Photochemical & Photobiological Sciences

PERSPECTIVE

Challenge and perspective: the relevance of ultraviolet (UV) radiation and the vitamin D endocrine system (VDES) for psoriasis and other inflammatory skin diseases

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During evolution, the ability of many organisms to synthesize vitamin D photochemically represented, and still represents, a major driving factor for the development of life on earth. In humans because not more than 10–20% of the requirement of vitamin D can be satisfied by the diet (under most living conditions in the US and Europe), the remaining 80–90% need to be photochemically synthesized in the skin through the action of solar or artificial ultraviolet-B (UV-B) radiation. The skin is a key organ of the human body's vitamin D endocrine system (VDES), representing both the site of vitamin D synthesis and a target tissue for biologically active vitamin D metabolites. Human keratinocytes contain the enzymatic machinery (CYP27B1) for the synthesis of the biologically most active natural vitamin D metabolite 1,25-dihydroxy-vitamin D_3 ($1,25(OH)_2D_3$), representing an autonomous vitamin D_3 pathway. Cutaneous production of $1,25(OH)_2D_3$ may mediate intracrine, autocrine and paracrine effects on keratinocytes and on neighboring cells. Many skin cells (including keratinocytes, sebocytes, fibroblasts, melanocytes, macrophages and other skin immune cells) express the vitamin D receptor (VDR), an absolute pre-requisite for exerting genomic effects of $1,25(OH)_2D_3$ and analogs. The VDR is a member of the superfamily of *trans*-acting transcriptional regulatory factors, which also contains the steroid and thyroid hormone receptors as well as the retinoid-X receptors (RXR) and retinoic acid receptors (RAR). A large body of evidence, including cDNA microarray analyses of mRNAs, indicates that as many as 500–1000 genes may be controlled by VDR ligands that regulate a broad variety of cellular functions including growth, differentiation, and apoptosis. Clinical and laboratory investigations, including the observation that $1,25(OH)_2D_3$ is very effective in inducing the terminal differentiation and in inhibiting the proliferation of cultured human keratinocytes have resulted in the use of $1,25(OH)_2D_3$ and analogs for the treatment of psoriasis. Focussing on the UV-induced cutaneous synthesis of vitamin D, this review gives an update on the relevance of the VDES and of UV radiation for the management of psoriasis and other inflammatory skin diseases.

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Vitamin D-dependent effects of UV-radiation on psoriasis and other inflammatory skin diseases

Introduction

The photochemical synthesis of vitamin D that depends on the action of UV-radiation represents one of the most important driving factors both for the development of life on earth and for human evolution. It has been estimated that phytoplankton and zooplankton have been producing vitamin D for more than 500 million years.[1–3] While up to 10–20% of the human organism's requirement of vitamin D can be obtained by the diet (under most living conditions in the US and Europe), approximately 80–90% of all needed vitamin D has to be photosynthesized in the skin through the action of solar or artificial UV-B.[1–3]

The cutaneous vitamin D endocrine system (VDES)

In the skin, vitamin D is photochemically synthesized from 7-dehydrocholesterol (7-DHC, pro-vitamin D) by the action of solar or artificial ultraviolet-B (UV-B, 280–315 nm) radiation (maximum of spectral effectiveness: ≈297 nm) (Fig. 1). It has been reported that, dependent on various factors including temperature and time, <15% of 7-DHC can be converted into pre-vitamin D which thereafter isomerizes to vitamin D.[1–3] It was reported that the effect on the vitamin D status of a single

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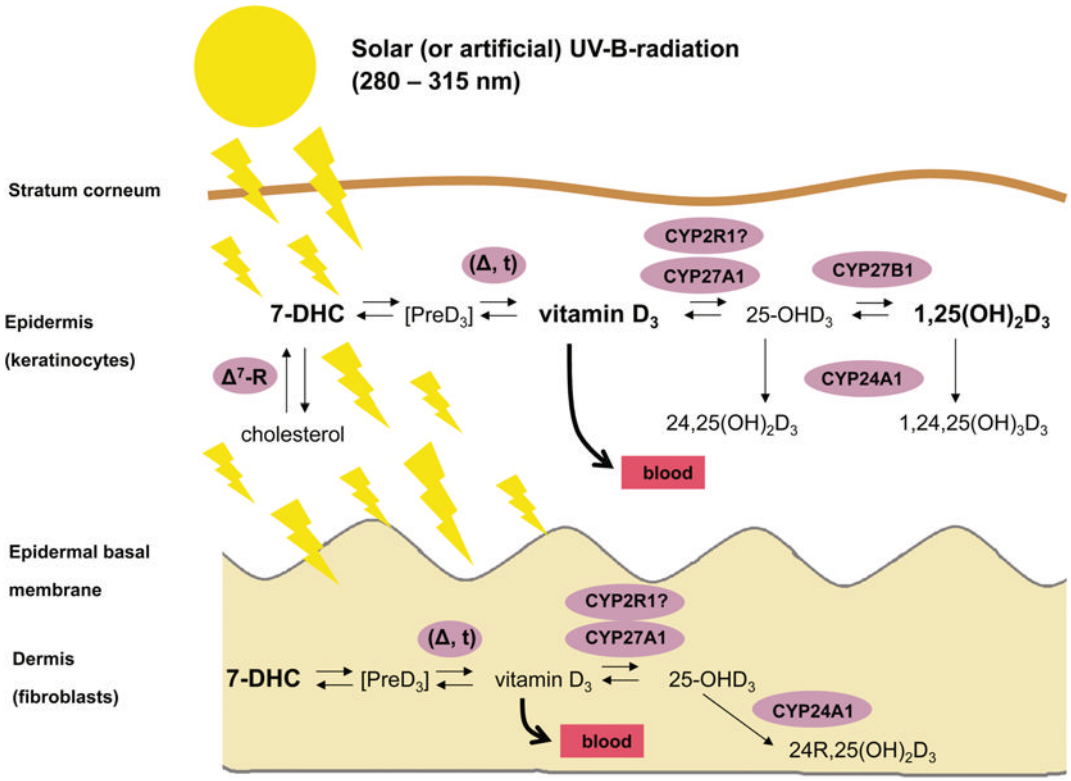

Fig. 1 The cutaneous vitamin D endocrine system. Δ7-R, delta-7-sterol reductase (encoded by the DHCR7 gene; the key enzyme of mammalian sterol biosynthesis that converts 7-dehydrocholesterol to cholesterol); 7-DHC, 7-dehydrocholesterol; preD, pre-vitamin D; t, temperature.

full-body exposure with 1.0 minimal erythemal dose (MED) UV-B corresponds to oral intake of 10 000–25 000 IU vitamin D and that only partial body exposure is sufficient to obtain sufficient amounts of vitamin D.[1–3] After binding to vitamin D binding protein (DBP, GC) and other carrier proteins in the blood, vitamin D is transported to the liver where it is hydroxylated (by CYP2R1 and CYP27A1) at the C25-position, generating 25-hydroxyvitamin D [25(OH)D],[1–3] the major circulating form of vitamin D in the human body. The investigation of 25(OH)D blood concentration is the best available laboratory parameter to analyze the vitamin D status of an individual person.[1–3] Various factors that influence a person's vitamin D status, including the skin type, body mass index (BMI), age and sun exposure have been identified; however, limited data exist on genetic determinants of serum 25(OH)D concentrations.[4,5] We have recently shown in a large cohort of Caucasian patients ("LURIC-study") that variants (SNPs) of genes (including EXOC2, TYR, TYRP1, and DCT) related to skin pigmentation are predictive of serum 25(OH)D levels.[4,5] After binding to DBP in the blood, 25(OH)D is transported to the kidneys and other tissues, where it is finally hydroxylated (by CYP27B1) at the C1α-position to generate hormonally active 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$].[1–3] $1,25(OH)_2D_3$ exerts potent effects in the kidney and is also transported by DBP to many other vitamin D receptor (VDR)-positive target tissues (including bone, intestine and parathyroid gland) to exert genomic and/or non-genomic effects.[1–3] Intracellular catabolism of $1,25(OH)_2D_3$ is induced by enzymatic hydroxylation (CYP24A1) at the C24-position followed by further oxidation generating water-soluble calcitroic acid that is excreted in the bile (Fig. 1).

The skin represents an important target tissue for the secosteroid hormone 1α,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$, calcitriol), the biologically active vitamin D metabolite.[1–3] Many skin cells (including keratinocytes, sebocytes, fibroblasts and melanocytes) express the VDR, an absolute prerequisite for the mediation of genomic effects of $1,25(OH)_2D_3$ and other biologically active vitamin D analogs.[1–3] However, clinical and laboratory investigations have convincingly shown that serum concentration of $1,25(OH)_2D_3$ is too low in humans to generate VDR-mediated hormonal effects in the skin.[1,6,7] Interestingly, an autonomous vitamin D_3 pathway has been demonstrated in human keratinocytes *in vitro*[8] and *in vivo*,[9] containing both the well characterized UVB-induced synthesis of vitamin D_3 and its enzymatically regulated further metabolism by vitamin D-25-hydroxylase (CYP2R1/CYP27A1) and 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) which generates substantial amounts of hormonally active $1,25(OH)_2D_3$. Moreover, *in vitro* investigations have demonstrated that dermal fibroblasts contain CYP27A1 but not CYP27B1. Therefore, it can be speculated that fibroblasts exert an important role in providing $1,25(OH)_2D_3$ precursors not only for various skin cells including keratinocytes but also for many other cell types *via* circulation.[1,10]

Recently, new alternative pathways of vitamin D activation, initiated by CYP3A4 [11] and CYP11A1,[12] have been described that appear to operate in the skin. An alternative pathway can be started by the action of CYP11A1 on the side chain of vitamin D_3, primarily producing $20(OH)D_3$, $22(OH)D_3$, $20,23(OH)_2D_3$, $20,22(OH)_2D_3$ and $17,20,23(OH)_3D_3$.[12] Some of these metabolites are hydroxylated by CYP27B1 at C1α, by CYP24A1 at C24 and C25, and by CYP27A1 at C25 and C26. It has been shown that the products of these pathways are at least in part present in the skin and are biologically active, including inhibiting skin fibrosis and melanoma cell proliferation, and consequently, it has been speculated that they may be of therapeutic value.[11,12]

As outlined above, epidermal keratinocytes are both: place of $1,25(OH)_2D_3$ production and target of this seco-steroid hormone. Cutaneous synthesis of $1,25(OH)_2D_3$ may exert intracrine, autocrine and paracrine effects on keratinocytes and on neighboring cells. It has been shown that VDES-mediated signaling regulates many important biological processes, including cellular growth, differentiation and apoptosis *via* non-genomic and genomic effects. Non-genomic effects of $1,25(OH)_2D_3$ and analogs are in part mediated by effects on intracellular calcium.[1,13,14] In epidermal keratinocytes and in other cell types, $1,25(OH)_2D_3$ rapidly increases free cytosolic calcium levels.[1,13,14]

Recently, it has been described that $1,25(OH)_2D_3$ initiates its calcium-dependent effects *via* binding to protein disulfide isomerase A3 (Pdia3), that has been identified as a corresponding membrane-associated receptor.[15] It was demonstrated that binding of $1,25(OH)_2D_3$ to Pdia3 triggers the interaction between Pdia3 and phospholipase A2 (PLA2)-activating protein (PLAA), resulting in downstream activation of calcium/calmodulin-dependent protein kinase II (CaMKII), PLA2, and protein kinase C (PKC).[15]

It has been shown that $1,25(OH)_2D_3$ exerts its genomic effects *via* binding to the classical VDR, a predominantly nuclear receptor protein that belongs to the superfamily of *trans*-acting transcriptional regulatory factors, which includes the steroid and thyroid hormone receptors as well as the retinoid-X receptors (RXR) and retinoic acid receptors (RAR).[1,16,17] Evolutionarily, VDR is most closely related to the pregnane X receptor (PXR) that regulates xenobiotic detoxification and to the farnesoid X receptor (FXR) which controls and governs bile acid metabolism.[1,16,17] VDR is present in target tissues and binds its ligand $1,25(OH)_2D_3$ with low capacity and high affinity (K_D: 10^{-9}–10^{-10} M),[16–20] resulting in heterodimerization with RXR followed by zinc finger-mediated binding to vitamin D response elements (VDREs) in the regulatory region of target genes that are directly governed by $1,25(OH)_2D_3$.[1,16,17] In conclusion, VDES-mediated cellular signalling depends upon the metabolic production or delivery of sufficient concentrations of the $1,25(OH)_2D_3$ ligand, expression of adequate VDR and RXR receptor proteins (and of nuclear accessory factors) and of cell-specific programming of transcriptional responses to control selected genes that encode proteins that finally exert the multiple biological effects of vitamin D-signaling.[1,16,17] Both VDR and RXR-α are expressed in keratinocytes, fibroblasts, sebocytes (sebaceous gland cells), endothelial cells, Langerhans cells, and most cell types of the skin immune system.[1,21,22] There is a large number of genes in keratinocytes which are regulated by $1,25(OH)_2D_3$, supporting the link between the therapeutic effect of UVB radiation in the treatment of psoriasis and the cutaneous vitamin D_3 pathway.[1–3]

Many laboratory investigations, including cDNA microarray-based analyses of mRNA expression, indicate that as many as 500–1000 genes may be directly controlled by VDR ligands.[1,16,17] Transcriptional regulation of cell cycle regulatory proteins including p21/WAF-1 (CDKN1A), and of other proteins relevant for cellular growth and differentiation, including β_3-integrin and fibronectin, by $1,25(OH)_2D_3$ has been reported.[1,16–20]

Interestingly, new candidates for alternative receptors to the classical VDR such as PDIA3 [15] and ROR alpha and gamma[12,23] have been described recently. Although the relevance of these findings for skin physiology has to be further elucidated, it can be speculated that these new potential alternative receptors may mediate, at least in part, the effects of some active forms of vitamin D in the skin and may help explain the pleiotropic effects of vitamin D.[23]

Biological effects of $1,25(OH)_2D_3$ on human skin

As outlined above, $1,25(OH)_2D_3$ is not only a calciotropic hormone. It controls in many cell types various important cellular functions including cell growth and differentiation *via* endocrine, paracrine and/or autocrine pathways.[1–3] *In vitro* studies have revealed that $1,25(OH)_2D_3$ is very effective in promoting terminal differentiation and in decreasing proliferation of cultured human keratinocytes in a dose-dependent manner.[24–26] Additionally, $1,25(OH)_2D_3$ mediates effects on many cell types present in the skin, that are involved in immunologic reactions, including lymphocytes, macrophages and Langerhans cells.[27,28] Antimicrobial innate immune responses are under the direct control of $1,25(OH)_2D_3$,[29–31] which, along with lipopolysaccharides (LPS), synergistically induces cathelicidin antimicrobial peptide (camp) expression in many cell types, including human keratinocytes, monocytes and neutrophils.[29–31] Moreover, toll-like receptor (TLR)-mediated activation of human macrophages stimulates expression of VDR and CYP27B1, leading to induction of cathelicidin and killing of intracellular *Mycobacterium tuberculosis*.[29–31] In conclusion, the effects of solar or artificial UV radiation on the innate and adapted immune system are not exclusively immunosuppressive, but also stimulate distinct immune response pathways.

Interestingly, vitamin D and analogs stimulate immunologic responses both in conventional dendritic cells (cDCs), and in plasmacytoid DCs (pDCs).[32] pDCs represent a specialized, naturally occurring DC subset that was shown to be of importance for psoriasis and other autoimmune diseases. pDCs from the blood rapidly infiltrate psoriatic skin lesions as an early event and may represent a key to the initiation of the

immune-mediated pathogenesis of the disease. It was shown that pDCs contain important proteins of the VDES, including VDR, Cyp27B1 and Cyp24A1, and that VDR is transcriptionally active in pDCs.[32] Moreover, vitamin D signaling impairs the capacity of human pDCs to stimulate T-cell proliferation and secretion of the T-helper 1 cytokine IFNγ. This inhibitory effect depends on the presence of the VDR in the DCs. It has been concluded that vitamin D signaling can act as a natural inhibitory mechanism on both cDCs and pDCs, which may instigate the development of vitamin D-based therapeutic procedures for psoriasis and other inflammatory skin diseases.[32]

A recent study indicated that cutaneous mast cells may exert their immunomodulatory effects at least in part *via* the VDES.[33] In this investigation, biopsies were taken from non-lesional and lesional skin of patients with actinic keratosis (AK), Bowen's disease/squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and psoriasis. The presence of CYP27A1 and CYP27B1 in mast cells was analysed by immunohistology using a sequential double-staining method. The percentage of mast cells immunoreactive for CYP27A1 was significantly higher in lesional as compared with non-lesional skin in all diseases, especially in SCC and BCC. The percentage of mast cells immunoreactive for CYP27B1 was significantly increased in BCC, AK, and psoriatic lesions as well. In human LAD2 mast cell cultures, about 30% and 15% of the mast cells showed CYP27A1 and CYP27B1, respectively.[33] It can be concluded that mast cells may promote an immunosuppressive environment, *e.g.*, in psoriasis or in skin carcinoma.[33]

Findings reported in the literature about the effects of the VDES on the melanin pigmentation system are still conflicting.

While some studies[34] suggested that (*e.g.* topical) administration of vitamin D_3 derivatives may increase skin pigmentation, other investigations do not support the concept that $1,25(OH)_2D_3$ might directly regulate melanogenesis in human skin.[1,35]

It was shown that human sebocytes (sebum-producing cells that form the sebaceous glands) represent target cells for biologically active vitamin D metabolites, expressing VDR and the enzymatic machinery to synthesize and metabolize biologically active vitamin D analogs.[1,36] Incubation of SZ95 sebocytes with $1,25(OH)_2D_3$ resulted in a cell culture condition-, time-, and dose-dependent modulation of cell proliferation, cell cycle regulation, lipid content and interleukin-6/interleukin-8 secretion *in vitro*, while RNA expression of VDR and CYP24A1 was upregulated along with vitamin D analog treatment.[1,36] It was concluded that the vitamin D endocrine system is of high importance for sebocyte function and physiology, and that sebaceous glands represent potential targets for therapy with vitamin D analogs or for pharmacological modulation of $1,25(OH)_2D_3$ synthesis and metabolism.[1,36]

From the bench to the clinic: biological effects of $1,25(OH)_2D_3$ and analogs on psoriasis vulgaris

The use of vitamin D compounds for the treatment of psoriasis vulgaris resulted from two independent lines of investigation. It seemed reasonable that the antiproliferative effects of $1,25(OH)_2D_3$ could be used for the treatment of this hyperproliferative and inflammatory skin disorder. However, before launching clinical trials in 1985, MacLaughlin and associates reported the observation that primary cultured fibroblasts from psoriatic skin are partially resistant to the antiproliferative effects of $1,25(OH)_2D_3$.[1,37] This observation prompted MacLaughlin and associates to speculate that $1,25(OH)_2D_3$ may be effective in the treatment of the hyperproliferative skin disease psoriasis. The other line of investigation resulted from a clinical observation. In 1985, Morimoto and Kumahara reported that a patient, who was treated orally with 1α-$(OH)D_3$ for osteoporosis, had a dramatic remission of psoriatic skin lesions.[38] Morimoto *et al.* reported a follow up study, demonstrating that almost 80% of 17 patients with psoriasis who were treated for up to 6 months orally with 1α-$(OH)D_3$ at a dose of 1.0 μg per day showed clinically significant improvement.[39]

Many studies have reported that $1,25(OH)_2D_3$ and various analogs, including calcipotriol, tacalcitol, hexafluoro-1,25-dihydroxyvitamin D_3,[40] and maxacalcitol are effective and safe in the topical treatment of psoriasis.[1,41–47] It was shown that topically applied $1,25(OH)_2D_3$ and its analogs are very effective and safe for the long term treatment of psoriasis.[1,47,48] Calcipotriol (MC 903) is a vitamin D analog with similar VDR binding properties compared to $1,25(OH)_2D_3$, but low affinity for DBP. *In vivo* studies in rats showed that effects of calcipotriol on calcium metabolism are 100–200× lower as compared to $1,25(OH)_2D_3$, while the *in vitro* effects on proliferation and differentiation on human keratinocytes are comparable.[49] These differential effects are probably caused by the different pharmacokinetic profiles of calcipotriol and $1,25(OH)_2D_3$ (different affinity for DBP). Serum half-life in rats of these vitamin D compounds was shown to be 4 min after treatment with calcipotriol in contrast to 15 min after treatment with $1,25(OH)_2D_3$.[1,49] The fast degradation of calcipotriol after systemic administration has limited its oral use but made it an ideal drug for topical use. Applied twice daily topically in amounts of up to 100 grams of ointment (50 μg calcipotriol per g ointment) per week, calcipotriol was shown to be slightly more effective in the topical treatment of psoriasis than betamethasone 17-valerate ointment.[1,48]

Vitamin D analogs have been shown not to exhibit tachyphylaxis during treatment of psoriatic lesions and topical treatment can be continued indefinitely. The results of four separate studies designed to evaluate specific local-safety parameters of various vitamin D analogs including cumulative irritancy, cutaneous contact sensitization, photoallergic contact sensitization and phototoxicity were analysed.[1,50] $1,25(OH)_2D_3$ (3 μg g^{-1}) ointment was classified as non-irritant when compared to calcipotriol, tacalcitol and white petrolatum (control). Petrolatum and tacalcitol were slightly irritant and calcipotriol was moderately irritant. No sensitization was observed with $1,25(OH)_2D_3$ (3 μg g^{-1}) ointment. With regard to phototoxic potential, sites treated with $1,25(OH)_2D_3$ (3 μg g^{-1}) ointment or vehicle ointment were less irritated than those treated with white petrolatum or those that were untreated. Using standard

photo-allergenicity testing methodology, there were no skin reactions of a photo-allergic nature to the study material.[50]

Interestingly, a long-term study has convincingly demonstrated the efficacy and safety of oral $1,25(OH)_2D_3$ as a potential treatment of psoriasis.[51] 88.0% of the 85 patients included in that study who received oral $1,25(OH)_2D_3$ for 36 months, had some improvement in their disease, while 26.5%, 26.3% and 25.3% had complete, moderate and slight improvement in their disease, respectively. Serum calcium concentrations and 24 h urinary calcium excretion increased by 3.9% and 148.2%, respectively, but were not outside the normal range. Bone mineral density of these patients remained unchanged. A very important consideration for the use of orally administered $1,25(OH)_2D_3$ is the dosing technique. To avoid its effects on enhancing dietary calcium absorption, it is very important to provide $1,25(OH)_2D_3$ at night time. Perez *et al.* showed that as a result of this dosing technique, doses of 2 μg per night to 4 μg per night are well tolerated by psoriatic patients.[51]

To date, the precise mechanisms underlying the therapeutic effectiveness of vitamin D compounds in psoriasis are still not completely understood. The results from immunohistochemical and molecular biology studies performed several decades ago indicate that the antiproliferative effects of topically applied vitamin D compounds on epidermal keratinocytes are more pronounced as compared to effects on dermal inflammation. Modulation of various markers of epidermal proliferation (proliferating cell nuclear antigen (PCNA) and Ki-67 antigen), and differentiation (involucrin, transglutaminase K, filaggrin, cytokeratins 10, 16) in lesional psoriatic skin after topical application of vitamin D analogs was shown *in situ*.[52] Interestingly, effects of topical treatment with vitamin D analogs on dermal inflammation are less pronounced (CD-antigens, cytokines, HLA-DR *etc.*) as compared to effects on epidermal proliferation or differentiation. One reason for this observation may be that the bioavailability of this potent hormone in the dermal compartment may be markedly reduced as compared to the epidermal compartment.[32,52–55]

Molecular biology studies have demonstrated that clinical improvement in psoriatic lesions treated topically with $1,25(OH)_2D_3$ correlates with an elevation of VDR mRNA.[56] It is well known that some patients suffering from psoriasis are resistant to topical $1,25(OH)_2D_3$ treatment. It was demonstrated that responders can be distinguished from non-responders at the molecular level since non-responders show no elevation of VDR mRNA in skin lesions along with the treatment and express relatively low levels of VDR. These findings indicate that the ability of $1,25(OH)_2D_3$ to regulate keratinocyte growth is closely linked to the expression of VDR. The target genes of topical $1,25(OH)_2D_3$ that are responsible for its therapeutic efficacy in psoriasis are still unknown. Major candidates for $1,25(OH)_2D_3$ target genes that are responsible for the $1,25(OH)_2D_3$-induced terminal differentiation in keratinocytes are distinct cell cycle associated proteins (*i.e.* INK4 family), including p21/WAF-1.[57,58]

Data analyzing VDR expression and genotype in psoriasis are somewhat conflicting, some studies report a correlation between VDR expression or individual VDR genotypes (SNPs) and the skin eruptions of psoriasis, as well as with responsiveness to treatment with vitamin D analogs.[56,59,60] While no differences in VDR genotype between controls and psoriasis patients were reported at the BsmI site, some studies reported significant difference in terms of ApaI SNP[61] and FokI SNP.[62] Additionally, it was shown that vitamin D receptor genotypes are not associated with a clinical response to calcipotriol, at least in Korean psoriasis patients.[63] Kontula *et al.* and Mee *et al.* investigated the BsmI polymorphism and the response to calcipotriol treatment in psoriatic patients and found no association between them.[64,65] According to Colin *et al.*, the FokI polymorphism was associated with the response to calcipotriol, and under conditions of vitamin D insufficiency this finding might have clinical implications.[66,67]

Data concerning serum levels of $1,25(OH)_2D_3$ or 25(OH)D in psoriatic patients are conflicting. Some studies report reduced levels of $1,25(OH)_2D_3$ in patients with manifest disease.[68] Additionally, the coincidence of pustular psoriasis with hypocalcemia[69] and the exacerbation of psoriasis under chloroquine therapy (thereby reducing $1,25(OH)_2D_3$ levels *via* inhibition of 1α-(OH)ase) are well known.[70]

Treatment of other inflammatory skin disorders with $1,25(OH)_2D_3$ or analogues

Targeting the vitamin D endocrine system (VDES) for the treatment of congenital and acquired ichthyoses. A comparative study (double-blind, bilaterally paired) has demonstrated the effectiveness and safety of topically applied calcipotriol ointment on congenital ichthyoses (Comel–Netherton syndrome, lamellar ichthyosis, ichthyosis bullosa of Siemens, and bullous ichthyotic erythroderma of Brocq).[1,71] In all patients with lamellar ichthyosis or with bullous ichthyotic erythroderma of Brocq, a marked reduction in scaling and roughness was seen on the calcipotriol-treated skin area. The only patient suffering from Comel–Netherton syndrome who received calcipotriol ointment showed mild improvement of skin lesions, while the only patient with ichthyosis bullosa of Siemens included in that study did not show any change in severity on the calcipotriol-treated as compared to the vehicle-treated skin lesions. Additional preliminary findings indicate that topically applied tacalcitol is not effective against various types of ichthyoses (including X-linked ichthyosis (XLI), ichthyosis vulgaris (IV), and acquired ichthyosis) that are characterized by a lack of epidermal hyperproliferation and by retentive hyperkeratosis.[1,72]

$1,25(OH)_2D_3$ or analogues for treatment of scleroderma. A pilot study supported the concept that $1,25(OH)_2D_3$ or analogues may be promising agents for the treatment of scleroderma. Humbert *et al.* reported that oral administration of $1,25(OH)_2D_3$ (1.0–2.5 μg per d) improves skin lesions, probably *via* modulation of fibroblast proliferation and dermal collagen synthesis and/or deposition.[1,73]

Targeting the vitamin D endocrine system (VDES) for the treatment of acne. The therapeutic efficacy and safety of vitamin D and analogs in acne had been investigated with

limited success in the middle of the last century.[1,74,75] Interestingly however, more recent laboratory and animal studies support the concept that vitamin D compounds may be effective and safe in acne therapy.[76,77] Acne vulgaris is potentially stigmatizing and represents the most common skin disorder affecting millions of people worldwide.[76] It was reported that inflammation caused by the immune response targeting *Propionibacterium acnes* (*P. acnes*) has a relevant role for its pathogenesis.[76] In human peripheral blood mononuclear cells (PBMCs) it was shown that *P. acnes* is a powerful stimulator of T helper 17 (Th17) and Th1, but not of Th2 responses. *P. acnes* induced expression of several genes critically involved in Th17-responses, including IL-17A, RORα, RORc, IL-17RA, and IL-17RC, and stimulated IL-17 secretion from CD4(+), but not from CD8(+) T cells. Supernatants of *P. acnes*-stimulated PBMCs induced differentiation of naive CD4(+)CD45RA T cells into Th17 cells. Interestingly, IL-17-expressing cells were observed in skin biopsies of patients suffering from acne vulgaris but not in skin biopsies from normal donors. Interestingly, $1,25(OH)_2D_3$ reduced *P. acnes*-induced Th17 differentiation.[1,76] The authors concluded that $1,25(OH)_2D_3$ and analogs may represent promising compounds to modulate acne vulgaris and other Th17-mediated diseases.[1,76]

Interestingly, a comedolytic effect of topically applied active vitamin D_3 analog maxacalcitol on pseudocomedones was demonstrated in the rhino mouse model.[1,77] The rhino (hr^{rh}/hr^{rh}) phenotype is due to an autosomal recessive mutation in the hairless (*hr*) gene.[77] In the rhino mouse, utriculi are derived from the infundibular zone of the initial follicular units, and are histologically similar to comedones.[77] In that study, rhino mice were treated topically with tretinoin and maxacalcitol once daily for 2 and 4 weeks, respectively. Histological analysis (observing the dermal side of the epidermal sheet in haematoxylin and eosin-stained vertical sections) revealed that application of maxacalcitol (25 μg g^{-1}) and tretinoin (0.1%) significantly reduced both size and diameter of the utricle after 1 week of treatment.[77] Histopathologically, maxacalcitol and tretinoin strongly induced epidermal hyperplasia associated with accumulation of a few inflammatory cells in the dermis, with and without hypercornification, respectively.[77] These interesting findings point to a comedolytic effect of topically applied maxacalcitol with underlying mechanisms of action that may differ from retinoids. These findings indicate promising clinical applications that remain to be elucidated in well designed future investigations.

Targeting the vitamin D endocrine system (VDES) for the treatment of rosacea. Rosacea represents a common, chronic inflammatory skin disease that predominantly affects the central skin area of the face. The underlying pathogenetic mechanisms are at present still only partly understood.[78] In affected skin areas, the expression of the antimicrobial peptide cathelicidin is strongly increased.[78] Moreover, the activity of several cutaneous proteases is greatly increased resulting in the generation of cathelicidin peptide fragments with strong pro-inflammatory activity.[78] UV irradiation and microbial factors increase this inflammatory cascade by enhancing vitamin D metabolism and the activation of toll-like receptors (TLR). These interesting findings indicate that the VDES may represent a new and promising target for the safe and effective therapy of this common, stigmatizing skin disease.[78]

The vitamin D endocrine system (VDES) and cutaneous wound healing. Laboratory and animal investigations support the concept that $1,25(OH)_2D_3$ and its analogs may stimulate cutaneous wound healing.[79] The effect of $1,25(OH)_2D_3$ or its analogs on wound healing is associated with an upregulated expression of the antimicrobial peptide cathelicidin.[1,79] However, the relevance of these interesting results has to be further investigated in the future in laboratory and clinical studies.

Vitamin D and other skin diseases. A number of case reports demonstrate positive effects of topical treatment with $1,25(OH)_2D_3$ or its analogs in a broad variety of independent skin diseases, including pityriasis rubra pilaris, transient acantholytic dermatosis (Grover's disease), inflammatory linear verrucous epidermal naevus (ILVEN), disseminated superficial actinic porokeratosis, epidermolytic palmoplantar keratoderma of Vorner, confluent and reticulated papillomatosis (Gougerot–Carteaud syndrome) and Sjögren–Larsson syndrome.[1,80,81] However, these interesting findings need to be further investigated in the future in well designed clinical trials.

Vitamin D-independent effects of UV-radiation on psoriasis and other inflammatory skin diseases

Ultraviolet-radiation for the treatment of psoriasis: a brief historical overview

The therapeutical efficacy of ultraviolet radiation for the treatment of skin diseases was first widely recognized in 1903 when Niels Finsen, who had treated patients with lupus vulgaris (tuberculosis of the skin), received the Nobel prize for the medical application of phototherapy.[82] Other important breakthroughs for dermatologic phototherapy were the introduction of ultraviolet phototherapy for the treatment of psoriasis by William Goeckerman in 1925 at the Mayo clinic ("Goeckerman therapy": hospital admission for several weeks with daily applications of crude coal tar to the entire body for several hours followed by exposure to hot quartz mercury vapour lamps),[83,84] the substitution of the crude coal tar with anthralin paste in the 1950s by Ingram ("Ingram therapy"), and the introduction of PUVA-therapy (exposure to UVA after topical application or ingestion of psoralen, a photosensitizing chemical) in the 1970s.[85] Psoralen was successfully isolated in 1948 and first used prior to UVA topically in 1973 and orally in 1974 for psoriasis treatment.[85] The most common psoralens used in North America and in Europe are 8-methoxypsoralen (8-MOP) and 5-MOP.[82] In 1984, Phillips introduced a lamp (TL-01) which emitted UV radiation in a very narrow range

(311 ± 2 nm) that provides at present probably the best available balance between a therapeutic response and limiting erythemogenic effects or skin burning. In general, phototherapy and photochemotherapy are at present indicated for patients with moderate-to-severe psoriasis who are unresponsive to topical therapy.[86]

Immunomodulatory effects of UV exposure on skin cells that contribute to the efficacy of dermatologic phototherapy

Many independent lines of investigation provide strong scientific evidence for potent UV-mediated immunoregulatory effects. The mechanisms that mediate these UV-induced immunomodulatory effects have been reviewed previously.[87] Unfortunately, there is not one good measure of immunosuppression.[87,88] Most studies have measured effects of UV on abrogating delayed hypersensitivity responses. This is clinically evident in the context of contact dermatitis patch testing where cell mediated responses are blunted by recent UV exposure and tests may be rendered falsely negative.[87,88] While some of the UV-mediated immunoregulatory effects are mediated *via* the UV-B-induced synthesis of vitamin D, others are independent of vitamin D signaling. Immunosuppressive effects of UV radiation were demonstrated by Margaret Kripke's laboratory in a series of well designed animal studies. In these important experiments,[87–89] UV-induced skin cancers were transplanted into synergetic mice which were either treated with UVB radiation or not. While the transplanted skin tumours continued to grow in UVB-treated mice, untreated animals were able to reject the skin tumours.[87–89] Interestingly, this immunosuppressive effect was also found when lymphocytes from UVB-treated mice were injected into untreated animals.[87–89] It is generally accepted that UV-mediated immunoregulatory effects are very complex and not exclusively caused by a single mechanism.[87,88] Notably, the action spectra are identical for UV-induced formation of CPDs and of tumour necrosis factor alpha (TNF-α)[87,88,90] which in turn is stimulated by interleukin-1.

UVB-induced immunosuppression is mediated locally in the skin at least in part *via* direct effects on skin immune cells, including Langerhans cells.[87,88] Even in low doses, UV depletes Langerhans cells that represent dendritic cells critical for the presentation of antigens to the immune system in exposed skin areas.[87,88,91–94] In a series of clinical investigations, dose-dependent effects of UV on Langerhans cells that may depend on the genetic background have been demonstrated in humans.[87,88] Interestingly, it has been reported that individuals who fail to deplete Langerhans cells when skin areas are initially exposed to the antigen in the setting of UV exposure, often present with the clinical manifestation of polymorphic light eruption (PLE).[87,88] Notably, it has been speculated that this lack of UV-induced Langerhans cell depletion may be protective against the development of non-melanoma skin cancer.[87,88,93] This hypothesis is supported by an epidemiological study that indicated a reduced prevalence of polymorphic light eruption that appeared reduced in skin cancer patients as compared to individuals without skin cancer, despite apparently comparable UV exposure in both groups.[87,88,95] Interestingly, a randomized double-blinded placebo-controlled intra-individual trial suggested a potential therapeutic benefit of topical 1,25-dihydroxyvitamin D_3 analogues as prophylactic treatment in patients with PLE.[34]

Kripke's experiments in mice suggest that cutaneous squamous cell carcinomas are highly antigenic and that mechanisms whereby the antigen is recognised are of high importance for preventing photocarcinogenesis.[87,88,94] In photocarcinogenesis the importance of mutated cells carrying highly relevant p53 mutations has been well described. Clones of cells carrying p53 mutations are found in chronically UV exposed skin.[87,88,96] It has been hypothesized that if the immune system is functionally intact, such mutant cells may be policed by antigen presenting cells and T memory cells and may not develop the malignant phenotype.[87,88,97] DNA photoproducts including cyclobutane pyrimidine dimers are connected with the suppression of T memory cells,[87,88,97] a mechanism that has been implicated in the UV-mediated reduction of immune surveillance. Failure of immune regulation that may be caused by ongoing sun-exposure, chronic lymphatic leukaemia or by long term systemic immunosuppression, may therefore result in progression of clones of cells carrying p53 mutations to actinic keratoses and frankly invasive squamous cell carcinomas.[87,88] Nucleotide excision repair is a very important protective mechanism against photocarcinogenesis.[87,88,98]

In the skin of UV-irradiated mice, pyrimidine dimer formation does not only initiate the tanning response.[87,88] Following UV, DNA repair results in DNA fragments being excised from the DNA molecule. These small DNA fragments (oligomers) directly cause immunoprotective effects when applied to the skin.[87,88,99] Thus cutaneous DNA repair exerts effects on the immune system but in a protective way.[87,88]

Another immunosuppressive effect of UV is mediated by the isomerisation of urocanic acid in the stratum corneum.[87,88,100] Urocanic acid is normally found in its *trans* isoform but with irradiation by UVB is transformed to its *cis*-isomer which has been shown to represent a potent systemic immunosuppressant.[87,88] The action spectrum for the induction of this transformation appears to be in the UVB range.[87,88] It has been suggested that *cis*-urocanic acid's ability to suppress cutaneous contact hypersensitivity is mediated *via* TNF-α.[87,88,101] Moreover, UV-irradiated urocanic acid inhibits delayed hypersensitivity reactions to herpes simplex in mice.[87,88,102]

Moreover, UV-exposure of the skin modulates several important growth factor receptor-mediated signaling pathways, including pathways mediated by epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and insulin receptor (IR).[87,88,103–106] Notably, UV exposure of skin areas has been reported to stimulate platelet-derived growth factor (PDGF), a growth factor thought to be pivotal both in UVB-induced[87,88,107] and in PUVA-induced immunosuppression.[87,88,108] UVB activates receptors for several important primary cytokines, including IL-1 and tumour necrosis factor-α,

and the death receptor Fas.[87,88,109,110] Moreover, various primary cytokines involved in immunosuppression, including IL-1, IL-6, and IL-10, have been shown to be induced by UV.[87,88] Induction of IL-1 like activity by UV has been reported in functional assays.[87,88,111] Interleukin-10 has been identified as a key mediator of systemic immunosuppression.[87,88,112] The induction of tolerance that is caused by UV-exposure of skin areas is transferable *via* regulatory T cells (CD4+CD25+) and depends on IL-10 produced by the host.[87,88,113]

UV also induces in exposed skin areas the paracrine secretion of melanocyte stimulating hormone (MSH) from keratinocytes; thereby locally regulating immunosuppression and proinflammation.[87,88,114] The receptor for pigment regulation within melanocytes, melanocortin receptor, is also regulated by UV.[87,88,115]

As outlined above, the immunomodulatory effects of UV are very complex and are both dose and wavelength dependent.[87,88,116] UVB and UVA exert different immunomodulatory effects, and the order of irradiation may determine the outcome.[87,88,117] The clinical consequences of these immunomodulatory effects may present as infection, carcinogenesis or, as previously mentioned, photoallergic reactions such as polymorphic light eruption.[87,88] The action spectrum for induction of herpes simplex has been shown to be in the UVB range.[87,88,118] UVB is up to 1000-times more biologically active compared with UVA. However, UVA also has immunosuppressive effects,[87,88] and as the UVA fluence rates are 100 times larger than those of UVB at noon, is prevalent both in winter and summer and for many hours more than UVB on a daily basis, the immunosuppression caused by UVA is significant.[87,88]

In summary, an increasing body of evidence convincingly demonstrates the relevance of the VDES and of UV radiation for the management of psoriasis and other inflammatory skin diseases. It can be assumed that further characterization of the impact of UV-induced photoproducts (including vitamin D metabolites) for skin physiology may result in promising new concepts for prevention and treatment of many diseases, including skin diseases.

Conflict of interest

None.

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