluated the interaction between VDR and CTNNB1 in transcriptional regulation, and identified putative response elements for VDR and CTNNB1/LEF1 in a number of genes including *Shh, Ptch1* and *2*, and *Gli1* and *2*. Furthermore, they found that the ability of *Ctnnb1* overexpression to induce trichofolliculomas was blocked by an analog of $1,25(OH)_2D$. Moreover, in the absence of VDR, BCC were induced rather than trichofolliculomas. In human tumors, Palmer et al. (2008) noted that trichofolliculomas have high nuclear levels of both CTNNB1 and VDR, whereas BCC have high levels of CTNNB1 but low levels of VDR. These observations are consistent with their animal data showing that lack of VDR in the skin of animals with activated CTNNB1 results in BCC. Saldanha et al. (2004) likewise found nuclear localization of CTNNB1 in 20 of 86 human BCC, which correlated with increased proliferative activity in these tumors, but they did not correlate these results with VDR levels. Thus, in humans as well as in mice, VDR appears to modulate the differential action of CTNNB1in the hair follicle and in the epidermis. On the other hand, when CTNNB1 transcriptional activity is deleted, hair follicle formation is blocked (Huelsken et al. 2001), and suppression of CTNNB1 transcriptional activity may protect against epidermal tumor formation (Wei et al. 2007), although our recent studies have not confirmed this hypothesis (Jiang et al. 2013).

Long noncoding RNAs (LncRNA) in epidermal tumor formation

LncRNAs are endogenous cellular RNAs larger than 200 bases. They are estimated to account for 80% of the transcriptome (Mercer et al. 2009). They are spliced and contain polyadenylation signals, much like messenger RNAs (Mattick 2011). LncRNAs have emerged as master regulators of embryonic pluripotency, differentiation, and body axis patterning, regulating histone modifications and so influencing the epigenetic programs of the transcriptome (Mattick 2011; Spitale et al. 2013). Of greater relevance to this review is that lncRNAs also regulate cancer development through mechanisms including tumor cell proliferation, evasion of growth suppressors, replicative immortality, angiogenesis, and invasion and metastasis (Gibb et al. 2011; Gutschner and Diederichs 2012; Li et al. 2013). As a first step to determining whether lncRNAs play a role in the protective effective of vitamin D signaling in epidermal carcinogenesis, we (Jiang and Bikle 2014) evaluated the profile of lncRNAs in the epidermis of VDR null mice and in keratinocytes lacking VDR. We found that *H19, HOTTIP*, and *Nespas* are significantly and consistently increased in both cultured keratinocytes and epidermis following VDR deletion, as were *Air, HOTAIR, Malat1*, and *SRA*. These lncRNAs are known to be oncogenic (Li et al. 2013). H19 is normally expressed during fetal development, but is re-expressed in adult tumors, and is essential for human tumor growth (Berteaux et al. 2005;Barsyte-Lovejoy et al. 2006; Matouk et al. 2007). *HOTTIP* (HOXA transcript at the distal tip) is expressed from the 5′ end of the *HoxA* locus and drives histone H3 lysine 4 trimethylation and gene transcription of HoxA distal genes through the recruitment of the WDR5/MLL complex (Wang et al. 2011). On the other hand, the 7 lncRNAs that decreased after VDR deletion in vivo or in vitro included *lincRNA-p21* and *Kcnq1ot1*, which are 2 well-characterized

tumor suppressors (Pandey et al. 2008; Li et al. 2013). LincRNA-p21 is a direct p53 target gene residing next to the p21 gene, which is up-regulated upon DNA damage in different tumor models (Huarte et al. 2010). LincRNA-p21 exerts its tumor suppressor function via association with hnRNP, a well-known RNA binding protein, and is itself a tumor suppressor (Huarte et al. 2010). Kcnq1ot1 localizes in the nucleus, interacting with chromatin and also with G9a (a H3K9- and H3K27-specific histone methyltransferase) and Ezh2 (histone-lysine *N*-methyltransferase), resulting in cluster-wide repressive histone marks, gene silencing, and DNA methylation of CpG islands. Hence it exerts its tumor suppressor effect via epigenetic gene silencing (Redrup et al. 2009). Together, our results indicate that part of the protective effect of VDR against epidermal carcinogenesis is due to reducing the expression levels of oncogenic lncRNAs while upregulating tumor suppressor lncRNAs.

Conclusions

VDR in combination with CaSR protects against epidermal carcinogenesis. In this paper we have reviewed 4 potential mechanisms by which this protective action is mediated. First, VDR is required for normal DNA damage repair (DDR). This appears to involve both genomic and nongenomic pathways. In the absence of VDR, DDR is impaired leading to accumulation of mutations predisposing to malignant transformation. The role for calcium signaling in DDR has not been tested. Calcium and vitamin D signaling are well known regulators of keratinocyte proliferation and differentiation of keratinocytes. Both the CTNNB1 and HH pathways contribute to the means by which calcium and vitamin D control these processes. Lack of VDR increases the activity of both HH and CTNNB1 signaling pathways, shifting the epidermis away from differentiation to poorly regulated proliferation. Finally, VDR regulates the expression of oncogenic and tumor suppressing lncRNAs in keratinocytes. The lack of VDR shifts the profile of these lncRNAs to one predisposing to malignancy. It is likely that these different mechanisms interact, a subject of investigation in our laboratory. Moreover, we expect calcium signaling via the CaSR will affect the role of VDR in regulating these mechanisms, but the extent and means of this interaction remain poorly understood. Finally, not all of the actions of VDR to suppress tumor formation in the skin appear to require its ligand, $1,25(OH)_2D$, although some clearly do. How VDR functions without its ligand remains unclear. Thus, although the role of VDR as a tumor suppressor in skin is established, we still have much to learn about the precise mechanisms by which it does so.

Acknowledgements

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