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# The Role of Classical and Novel Forms of Vitamin D in the Pathogenesis and Progression of Nonmelanoma Skin Cancers

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## Abstract

Nonmelanoma skin cancers including basal and squamous cell carcinomas (SCC and BCC) represent a significant clinical problem due to their relatively high incidence, imposing an economic burden to healthcare systems around the world. It is accepted that ultraviolet radiation (UVR: $\lambda$ = 290–400 nm) plays a crucial role in the initiation and promotion of BCC and SCC with UVB ($\lambda$ = 290–320 nm) having a central role in this process. On the other hand, UVB is required for vitamin D3 (D3) production in the skin, which supplies >90% of the body's requirement for this prohormone. Prolonged exposure to UVB can also generate tachysterol and lumisterol. Vitamin D3 itself and its canonical (1,25(OH)2D3) and noncanonical (CYP11A1-intitated) D3 hydroxyderivatives show photoprotective functions in the skin. These include regulation of keratinocyte proliferation and differentiation, induction of anti-oxidative responses, inhibition of DNA damage and induction of DNA repair mechanisms, and anti-inflammatory activities. Studies in animals have demonstrated that D3 hydroxyderivatives can attenuate UVB or chemically induced epidermal cancerogenesis and inhibit growth of SCC and BCC. Genomic and non-genomic mechanisms of action have been suggested. In addition, vitamin D3 itself inhibits hedgehog signaling pathways which have been implicated in many cancers. Silencing of the vitamin D receptor leads to increased propensity to develop UVB or chemically induced epidermal cancers. Other targets for vitamin D compounds include 1,25D3-MARRS, retinoic orphan receptors α and γ, aryl hydrocarbon receptor, and Wnt signaling. Most recently, photoprotective effects of lumisterol hydroxyderivatives have been identified. Clinical trials demonstrated a beneficial role of vitamin D compounds in the treatment of actinic keratosis. In summary, recent advances in vitamin D biology and pharmacology open new exciting opportunities in chemoprevention and treatment of skin cancers.

### Keywords

Squamous cell carcinoma; Basal cell carcinoma; Vitamin D; Ultraviolet radiation; VDR; RORα; RORγ

## Introduction to the Ultraviolet Spectrum of Solar Radiation

Ultraviolet radiation (UVR: $\lambda$ = 290–400 nm), depending on its wavelength (UVB: $\lambda$ = 290–320 nm; UVA: $\lambda$ = 320–400 nm), penetrates in different layers of the skin, with UVB being predominantly absorbed by the epidermis and reaching the upper portion of the papillary dermis, while UVA penetrates deep into the reticular dermis [69, 135, 164, 210, 238, 246]. UVR affects the integrity of DNA, RNA, and proteins and cell and tissue homeostasis, induces mutations, and changes the expression of a plethora of genes including oncogenes and tumor suppressor genes [29, 51, 132, 210, 241, 242]. It can also modify the expression and activity of growth factors, cytokines, neurohormones, neuropeptides, and their receptors and have local and systemic immunosuppressive [2, 30, 32, 62, 82, 105, 106, 126, 144, 156, 172, 174, 177–181, 193, 196, 210] as well as pro-pigmentary effects [148, 176, 182].

Excessive exposure to UVR results in skin aging, precancerous states such as solar/actinic keratosis (SA), and finally skin cancers including squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and melanoma (Fig. 13.1). Therefore, UVR (UVB and UVA) is defined as a major environmental stressor and full carcinogen responsible for the development and progression of BCC, SCC, and melanoma [11, 51, 100, 200].

UVB, while representing only ~5% of UVR spectrum, exhibits a high efficiency for inducing biological effects in the skin through its interaction with cutaneous chromophores. It causes direct damage to DNA (a chromophore for UVB) by inducing covalent bond formation between adjacent pyrimidines, which leads to the production of mutagenic photoproducts such as cyclobutane pyrimidine dimers (CPD) and pyrimidine-pyrimidine adducts [29, 121, 241, 242]. To a lesser degree, its mechanism of action is linked to production of reactive oxygen species (ROS). UVB is an important etiological factor of BCC and SCC [121, 200, 241, 242]. UVB fingerprint mutations in p53 and CDKN2A genes have been identified in BCC and SCC [83]. UVB is more efficient in inducing SCC and BCC than UVA [52, 141] with some exceptions [151–153, 159]. The damaging effect of UVA, which is approximately 1,000 less efficient than UVB due to the limited number of target chromophores, is predominantly secondary to the action of ROS [24, 71, 245] or production of nitric oxide (NO) and nitroxyl (HNO) [1, 170, 210].

## Vitamin D in the Skin

### Vitamin D and Related Compounds in a Nutshell

UVB is also required for vitamin D3 formation in the skin which usually supplies >95% of the i body's requirement for this prohormone [18, 84, 85] (Fig. 13.1). The transformation of 7-dehydrocholesterol (7DHC) to vitamin D3 (D3) after absorption of UVB energy represents the most fundamental reaction in photobiology [84, 87]. The initial photoproduct, previtamin D3, undergoes thermal isomerization to vitamin D3 in the skin. With sustained UVB, previtamin D3 can undergo further photoisomerization to lumisterol (L3) and tachysterol (T3) [84]. These reactions are reversible and are dependent on the temperature and UVB dose.

Vitamin D3 is a prohormone that is activated by sequential hydroxylations in positions C25 and C1α, both at the systemic (liver and kidney) and local (skin) levels, to produce $1,25(OH)_2D3$ ) [13, 84, 85]. The first reaction is catalyzed by CYP2R1 or CYP27A1, while the C1α hydroxylation is catalyzed by CYP27B1 [15, 16, 84, 85]. Dietary vitamin D2 is activated to $1,25(OH)_2D2$ by CYP2R1 and CYP27B1, and inactivated by CYP24A1, by similar pathways [15, 16, 228].

Vitamin D can also be activated by CYP11A1, the first enzyme in the steroid biosynthesis pathway [78, 184, 185]. The major products of CYP11A1 action on vitamin D3 are 20(OH)D3 and $20,23(OH)_2D3$ [192, 224]. Other products of CYP11A1 action on vitamin D3 are 22(OH)D3, $20,22(OH)_2D3$, $17,20(OH)_2D3$, and $17,20,23(OH)_3D3$ [184, 224, 225]. The CYP11A1-derived metabolites can be further hydroxylated by CYP27A1, CYP27B1, CYP2R1, and/or CYP3A4 producing many more metabolites including $1,20(OH)_2D3$, $1,20,23(OH)_3D3$, $20,24(OH)_2D3$, $20,25(OH)_2D3$, and $20,26(OH)_2D3$ [213, 215, 217, 218,

223, 228]. Most of these metabolites have been detected in the human skin and/or serum indicating that the pathways occur in vivo (Fig. 13.2), and most have been tested in cultured cells and found to display biological activity, including inhibition of skin cell proliferation [192, 202–204, 228]. CYP11A1 can also act on vitamin D2 producing 20(OH)D2, which displays activities similar to 20(OH)D3, plus a number of other metabolites, including 17,20$(OH)_2$D2 [140, 185, 188, 198, 228]. 20(OH)D2 can also be metabolized further by CYP27B1.

Lumisterol (L3), the major 7DHC photoproduct found in the skin following prolonged UVB radiation [86], can be metabolized by both CYP11A1 and CYP27A1 [206, 226, 227]. CYP11A1 produces primarily 22(OH)L3, 24(OH)L3, and 20,22$(OH)_2$L3, with only minor production of pregnalumisterol which contains a cleaved side chain [226]. Lumisterol and its hydroxyderivatives have been detected in the skin and serum, illustrating that this pathway occurs in vivo (Fig. 13.3). The presence of relatively high concentrations of L3 in the serum indicates that it can leave the site of its production in the skin and potentially be delivered to tissues, such as the adrenal cortex, which expresses a high level of CYP11A1, for further metabolism [206]. The major products of CYP11A1 action on L3 are biologically active, with some, but not all activities, being similar to those of 1,25(OH) 2D3 (see below) [41, 206]. More recently, we reported that lumisterol is an excellent substrate for CYP27A1, which converts it to 25(OH)L3 and both C25 epimers of 27(OH)L3, which in initial testing are able to inhibit melanoma cell proliferation [227].

Finally, tissues expressing CYP11A1 are able to transform 7DHC to 22(OH)7DHC, to 20,22$(OH)_2$7DHC, and finally to 7-dehydropregnenolone (7DHP) [183, 186, 191]. The latter can be further hydroxylated or converted to dehydroprogesterone by steroidogenic enzymes [191]. 20(OH)7DHC has been identified in human epidermis [206], while 22(OH)7DHC, 20,22(OH)27DHC, and 7DHP were detected in human epidermis and serum (Fig. 13.2) [202]. 7DHP and its metabolites can be transformed by UVB to the corresponding secosteroids, as predicted [183] and as has been experimentally substantiated [251–253] (Fig. 13.4). In addition, 20(OH)7DHC, 22(OH) 7DHC, and 20,22$(OH)_2$7DHC can be converted to the corresponding vitamin D3, lumisterol and tachysterol hydroxyderivatives, after absorption of UVB energy by the B-ring (Fig. 13.4).

## Phenotypic Effects of Active Forms of Vitamin D: An Overview

1,25$(OH)_2$D3, in addition to regulating calcium homeostasis, has important pleiotropic activities that include stimulation of differentiation and inhibition of proliferation of different cell types, anti-cancerogenic effects, stimulation of innate immunity, and inhibition of adaptive immunity and inflammation [13, 15, 28, 46–48, 55, 65, 73–75, 84, 85, 149, 240]. In the skin, vitamin D3 plays a significant role in the formation of the epidermal barrier and adnexal structures, including hair follicles, and has a wide variety of ameliorating effects in skin cancer and proliferative and inflammatory cutaneous diseases [12, 14, 23, 63, 84, 85, 94, 143, 157, 158]. These properties of 1,25$(OH)_2$D3 have been extensively reviewed as listed above and, therefore, will not be detailed.

Similar effects are exerted by CYP11A1-derived hydroxyderivatives of vitamin D3, including mono, dihydroxy, and trihydroxy forms with or without the hydroxyl group at

position C1α (reviewed in [197, 205, 207, 208]). Specifically, they exert antiproliferative, pro-differentiation, and anti-inflammatory effects in cultured cells that are comparable or stronger I than those of 1,25$(OH)_2$D3 [41, 95, 96, 112, 114–116, 119, 123, 189, 190, 194, 195, 207, 225, 248]. In addition, they exhibit antifibrotic i activities both in vitro [189, 194, 195] and ‘ in vivo [194]. They also display anti-melanoma and antitumor properties that are cell type-dependent [44, 97, 173, 187, 188, 190, 195, 207, 234, 235, 237]. Moreover, similar to 1,25$(OH)_2$D3, they can stimulate different elements of the cutaneous hypothalamus-pituitary-adrenal axis in human keratinocytes including CRH, urocortins, and POMC, together with their corresponding receptors CRHR1, CRHR2, MC1, MC2, MC3, and MC4 [238]. The newly identified hydroxyderivatives of lumisterol also show antiproliferative and pro-differentiation properties in human normal and malignant epidermal keratinocytes [41, 206]. Finally, vitamin D-, lumisterol-, and tachysterol-like compounds with a short or absent side chain also show antiproliferative and antitumor properties [102, 145, 186, 187, 195, 235, 252, 253]. Importantly, 20(OH)D3 and 20,23(OH)2D3 i non-calcemic, while 1,20$(OH)_2$D3 show ‘ low-calcemic activity [44, 187, 194, 234].

## Receptors for Vitamin D in the Skin

### Vitamin D Receptor (VDR)

**An Overview—**The main phenotypic activities of canonical hydroxyderivatives of vitamin D are mediated through their interaction with the ligand-binding domain of the nuclear receptor, vitamin D receptor (VDR, NR1I1) [22, 28, 39, 46, 81, 130, 131, 142]. This interaction promotes heterodimerization of the VDR with the retinoid X receptor (RXR) and its translocation to the nucleus where it interacts with VDR-responsive elements (VDRE) to regulate the transcription of target genes (transactivation or repression). VDR is expressed in all tissues, including the skin [22, 28, 39, 157], and is reported to regulate approximately 3% of the mammalian genome. The human epidermis is rather unique in this context in that it is both the source of vitamin D3 and a target tissue. The CYP11A1-derived secosteroids with a full-length side chain can bind to the VDR and act via a VDRE-dependent mechanism, with compounds containing a hydroxyl group at C1α exhibiting a higher affinity than those without it [102, 118, 119, 188, 207]. Most importantly, the crystal structures of 20(OH)D3, 1,25(OH)2D3, and 1,25(OH)2D3 bound to the genomic LBD of the VDR were obtained [118, 119] which illustrated similarities and differences between these compounds in their interaction with the VDR receptor (Fig. 13.5), as reported in [119].

VDR transcriptional activity is dependent on the availability of VDR agonists and antagonists and their effect on receptor conformation (allostery [160], the recruitment of different cofactors [18, 22], and chromatin accessibility [39, 136, 142]). Moreover, VDR activity can be influenced by single-nucleotide polymorphisms (SNPs) [254]. This plays, for example, a role in the etiology of nonmelanoma skin cancers (NMSC) and melanoma [38, 54, 104, 111, 117]. Interestingly, CYP11A1-derived D3 hydroxyderivatives without a hydroxyl group at C1α display a subset of the activities possessed by 1,25$(OH)_2$D3 (see above) and lack calcemic activity, acting as biased agonists on the VDR [197, 207].

In addition to genomic (G), VDRE-mediated regulation of gene expression, the VDR can also induce rapid responses via a non-genomic, membrane-associated mechanism that

involves an alternative ligand-binding site (A-pocket) [81, 130, 131]. The list of ligands interacting with the A-pocket of VDR includes 25(OH)D3, 1,25$(OH)_2$D3, 1,25$(OH)_2$L3 [57, 130], and some CYP11A1-derived hydroxylumisterol derivatives [206], but not CYP11A1-derived vitamin D3 hydroxyderivatives [207]. An additional cell membrane-linked mechanism of action includes the interaction between VDR and caveolin-associated signal transducers [249].

Finally, different alternatively spliced forms of VDR have been described [5, 64, 68, 212]. It has been suggested that they can have different transcriptional activity and promote VDR-ligand-independent functions [5]. Most recently, alternatively spliced forms have been detected in human melanoma cells [236]. Using the same methodology and the same primers with sequencing of the resulting cDNA fragments [49, 236], we identified VDR isoforms a, b, c, 1a, 1d, and 1f, similar to those described previously [49, 236], in normal adult and neonatal human epidermal keratinocytes and the skin fragments from white and black subjects. The immediate challenges in this area are to determine whether alternatively spliced VDR isoforms exhibit distinct functions in skin cells and regulate the expression of different genes and whether the alternative splicing is regulated by endogenous or environmental factors, as has been shown for other receptors such as CRH-R1 [146, 147, 196, 250]. In addition, it further needs to be determined whether these isoforms display different affinities for different vitamin D3 hydroxyderivatives and exhibit differences in their interaction with RXR, cofactors, and DNA or to understand mechanisms by which they regulate VDR-ligand-independent functions.

**VDR in the Skin—**VDR is expressed in all skin cell types [17]. However, its level of expression can change depending on the specific pathology, as documented in VDR knockout mice. For example, $VDR^{-/-}$ mice show significant defects in cutaneous structures, alopecia [46, 143], and have significantly increased propensity to develop epidermal skin cancer [21, 23, 216]. The later indicates that VDR functions as a tumor suppressor [19, 20].

With respect to melanomagenesis, significant changes in the level of VDR expression were observed during progression of melanocytic tumors, with reduced nuclear and cytoplasmic VDR levels correlating with tumor progression and Clark levels, with highest VDR levels in normal skin and common melanocytic nevi, and with lowest VDR levels in advanced and metastatic melanomas [33, 35]. Low or lack of VDR expression also positively correlated with poor prognostic markers of melanoma and poorer outcome of the diseases as measured by shortening of the survival and disease-free times [33, 35]. The combined analysis of CYP27B1 and VDR showed an even stronger correlation with disease progression, with the lowest levels of expression in highly advanced melanomas and metastases [34]. Interestingly, an inverse correlation between VDR and nuclear expression of HIF-1a was found with the highest HIF-1a expression observed in pT3-pT4 VDR-negative melanomas (37). Also, nuclear VDR expression was significantly lower than in normal uveal cells including melanocytes [125]. Finally, VDR single-nucleotide gene polymorphisms are associated with a higher probability of developing melanoma and a poorer disease outcome (reviewed in [205]).

NMSC studies performed in animal models have convincingly demonstrated a role for VDR in photoprotection and prevention or attenuation of skin cancer development [12, 21–23, 40, 57, 92, 94, 233]. The latter involves inhibition of the hedgehog and Wnt signaling pathways and induction of keratinocyte differentiation [3, 79, 120, 216, 230]. Inhibition of the hedgehog pathway has also been implicated in the attenuation of other tumors, including rhabdomyosarcoma [231] and renal carcinomas [60]. The inhibition of hedgehog signaling by vitamin D compounds might be mediated by VDR-dependent and VDR-independent mechanisms [214].

Although VDR polymorphisms have been linked to various malignancies, including cutaneous melanomas [205, 208], studies on the relationship between VDR polymorphisms and the risk of developing NMSC (A*pa*I, B*sm*I, and T*aq*I) [54, 80, 111] were not fully conclusive with some, but limited, evidence indicating a relationship between VDR SNPs and NMSCs. In a German population, a correlation between the combined ApaI/TaqI/BglI AaTtBb genotypes of VDR with BCC risk was observed (aaTTBB VDR genotype was found only in controls). The aaTTbb VDR genotype was much more frequent in BCCs and SCCs that in the control population. Also, a higher frequency of the BB VDR genotype on sun-exposed versus nonexposed areas both in BCCs and SCCs was identified. In addition, Apa1 and Taq1 genotypes were associated with BCCs, but not with SCC photocarcinogenesis [104]. In a Polish population, the TT genotype of FokI VDR polymorphism was correlated with greater than tenfold higher risk of BCC development [111]. Burns et al. found that the BsmI b or TaqI t genotypes of VDR were more frequent in NMSC patients, suggesting that individuals with these genotypes are more likely to develop skin cancer [38]. A very recent nested case control study and meta-analysis showed that patients with rs2228570, rs927650, and rs1544410 recessive genotypes were characterized by a lower risk of SCC development, while rs7975232 and rs739837 recessive genotypes were related to decreased BCC risk [107]. Another study identified two new SNPs in VDR binding sites (rs16917546 and rs79824801) associated with BCC risk. This study also confirmed the association of the rs3769823 SNP in the VDR binding site with increased BCC risk [117], while a study performed on a population in the mid-south of the USA (96 cases vs. 100 controls) showed that subjects with *Bsm*I SNP had two times higher probability of developing NMSC in comparison to controls [38]. Thus, VDR polymorphisms should be considered as factors related to NMCS risk; however, additional studies are needed with larger population cohorts.

The vitamin D system has been analyzed in cell cultures and clinical samples of NMSCs. Reichrath's group found a significant increase in nuclear VDR expression (as detected with immunohistochemistry) in SCC samples compared to normal skin; however, without a correlation with histological type, grading or markers for proliferation, differentiation, or apoptosis, and increased expression of *VDR, CYP27A1, CYP27B1* and *CYP24A1* in SCC [155]. Reichrath et al. [154] and Mitschelle et al. [129] also analyzed the expression of VDR in BCCs and found a pattern similar to SCC, with significantly elevated nuclear expression of VDR in BCCs in comparison to normal skin, adjacent epidermis, and unaffected epidermis. VDR expression was moderate or strong, and the strongest VDR expression was found in peripheral *palisade cells.* VDR expression was not correlated with a particular histological type of BCC. Similar to SCCs, the expression of *VDR, CYP27B1*, and

*CYP24A1*, but not of *CYP27A1*, was increased in comparison to normal skin [129]. We also detected the VDR in human biopsies of BCC and SCC (Fig. 13.6). These studies show that both receptors for active forms of vitamin D and enzymes activating or inactivating vitamin D are expressed in NMSC, providing a rationale for targeting vitamin D signaling in the therapy of NMSC.

## Other Receptors for Vitamin D: An Overview

Other receptor candidates for $1,25(OH)_2D3$ include the 1,25D3-membrane-associated, rapid-response steroid-binding protein (1,25D3-MARRS), which is also known as ERp57/GRp58 and also serves as a protein disulfide isomerase A3 (PDIA3) that acts as a chaperone protein [101, 137] and has additional unexpected functions [138, 219]. According to some reports, it functions as a membrane-bound receptor for active forms of D3 and is involved in the regulation of some of its phenotypic functions [101, 137]. Other studies have shown interactions between plasma membrane 1,25D3-MARRS, VDR, and calveolin-1 via a non-genomic signal transduction pathway initiated by $1,25(OH)_2D3$ [43, 169]. Our molecular modeling predicts that the CYP11A1-derived secosteroids are unlikely to interact with 1,25D3-MARRS [207].

Retinoic acid-related orphan receptors (ROR) α and γ, members of the nuclear receptor superfamily, provide an alternative mechanism by which vitamin D3 and its derivatives can regulate biological functions and gene expression and affect pathology [99, 199, 207]. CYP11A1-derived hydroxyderivatives of D3 can act as inverse agonists on RORa and RORγ. Similarly, hydroxyderivatives of lumisterol can function as RORa and RORγ inverse agonists [206]. Molecular modeling where these vitamin D3 metabolites exhibit high docking scores predicts that they interact strongly with the ligand-binding pocket of RORα/RORγ [208]. These receptors are expressed in normal and pathological skin [36, 199], including BCC and SCC (Fig. 13.6). Their expression inversely correlates with human melanoma progression, and higher expression in the nucleus correlates with significantly longer overall and disease-free survival times [36]. Interestingly, RORa and RORγ expression positively correlates with HIF-1 expression in cutaneous melanomas [37]. In uveal melanoma, expression of RORs was lower than in normal uveal cells [125]. This suggests that RORs may play an important role in melanomagenesis, melanoma progression, and host responses against the tumor [205, 208]. RORγ is essential for the generation of T-helper 17 (Th17) cells and production of the pro-inflammatory cytokine interleukin 17 (IL-17) which plays a critical role in various autoimmune diseases, including psoriasis, and also has antitumor as well as pro-tumor effects in melanoma [42, 99, 211]. Thus, these hydroxyderivatives could potentially inhibit inflammation and tumor progression in the skin through an RORγ-mediated mechanism.

Most surprising was a recent discovery showing that hydroxyderivatives of vitamin D3, including 20(OH)3, $20,23(OH)_2D3$, $17,20,23(OH)_3D3$, and classical $1,25(OH)_2D3$, can act on the aryl hydrocarbon receptor (AhR) in a manner dependent on the positions of hydroxyl groups on the structure [209]. This discovery is consistent with the promiscuous nature of AhR and its activity [134]. It opens up an exciting opportunity to study the regulation of the skin phenotype by different vitamin D3 hydroxyderivatives acting via AhR signaling, taking

into consideration its complex role in skin physiology and pathology [27, 67, 93, 133] (Fig. 13.7).

Thus, different forms of vitamin D3, in addition to acting via the genomic canonical pathway of VDR, can potentially act via noncanonical pathways, including those involving the nuclear receptors, RORs and AhR (Fig. 13.7). While the classical $1,25(OH)_2D3$ can exert non-genomic activities through action via the non-genomic binding site of VDR or via 1,25D3-MARRS, similar functions for CYP11A1-derived secosteroids are less likely [207] and remain to be established experimentally. The receptors for pregnacalciferol derivatives [195] remain to be identified.

In summary, vitamin D hydroxyderivatives exhibit different affinities for multiple receptor targets and through their modulation of these distinct receptor signaling pathways regulate different physiological functions and influence pathologies in different ways (Fig. 13.7).

## Nonmelanoma Skin Cancers

### Human Skin Cancer: An Overview

NMSCs, encompassing SCC and BCC, are the most common malignancies in humans. The cost of their treatment is an enormous economic burden to the healthcare system of the USA and to healthcare systems worldwide [113]. The role that UV radiation plays in the pathogenesis was first proposed in the late nineteenth century by Unna, who made the important observation that sailors, who had chronic exposure to sunlight, had a disproportionate increase in the incidence of skin cancer [25]. In fact, over 80% of NMSCs occur in sun-exposed skin sites, i.e., head and neck and back of the hands [11, 51, 100, 162, 200]. Studies in experimental animal models have demonstrated that wavelengths within the UVB range are primarily responsible for these malignancies [25, 66]. Immunocompromised patients, including solid organ transplant recipients who require drugs that suppress immunological function in order to prevent rejection of their transplanted organ, are at greatly increased risk of developing nonmelanoma skin cancers, particularly cutaneous squamous cell carcinomas [6]. Tumors in this population behave more aggressively and are more likely to metastasize [6]. Military personnel also have an increased risk of NMSCs [7]. They are exposed to high doses of UVR during deployment to locations with high solar radiation including the desert and high-altitude environments. This often happens in situations in which adequate attention to photoprotective measures is unavoidable. It should be noted that there was an unusually high incidence of NMSCs in World War II veterans who served in the Pacific and elsewhere in the tropics. Currently, the incidence of skin cancer in the military is greater than in the general population.

Although there has been an intensive effort by healthcare institutions around the world to take preventative measures against excessive sun exposure, the incidence of these malignancies continues to rise [161]. Therefore, there is an urgent need to establish proper measures to stimulate photoprotective or reparative mechanisms in the skin of civilian and military personnel against UVR-induced damage. These measures need to be taken at as early an age as possible for young and older individuals alike, since skin cancers often develop after a long latency period.

## Therapy of NMSC

The mortality for most NMSCs is low. However, they, and the treatment required for their removal, can be disfiguring with significant morbidity. Given the frequency with which they occur, the management of NMSC is a tremendous economic burden [113]. In the USA alone, the estimated cost for the treatment of actinically damaged skin is $1.68 billion [113].

Guidelines and appropriate use criteria for the management of both basal cell carcinomas and squamous cell carcinomas have been created by the American Academy of Dermatology and the National Comprehensive Cancer Network [4, 9, 10, 103, 244]. In most instances, the treatment of nonmelanoma skin cancers is surgical. This includes electrodessication and curettage, excision with appropriate tumor-free margins, and Mohs micrographic surgery. Electrodessication and curettage is used primarily for lower risk skin cancers, chiefly on the trunk and extremities. The procedure involves scraping away malignant tissue with a curette followed by electrodessication of the treatment area; the procedure is repeated up to three times. The cure rate has been reported to be up to 95% for low-risk lesions but is considerably lower for higher-risk tumors [9, 45, 108]. Standard excision followed by histological evaluation of margins is another option. Recurrence or metastasis rates of less than 6% can be achieved for primary tumors; cure rates for recurrent lesions, however, are substantially lower [163]. Subclinical involvement for cutaneous squamous cell carcinomas is present in up to 15% of primary tumors and up to 50% of recurrent squamous cell carcinomas [8, 110]. For this reason, Mohs micrographic surgery is the treatment of choice for most high-risk nonmelanoma skin cancers. Mohs micrographic surgery is an outpatient surgical procedure in which the tumor is debulked. Then a thin layer of underlying tissue is removed and examined histologically by frozen section to determine if it is free of tumor. If not, then further surgical layers are removed until there is no microscopic evidence of tumor. Surgery is performed all in one session with the patient remaining in the clinic while tissue sections are evaluated. Mohs micrographic surgery minimizes the amount of normal tissue that must be taken and provides microscopic verification that the tumor has been completely removed. Retrospective studies have found a 5-year cure rate of 97% for primary tumors and 90% for recurrences [229]. This is compared with 92% for primary tumors and 77% for recurrences with other procedures.

Radiotherapy, especially for low-risk tumors, is employed in some situations based on patient preference or other factors [9, 10]. It is contraindicated in patients with certain genodermatoses such as basal cell nevus syndrome and in individuals less than 60 years of age because of the potential for long-term consequences. Five-year cure rates of 93% for primary tumors and 90% for recurrent tumors have been accomplished with radiotherapy [9].

Topical imiquimod has received regulatory approval for treatment of superficial BCCs and premalignant actinic keratoses [10, 70, 139, 150, 166, 171]. It has also been used off-label for nodular BCCs [77, 239]. Imiquimod stimulates innate and acquired immunity by binding to the TLR7 and, as a consequence, stimulates dendritic cells and augments production of interferon-gamma, TNF-alpha, and other pro-inflammatory cytokines [77]. Recent studies have shown that it also has actions independent of TLR7 stimulation [232]. The end result is an antitumor immune response capable of eradicating BCCs. Treatment requires daily

application of imiquimod for 6 (superficial BCC) to 12 (nodular BCC) weeks. Five-year response rates with imiquimod are significantly less than with surgical excision [239].

While metastasis of BCC is very rare, it can occur. Furthermore, neglected BCCs can enlarge to the point at which sufficient destruction of cutaneous and even non-cutaneous tissue occurs, making it impossible to remove the lesions surgically. The sonic hedgehog pathway plays an essential role in BCC pathogenesis. Two oral sonic hedgehog inhibitors, vismodegib and sonidegib, are commercially available, and both cause BCC regression [61, 122, 128, 168]. They are employed for the treatment of locally advanced and metastatic BCC. These agents have many adverse effects including hair loss, muscle spasms, weight loss, and dysgeusia, which reduce patient compliance. Moreover, BCCs can develop resistance to these medications, and discontinuation often results in BCC regrowth. Thus, these medications are not used for routine BCCs.

Other treatment options for nonmelanoma skin cancers include cryotherapy, PDT, 5-FU, and intralesional methotrexate but are only utilized in special circumstances [9, 10, 103, 244].

## Vitamin D in Chemoprevention of NMSC

### Photoprotective Activity of Active Forms of Vitamin D3

A significant number of studies have shown protective effect of different vitamin D analogs against UVR in human skin cells and hairless mice [53, 56, 58, 59, 72, 76, 109, 127, 220, 243]. Specifically, 1,25$(OH)_2$D3 and 1,25$(OH)_2$L3 reduced UV-induced DNA damage including formation of CPD and reduced production of pro-inflammatory cytokines in cultured human keratinocytes in culture and in mouse and human skin [127]. The photoprotective effects of these compounds were also connected with increased expression of P53 in the nucleus and a decrease in the number of apoptotic sunburn cells and attenuation of UVB-induced immunosuppression [57]. The authors suggested non-genomic actions of 1,25$(OH)_2$D3 and 1,25(OH)2L3 [57]. Similarly, topical application of CYP11A1-derived 20(OH)D at 23 or 46pmol/$cm^2$ protected mouse skin against UVB-induced DNA damage at comparable level to that of 1,25$(OH)_2$D3 [221]. It also reduced the sunburn edema and protected against UVR-induced immunosuppression in a similar manner to 1,25$(OH)_2$D3. Thus, these in vivo photoprotective effects were independent of C1α-hydroxylation [221]. The same group demonstrated that in addition to 1,25$(OH)_2$D3, low-calcemic analogs of D3 reduced UV-induced CPDs in both skin fibroblasts and keratinocytes and their cell death after UV exposure [58]. They were equally effective as 125$(OH)_2$D3 in increasing levels of p53 in cultured human keratinocytes. In a hairless mouse line, these compounds reduced UV immunosuppression. However, the low-calcemic analog was not as effective as 1,25$(OH)_2$D3 in reducing tumorigenesis [58]. Most recently, an interesting mechanism of action for 1,25(OH)2D3 in UVB-irradiated keratinocytes was demonstrated. Specifically, it enhanced glycolysis along with energy-conserving processes such as autophagy and mitophagy, resulting in increased repair of CPDs and decreased oxidative DNA damage [165]. Finally, high doses of vitamin D3 given orally shortly after exposure to UVB could reverse the induced skin damage with attenuation of the inflammation and induction of barrier repair mechanisms [167].

Our studies on photoprotective functions of 20(OH)D3 and 20,23$(OH)_2$D3 in cultured human epidermal keratinocytes, melanocytes, and HaCaT keratinocytes have shown that they can attenuate ROS, $H_2O_2$, and NO production induced by UVB to a similar level to that for 1,25$(OH)_2$D3, with 25(OH)D3 and 20(OH) 7DHC having lower efficiency [201]. The photoprotection was accompanied by increased expression of genes involved in defense against oxidative stress. Furthermore, these compounds reduced the UVB-induced CPDs and DNA fragmentation in comet assay and enhanced expression of p53 phosphorylated at Ser-15, but not at Ser-46 [201]. The most recent tests on an extended list of CYP11A1-derived vitamin D3 and lumisterol hydroxymetabolites (1,25(OH) 2D3, 20(OH)D3, 1,20$(OH)_2$D3, 20,23$(OH)_2$D3, 1,20,23$(OH)_3$D3, 20(OH)L3, 22(OH)L3, 20,22$(OH)_2$L3, and 24(OH)L3), and lumisterol itself, have shown that they can protect human epidermal keratinocytes against UVB [41]. Treatment of cells with the D3 or lumisterol derivatives showed a dose-dependent reduction in UVB-induced oxidant formation, protection against DNA damage, and/or induction of DNA repair by enhancing the repair of 6–4PP and attenuating CPD levels and the tail moment of comets. They also stimulated the expression of antioxidant response genes downstream of Nrf-2 (GR, HO-1, CAT, SOD1, and SOD2) and expression at the protein level of HO-1, CAT, and MnSOD [41]. With respect to their mechanism of action, these compounds increased the phosphorylation of p53 at Ser-15 with stimulation of p53 and Nrf2 translocation into the nucleus. We have also shown that not only pre-treatment but also posttreatment of keratinocytes with D3 and lumisterol derivatives can reverse UVB-induced keratinocyte damage [41] which is similar to other natural products [98, 175]. Thus, CYP11A1-derived D3 or lumisterol derivatives, and to some degree lumisterol itself, act as photoprotectors with their mechanism of action involving stimulation of the Nrf2-dependent and p53 responses, as well as stimulation of the DNA repair system.

### Chemoprevention Against UVR and Chemically Induced NMSC in Animal Models

As discussed in Sect. 2.3.1, the chemopreventive and potentially therapeutic roles of D3 hydroxyderivatives in NMSC are indicated by experiments with $VDR^{-/-}$ and $RXR^{-/-}$ (partner for VDR) mice on cutaneous carcinogenesis [12, 21–23, 40, 57, 92, 94, 233]. For example, Dixon et al. [57] have shown that 1,25$(OH)_2$D3 and 1,25$(OH)_2$L3 inhibited UVB-induced development of papillomas and squamous cell carcinomas in immunocompetent mice (Skh:hr1). They suggested a non-genomic mechanism of action, at least in part [57]. Studies on low-calcemic analog, 1α-hydroxymethyl-16-ene-24,24-difluoro-25-hydroxy-26,27-bis-homovitamin D3, have shown that while it protected against UVB-induced damage, it was not as effective as 1,25$(OH)_2$D3 in reducing tumor formation and progression [58].

Others using 1,25$(OH)_2$D3 have shown that it inhibits proliferation and growth of BCC of Ptch mutant mice in vivo and of established murine BCC lines in vitro [230]. Two mechanisms of action have been shown, e.g., the activation of the VDR and induction of keratinocyte differentiation and inhibition of Hh signaling at the level of Smo in a VDR-independent manner [230]. The 1,25$(OH)_2$D3 effects on BCC growth were stronger than those of the cyclopamine (Hh inhibitor), indicating that its dual action makes 1,25$(OH)_2$D3 an excellent therapeutic for BCC and other tumors in which Hh signaling is disrupted [230]. Of great interest was the study showing that unmodified D3 inhibited Hh signaling and

growth of murine BCCs both in vitro and in vivo [214]. D3 blocked both proliferation and Hh signaling to similar degree as cyclopamine. 7DHC, 25(OH)D3, and 1,25$(OH)_2$D3 were less effective in these actions. The D3 effect appeared to be independent of the VDR [214]. An important study led by Epstein on UVB-induced BCC carcinogenesis in Ptch1(+/−) mice showed that inhibition of UVB-induced production of D3 in the skin accelerated BCC carcinogenesis [124]. Furthermore, topical application of the D3 prohormone inhibited UVB-induced BCC tumorigenesis, while orally delivered D3 had no protective effect [124]. The authors concluded that UVB-induced production of D3 in keratinocytes significantly restrains murine BCC tumorigenesis and that UVB has anti-BCC carcinogenic effects through induction of D3 formation [124].

Studies on the chemically induced development and progression of SCC in mice showed that calcipotriol (analog of 1,25$(OH)_2$D3) inhibited the cancerogenesis and growth of tumors [50]. The mechanism of anti-cancerogenic action included induction of thymic stromal lymphopoietin [50].

## Vitamin D in Chemoprevention or Adjuvant Therapy in NMSC in Humans

Currently, a few clinical trials have investigated the effects of vitamin D on NMSCs. The synergistic effects of calcipotriol and 5-FU treatment in optimally activating a CD4+ T cell-mediated immunity against actinic keratoses in randomized, double-blind clinical trial involving 131 participants were reported [50]. Another human trial has shown that calcipotriol combined with methyl aminolaevulinate photodynamic therapy (MAL-PDT) was more efficacious than MAL-PDT alone and well tolerated [222]. The already completed Dutch phase II clinical trial (ChnicalTrials.gov Identifier: NCT01358045, start date November 2011, completed date May 2013) ([31], https://clinicaltrials.gov/ct2/show/NCT01358045?term=vitamin+d&cond=BCC&rank=3) was a randomized trial on the treatment of primary, histologically confirmed BCC (nodular of superficial subtype) with topical application of vitamin D3, diclofenac, or a combination of both twice daily under occlusion on BCC lesion. After 8 weeks, tumors were excised, and proliferation (Ki-67) and antiapoptotic (Bcl-2) markers were examined, and no effect of calcitriol alone was found. Combination therapy resulted in decreasing Ki-67 level in superficial BCC subtype, while diclofenac application was related to a significantly reduced expression of both Ki-67 and B-cl2 in superficial BCC. Another two clinical trials are related to BCC in basal cell nevus syndrome (BCNS) treatment with photodynamic therapy (PDT) and vitamin D as neoadjuvant. The first one is a clinical, double-blinded, randomized trial (ClinicalTrials.gov Identifier: NCT03467789, start date October 2018) (https://clinicaltrials.gov/ct2/show/NCT03467789?term=vitamin+d&cond=BCC&rank=2) on the vitamin D effect (10,000 IU/day) prior to the first or second PDT visit (treatment for 14 days when patients are deficient for 25-hydroxy-D3 serum levels or 5 days when 25-hydroxy-D3 levels are normal, and to maintain vitamin D3 level patients are supplemented with 2000 IU/day or 1000 IU/day for adults and children, respectively). The tumor clearance measured as change in lesion diameter per month is the primary outcome of this trial. The second one is randomized Phase 1 clinical trial (ClinicalTrials.gov Identifier: NCT03483441, start date March 2018, (https://clinicaltrials.gov/ct2/show/study/NCT03483441?term=vitamin+d&cond=BCC&rank=1), with a similar study design. Patients will take 10,000 units of

cholecalciferol for several days prior to PDT, and differences in tumor BCC tumor diameter between treatments will be measured. The recruitment to these clinical trials has been opened; however, no results are available yet. There is also a completed early Phase 1, double-blinded clinical trial on actinic keratosis, a precursor of SCC, treated with calcipotriol plus 5-fluorouracil (5-FU) in patients with multiple actinic keratoses (ClinicalTrials.gov Identifier: NCT02019355, start date October 2013, completed date March 2015, ([50], https://clinicaltrials.gov/ct2/show/NCT02019355)). A significantly reduced number of actinic keratosis was found in patients treated for 4 days with calcipotriol plus 5-FU when compared to only 5-FU treated patients. Currently, there is no open clinical trial on SCC treatment with vitamin D. Thus, vitamin D could enhance NMSC treatment; however, additional clinical trials are needed to fully justify its use and to select the most optimal vitamin D derivative for treatment of keratinocyte-derived cancers.

## Perspective and Conclusions

The pleiotropic activities of D3 that are in addition to the regulation of body calcium homeostasis and include radioprotective and anticarcinogenic activities are consistent with the actions of multiple vitamin D derivatives produced in the human body and multiple target receptors in addition to the VDR. In vivo and in vitro studies reviewed above clearly document important if not crucial role for different vitamin D compounds and the VDR, not only in photoprotection but also in the prevention or attenuation of NMSCs. With respect to cutaneous carcinogenesis, a key question is which chemical configurations of vitamin D compounds are the most efficacious with relatively minimal site effects and what is their mechanism of action, e.g., genomic or no-genomic. For genomic activities, new receptor candidates in addition to the VDR are emerging such as RORa and ROR$\gamma$ and AhR, which may be targeted in addition to the targeting of the Hh signaling pathway (Fig. 13.7). Finally, different routes of delivery with preferred topical application have to be considered that require proper formulation.

Due to toxic (calcemic) effects, the therapeutic use of 1,25$(OH)_2$D3 at pharmacological doses or chronic oral use of D3 has its limitations. The discovery of an alternative pathway of D3 activation initiated by CYP11A1, producing at least 15 metabolites $(OH)_n$D3) with a full-length side chain and potentially several others with a short or absent side chain, opens new possibilities for treatment, since they have antiproliferative, pro-differentiation, anti-inflammatory photoprotective effects on normal and malignant epidermal cells. Many of them are non-calcemic *7* and non-toxic at suprapharmacological doses. Furthermore, with the contribution of UVB acting on Δ7-steroids or sterols produced in the skin, the corresponding lumisterol and tachysterol compounds can be produced with photoprotective properties. Thus, novel secosteroids, lumisterol, and/or tachysterol compounds are excellent candidates to serve as radioprotectors and chemopreventive agents for skin cancers. They potentially can induce the repair of damaged DNA and/or attenuate or reverse UVR-induced skin aging [26].

In summary, recent advances in vitamin D, lumisterol and 7DHC biochemistry, skin biology, and pharmacology are opening up new exciting opportunities in skin healthcare and treatment of different cutaneous pathologies.

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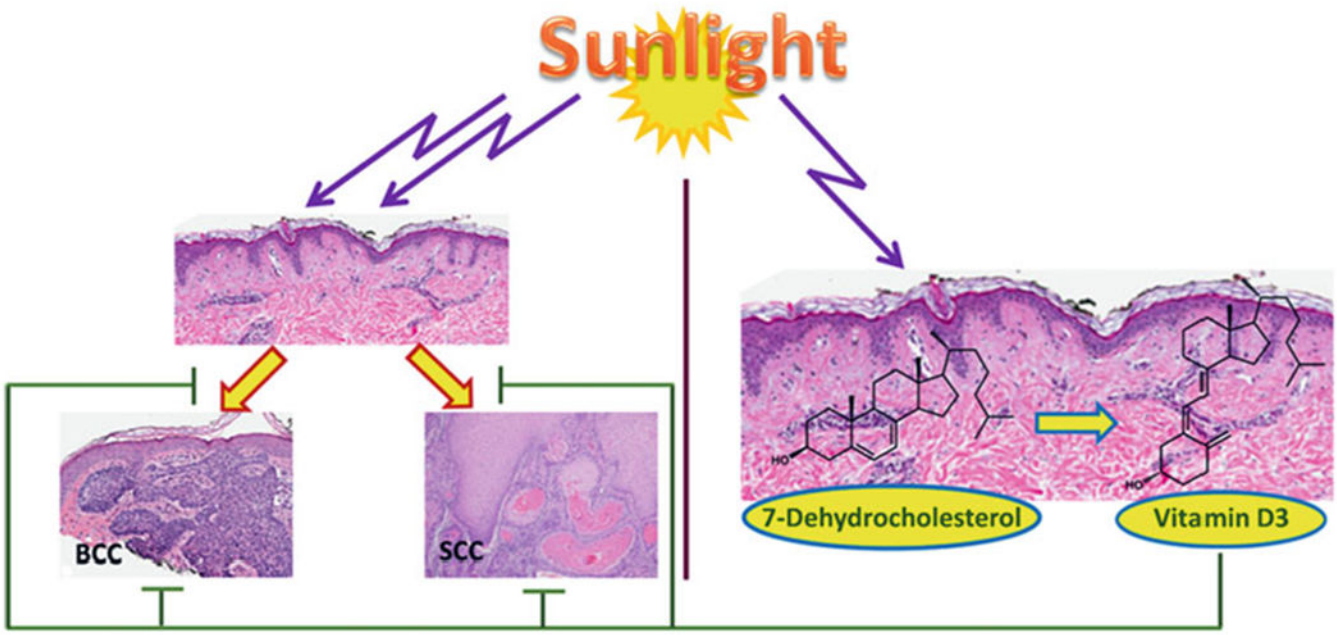


**Fig. 13.1.**

Ultraviolet B as the double-edge sword in skin health

UVB not only induces skin cancers but also is necessary for phototransformation of 7DHC (7-dehydrocholesterol) to vitamin D3. *BCC* basal cell carcinoma, *SCC* invasive squamous cell carcinoma. (Reprinted from [208] with permission from Elsevier)

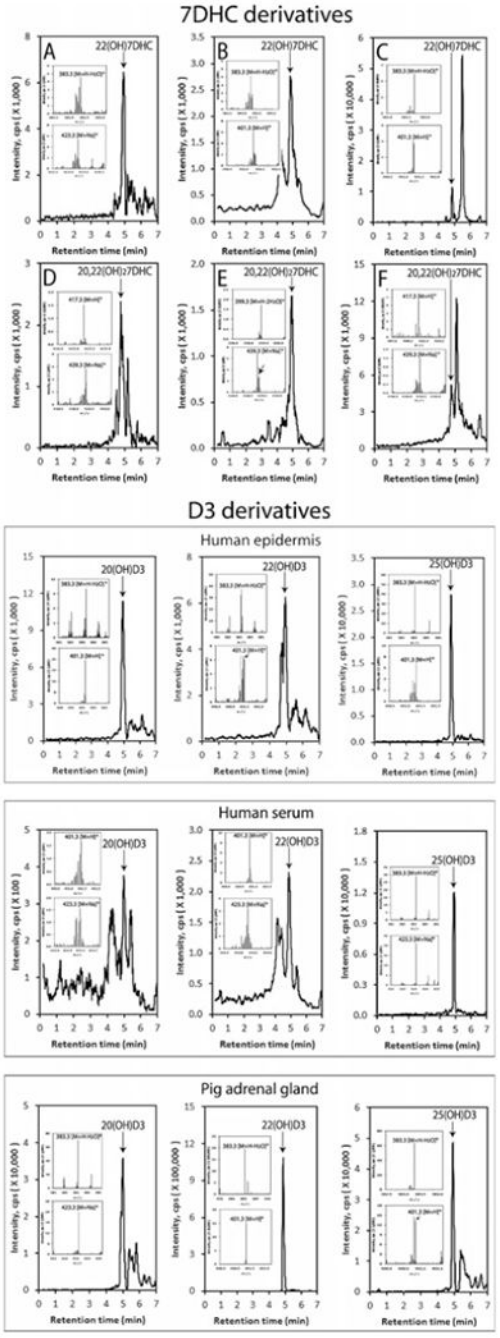


**Fig. 13.2.**

Detection of CYP11A1-derived 7DHC and D3 hdroxyderivatives in the human epidermis and serum

LC-MS spectra were measured on fractions with retention times corresponding to either 22(OH)7DHC or 20,22(OH)$_2$7DHC or 20(OH)D3, 22(OH)D3, or 25(OH)D3 that were pre-purified on a Waters C18 column (250 × 4.6 mm, 5 μm particle size) with a gradient of acetonitrile in water as described in [202]. Arrows indicate the retention times of the corresponding standards. Inserts show the mass spectra corresponding to the retention time

of detected compound. In the outer panel, extracted ion chromatograms are shown for human epidermis (**a** and **d**), serum (**b** and **e**), and the pig adrenal (**c** and **f**). The work is reprinted from [202] under the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/) with small modifications

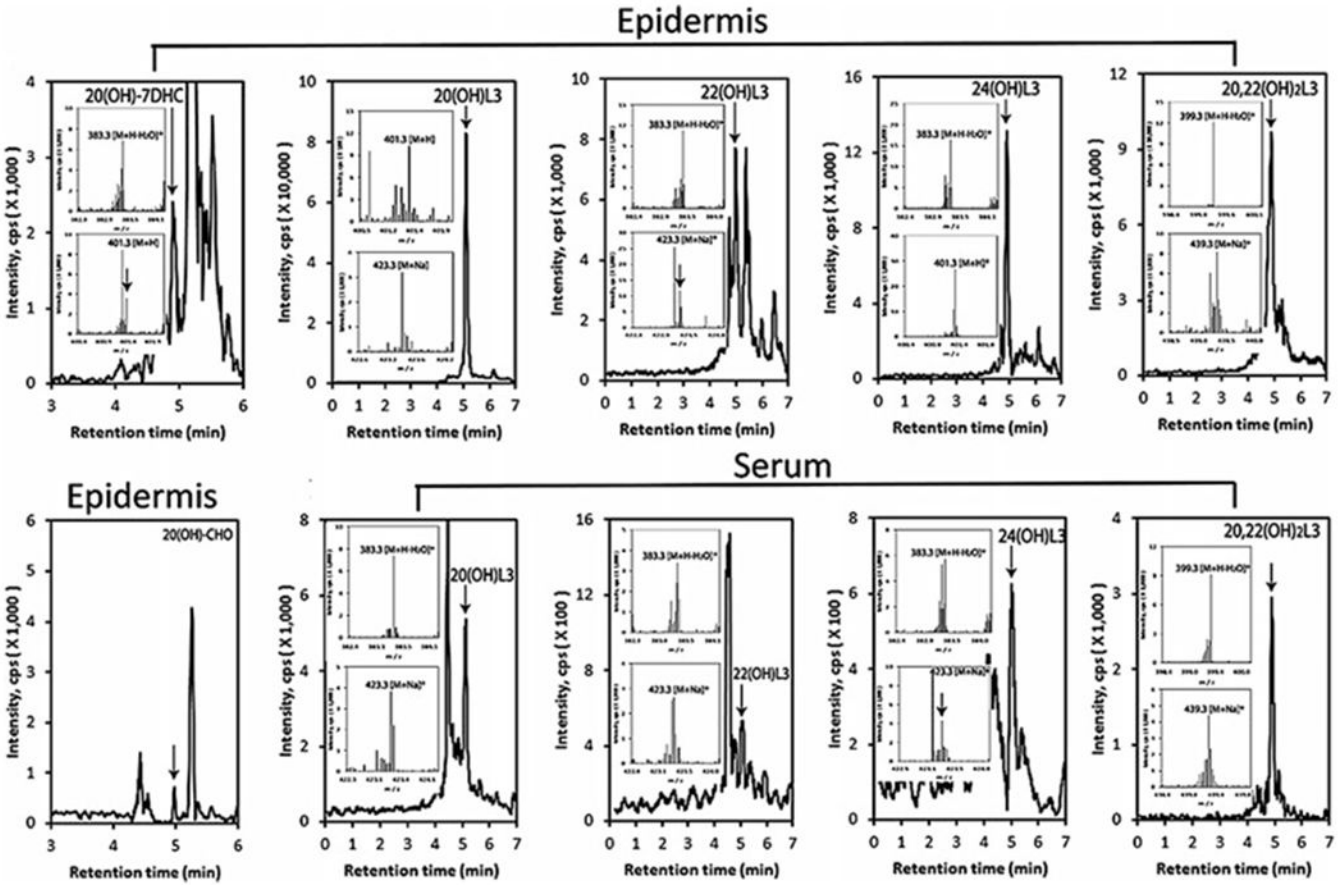


**Fig. 13.3.**

Detection of novel lumisterol hdroxyderivatives in the human epidermis and serum

LC-MS spectra were measured on fractions with retention times corresponding to either of the hydroxyderivatives listed that were pre-purified on a Waters C18 column as described in [202]. Arrows indicate the retention times of the corresponding standards. Inserts show the mass spectra corresponding to the retention time of the detected compound. The work is reprinted from [202] under the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/) with small modifications

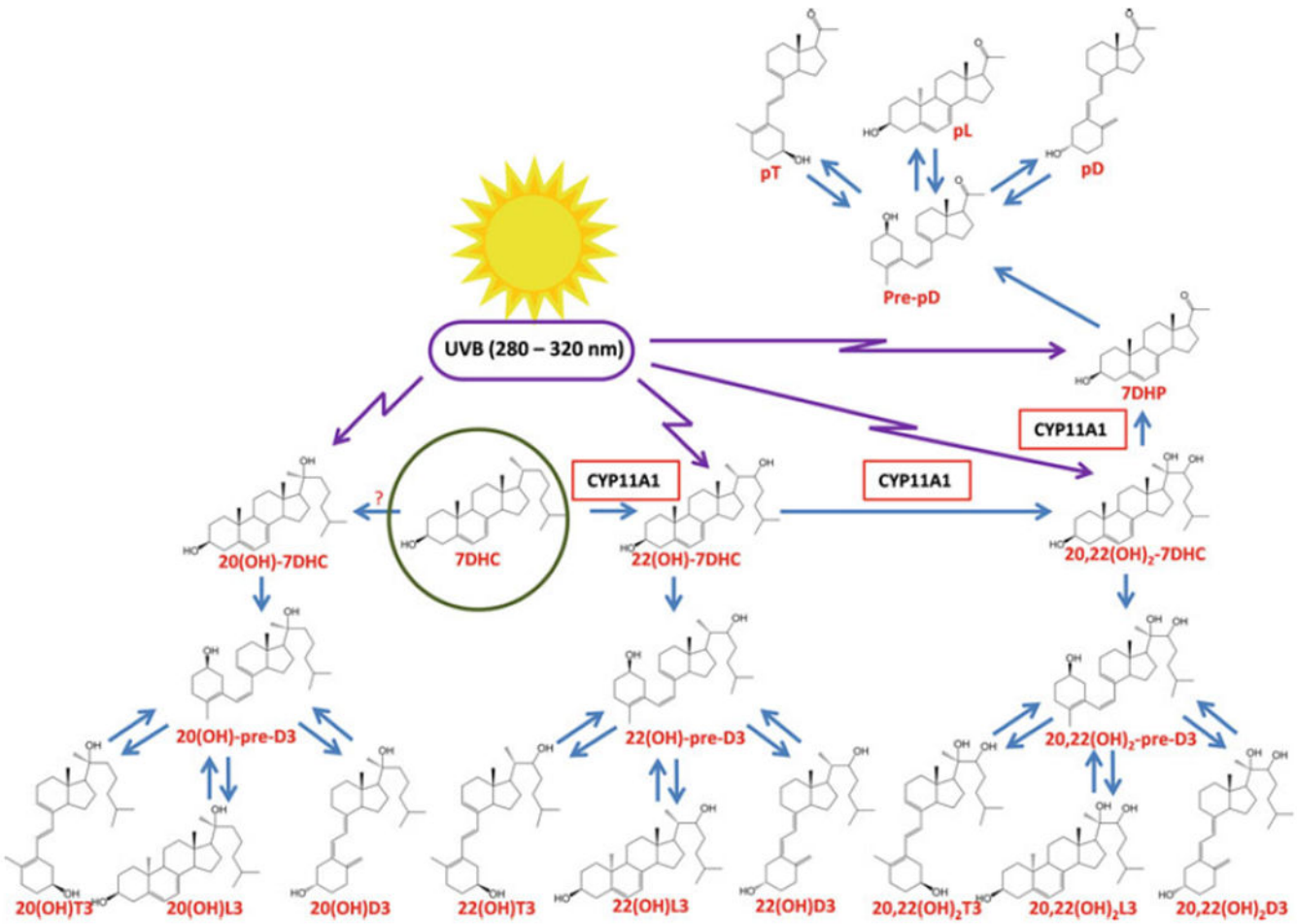


**Fig. 13.4.**

UVB-induced phototransformation of 7DHC, its hydroxyderivatives, and 7DHP to the corresponding secosteroidal, lumisterol, and tachysterol compounds

Shown is the metabolism of 7DHC by CYP11A1, the skin, and the subsequent transformations to the corresponding photoproducts after exposure to UVB. (?) – the enzyme transforming 7DHC to 20(OH)7DHC remains to be identified, since none of the products of 7DHC hydroxylation by CYP11A1 has its retention time. Because of the similarity of 20(OH)7DHC and 20-hydroxycholesterol, it is likely to be the same enzyme that transforms cholesterol into 20-hydroxychaolesterol, which is also detectable in the epidermis. (Reprinted from [208] with permission from Elsevier)

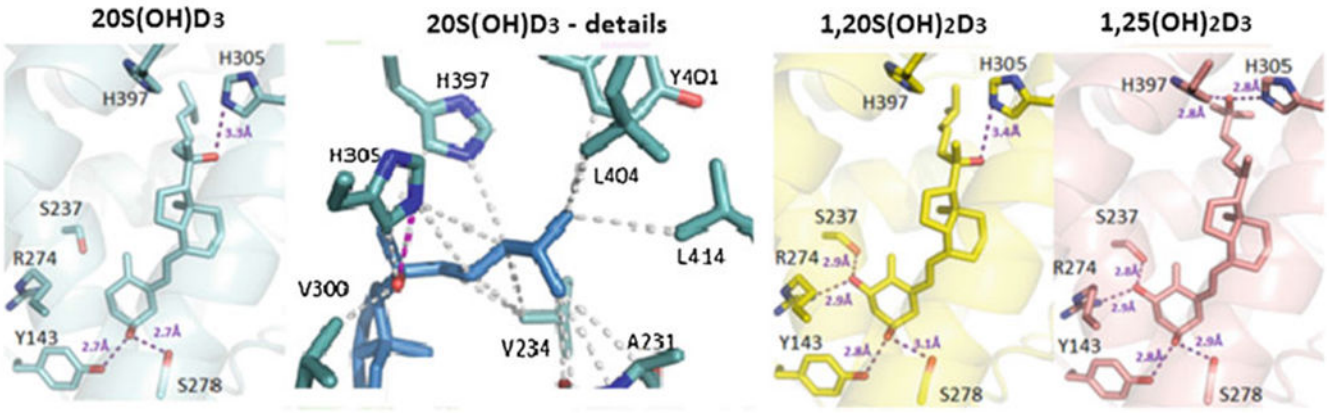


**Fig. 13.5.**

Crystal structures of 20(OH)D3, 1,20(OH)D3, and 1,25(OH)2D3 in complexes with the VDR ligand-binding domain

The crystal structures of 20*S*(OH)D3, in complex with the *Danio Rerio* VDR (zVDR) LBD, were determined and compared to those of 1,20$(OH)_2$D3 and 1,25$(OH)_2$D3 VDR complexes as described previously [119]. The complexes with 20(OH)D3 (PDB ID 5OW9), 1,20$(OH)_2$D3 (PDB ID 5MX7), and 1,25$(OH)_2$D3 (PBD ID 2HC4) are shown in cyan, yellow, and salmon, respectively. Hydrogen bonds between the ligands and LBD are represented by purple dashed lines. Details of the interactions mediated by the side chains of 20(OH)D3 are in the second image from the left. Hydrophobic interactions are indicated by gray dashed lines, and hydrogen bonds are depicted as pink dashed lines. Only residues within 4 Å of the ligand are shown by stick representation. The residue numbers correspond to human VDR. The detailed description and analysis are in [119]. (The work is reprinted from [119] under the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/) with small modifications)

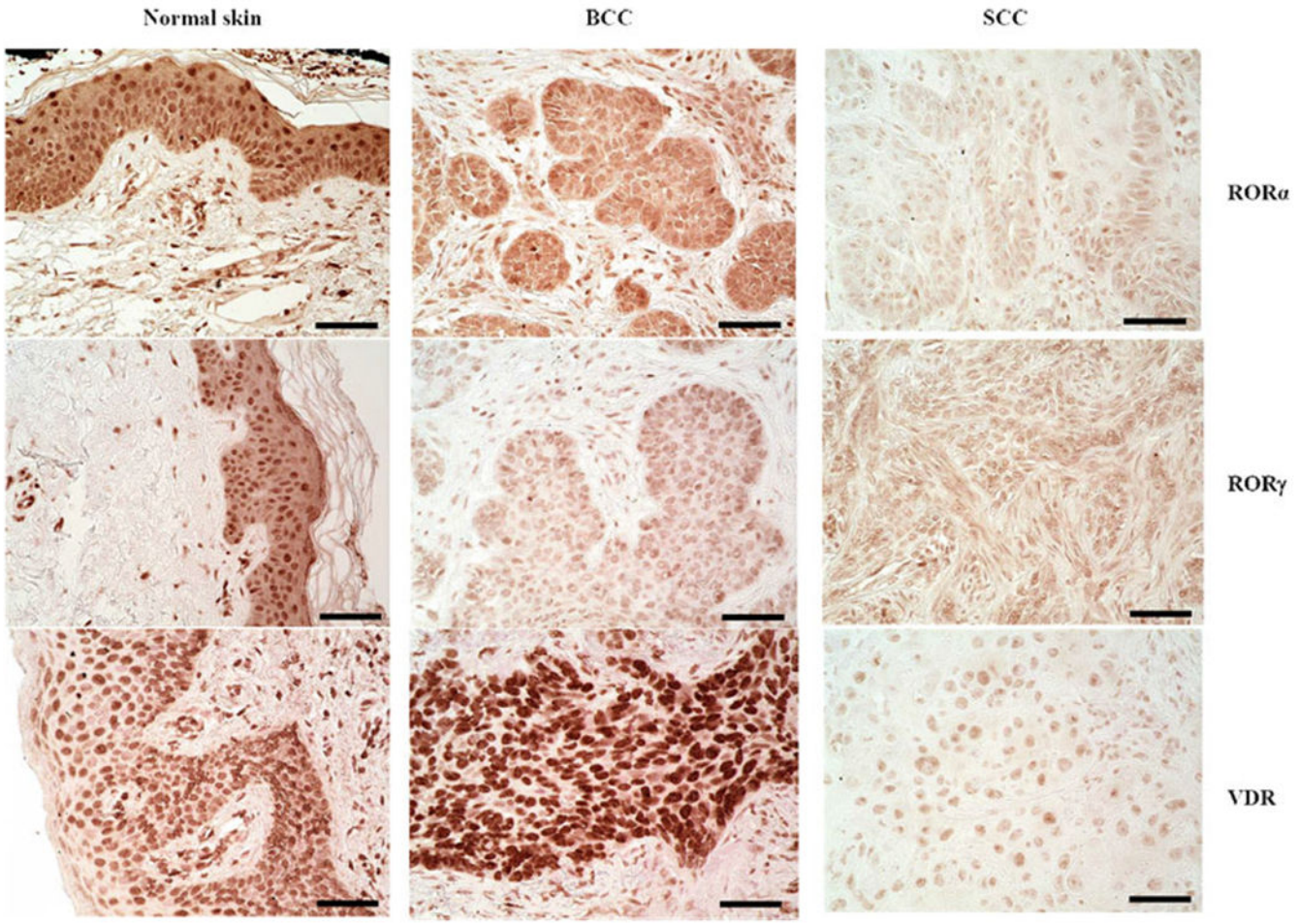


**Fig. 13.6.**

Immunohistochemical detection of RORα(upper), RORγ (middle), and VDR (lower) in normal skin (left panel), BCC (middle), and SCC (right). Scale bar: 50 μm. Archival formalin-fixed paraffin-embedded sections, after heat-induced antigen retrieval in Trisbased antigen unmasking solution (Vector Laboratories, Inc., Burlingame, CA) and endogenous peroxidase blocking, were incubated over night at 4 °C with primary antibodies (rabbit anti-RORα (provided by Dr. Anton M. Jetten), 1:400; rabbit anti-RORγ (provided by Dr. Anton M. Jetten), 1:50; rat anti-VDR (Abcam, MA1-710; Thermo Fisher Scientific, Waltham, MA)). Next, sections were incubated with secondary antibodies conjugated with HRP (anti-rabbit ImmPRESS antibody (ready to use, Vector Laboratories, Inc., Burlingame, CA) for RORα and RORγ; anti-rat antibody (1:200, Abcam, Cambridge, UK) for VDR), followed by peroxidase substrate ImmPACT NovaRED (Vector Laboratories Inc., Burlingame, CA, USA) application and mounting with permanent mounting media and glass coverslip (Thermo Fisher Scientific, Waltham, MA)

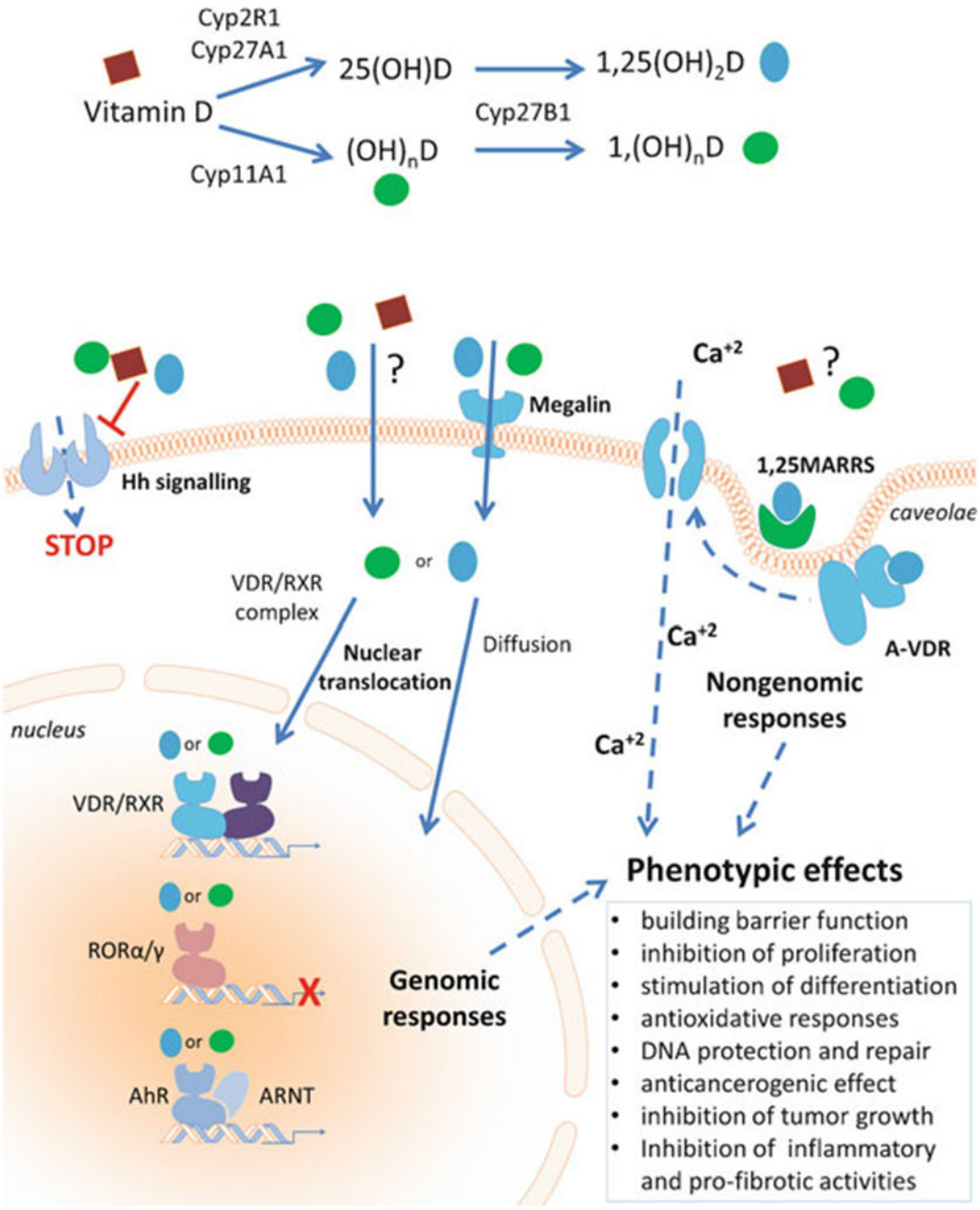


**Fig. 13.7.**