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Review

Relevance of Vitamin D in Melanoma Development, Progression and Therapy

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Abstract. *Melanoma is one of the most lethal types of skin cancer, with a poor prognosis once the disease enters metastasis. The efficacy of currently available treatment schemes for advanced melanomas is low, expensive, and burdened by significant side-effects. Therefore, there is a need to develop new treatment options. Skin cells are able to activate vitamin D via classical and non-classical pathways. Vitamin D derivatives have anticancer properties which promote differentiation and inhibit proliferation. The role of systemic vitamin D in patients with melanoma is unclear as epidemiological studies are not definitive. In contrast, experimental data have clearly shown that vitamin D and its derivatives have anti-melanoma properties. Furthermore, molecular and clinicopathological studies have demonstrated a correlation between defects in vitamin D signaling and progression of melanoma and disease outcome. Therefore, adequate vitamin D signaling can play a role in the treatment of melanoma.*

Skin cells are able to activate vitamin D *via* classical and non-classical metabolic pathways (1-9). Vitamin D derivatives have anticancer properties and promote differentiation and inhibit proliferation of various cells, including melanoma, the most aggressive and lethal type of skin cancer. In this review, we provide an overview on the endogenous synthesis and activation of vitamin D *via* classical and non-classical pathways. We also present the association of vitamin D and melanoma based on epidemiological, experimental and clinical evidence, showing that defects in vitamin D signaling correlate with progression of melanoma and disease outcome. Therefore, restoration of the adequate vitamin D signaling can play a role in melanoma therapy.

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Introduction to the Ultraviolet B (UVB) in Skin Biology: A Two-edged Sword

Cutaneous synthesis and activation of vitamin D. The main natural source of vitamin D in the body is its cutaneous synthesis. Vitamin D_3 formation in the skin requires exposure to ultraviolet B radiation (UVB, λ=290-320 nm) leading to photolysis of 7-dehydrocholesterol, to form previtamin D_3 (precholecalciferol), which is then isomerized to vitamin D_3 (cholecalciferol), or phototransformed to tachysterol and lumisterol depending on the UVB dose (1-9). Subsequently, vitamin D_3 is released from keratinocyte membranes to the extracellular space. Vitamin D_3 enters the circulating system bound to vitamin D_3-binding protein (4) (Figure 1). The serum level of hydroxyvitamin D_3 is regulated *via* a negative feedback mechanism. Inactivation of both 25(OH)D_3 and 1,25$(OH)_2D_3$ is catalyzed by cytochrome P450 family 24 subfamily A member 1 (CYP24A1) *via* hydroxylation (9-13).

Vitamin D_3 activation requires a two-step hydroxylation in the canonical pathway (Figure 1). The first step includes C25 hydroxylation catalyzed by cytochrome P450 family 2

subfamily R member 1 (CYP2R1) and/or cytochrome P450 family 27 subfamily B member 1 (CYP27A1), generating 25-hydroxyvitamin D [calcidiol; $25(OH)D_3$]. The second hydroxylation is mediated by cytochrome P450 family 27 subfamily B member 1 (CYP27B1), which generates calcitriol [$1,25(OH)_2D_3$], the biologically active form of vitamin D. The systemic levels of active forms of vitamin D_3 are regulated by hydroxylation in the liver and kidneys (9, 14-18). In addition, the above vitamin D_3 activation pathways operate in other tissues including the skin (9, 10, 19-28).

In the non-canonical pathway, vitamin D_3 is activated by the action of steroidogenic enzyme CYP11A1 with initial production $20(OH)D_3$ and $22(OH)_2D_3$, and further hydroxylation of the side chain by the same enzyme (Figure 1) (9, 29, 30). CYP11A1-derived metabolites can be hydroxylated by CYP3A4, CYP27A1, CYP24A1 and importantly by CYP27B1 producing variety of vitamin D hydroxy-derivatives (9, 30, 31). These pathways operate *in vivo* (32, 33), including in the skin, since CYP11A1 is expressed in skin cells (34). In addition, 7-dehydrocholesterol (7DHC) can be metabolized by CYP11A1 to produce 22(OH)7DHC and $20,22(OH)_2$7DHC, and finally 7-dehydropregnenolone after cleavage of the side chain (35, 36). After exposure to UVB, these compounds can be transformed to corresponding vitamin D derivatives (37, 38).

UV and development of melanoma and skin cancer. UVR reaching the Earth's surface is comprised 95% by UVA (λ=320-400 nm) and 5% by UVB (λ=280-320 nm) (39-43). UVB is highly mutagenic, generating mostly 6-4 photoproducts and pyrimidine or cyclobutane dimers, while UVA is less carcinogenic and modifies DNA mostly *via* oxidation of guanine and by generating 8-hydroxyguanine [reviewed in (39, 40, 44)].

Both artificial and natural UVR are a major risk factors for non-melanoma skin cancer, such as basal cell (BCC) and squamous cell (SCC) carcinomas, as well as melanomas. Intense UV exposure during childhood or adolescence is a risk factor for BCC (45, 46). UVB is much more efficient in inducing SCC than is UVA (47, 48). The UV spectrum involved in BCC pathogenesis is under the discussion (49-52). UVR is the major risk factor for cutaneous melanoma and acts as a full carcinogen (initiator and promoter) (48, 51-54). There are several other factors affecting melanomagenesis such as viruses, chronic inflammation and persistent stress, as melanomas can develop on sun-protected areas such as mucosa, acral skin and other anatomical sites (55, 56). Intermittent sun exposure and sunburn during childhood and adolescence increase the risk of melanoma, especially in fair-skinned people with blond or red hair and multiple nevi (53, 57). Individuals with genetically conditioned disease, such as *xeroderma pigmentosum*, related to mutations in *XP* (58) genes, encoding proteins crucial for nucleotide excision repair whereby they are unable to repair UV-induced DNA damage, are more susceptible to both melanoma (more than 2,000-fold increased risk in comparison to the general population) and non-melanoma skin cancer (more than a 10,000-fold increased incidence in comparison to the general population) (59). Artificial sources of UV such as solar lamps, tanning beds and UV-based therapies have been reported to be linked to melanoma development (48, 60-67). It is unclear whether UVB or UVA plays a major role in melanomagenesis (58, 68-71).

The mechanism involved in UV-induced carcinogenesis is complex and is related to such processes as immunosuppression, induction of mutations in a broad range of genes, stimulation of growth *via* altered expression of growth factors, cytokines, neuropetides and their receptors, and which can affect keratinocytes and melanocytes, and promote melanocyte-fibroblast interactions, and modify cadherins, integrins, melanoma inhibitory activity and expression of other genes (Figure 1) (39, 54, 72-83). Although UV fingerprint mutations have been identified in genes *p53* and cyclin-dependent kinase inhibitor 2A *(CDKN2A)* in BCC and SCC, the role of p53 in melanomagenesis is not defined [reviewed in (84)].

Melanoma

Epidemiology of cutaneous melanoma. Cutaneous melanoma is the most common melanoma subtype, with an increasing (4-6%) annual incidence rate, mainly in older, fair-skinned populations of Australia, New Zealand, Northern Europe and North America (53, 85-87). At the same time, a stabilization in the cutaneous incidence rate in younger populations (except USA) has been observed (85). In countries with a high incidence rate, such as Australia, New Zeeland and North America, a preponderance of melanomas among men is observed. On the other hand, an increasing incidence rate has been found in younger (<40 years) female population, especially in the US, while men have a higher incidence rate at an older age (>40 years) (85).

Surgical removal of melanoma is limited to localized disease (stage I and II) and chemotherapy for melanoma has a low response rate. Therefore, there is a need to develop new treatment modalities (81, 88-91). The use of molecular-targeted drugs and immune therapies is limited, due to high cost, side-effects and relatively unsatisfactory responses (85). A promising treatment option appears to be anti-programmed death receptor 1 (PD1) therapy (92). Vitamin D represents a new, promising agent, both as chemopreventive and therapeutic agent.

Epidemiology of uveal melanoma. Uveal melanoma is the most frequent primary intraocular cancer, developing mostly within the choroid (85-90%), ciliary body (5-8%) and iris (3-

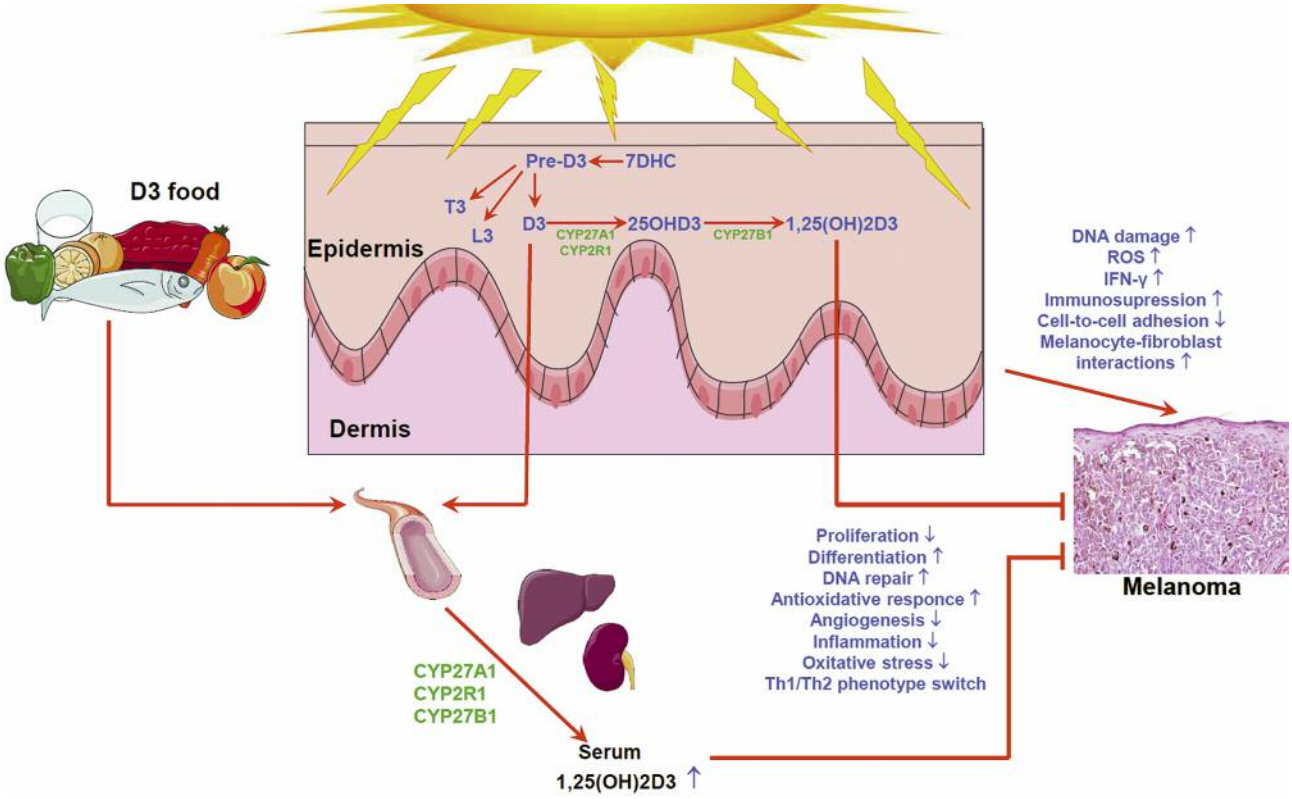

Figure 1. *Schematic of vitamin D synthesis, activation and attendant effects on melanoma biology. 7DHC: 7-Dehydrocholesterol; CYP2R1: cytochrome P450 family 2 subfamily R member 1; CYP27A1: cytochrome P450 family 27 subfamily A member 1; CYP27B1: cytochrome P450 family 27 subfamily B member 1; D3: vitamin D3; INFg: interferon gamma; L3: lumisterol 3; pre-D3: pre-vitamin D3; ROS: reactive oxygen species; T3: tachysterol 3; Th1: T-helper cell type 1 phenotype; Th2: T-helper cell type 2 phenotype.*

5%) (93). It is the second most common melanoma subtype (93-95). Uveal melanoma affects mostly the Caucasian population and people over 50 years of age (93-95). Over the past 40 years, the incidence rate has been stable, with slight, but significant increase of incidence for Caucasians (96). Similarly to cutaneous melanoma, the incidence rate in Europe increases with latitude, and in the USA a higher incidence rate was observed in California (94). There is slightly higher incidence rate among men (94, 96). The therapeutic options for uveal melanoma include surgery, enucleation, radiation, or combination treatment (94, 96). The 5-year survival rate (about 75-80%) has been stable for the past 40 years (94, 96). The efficacy of immunotherapy against uveal melanoma is limited and molecular-targeted therapies are still being investigated (93). Thus, similarly to cutaneous melanomas, vitamin D-based treatment might serve as novel, adjuvant antitumor therapy (97).

Risk factors for melanomas. The most important environmental risk factor for cutaneous melanoma is natural and artificial UV radiation. The involvement of UV in melanoma development is, in part, related to genetic factors, such as germline mutations, pigmentation, UV-induced mutations or inability to repair UV-induced DNA damages. Most melanoma cases are sporadic, but 5-12% of all melanomas have family history of melanoma (44). Patients with multiple nevi are also prone to developing melanoma (98). About 20% of patients with susceptibility to melanoma are carriers of a *CDKN2A* (called also *INK4a/ARF*) gene mutation, coding two structurally distinct proteins, $p14^{ARF}$ and $p16^{INK4a}$, involved in cell-cycle regulation (99). Mutations in the cyclin-dependent kinase-4 (*CDK4*) gene confer susceptibility to cutaneous melanoma, but mutations in *CDK4* are not as frequent as those in *CDKN2A* (100, 101). In addition, germline mutations in the tumor-suppressor *BRCA*-associated protein-1 (*BAP1*) gene, ubiquitin *C*-terminal hydrolase, encoding the protein interacting with BRCA1, have been identified in fewer than 1% of cutaneous melanomas. Melanocortin 1 receptor (*MC1R*) mutations increase susceptibility to melanoma in general population (102).

Atypical cutaneous nevi, light eye color fair skin color, predisposition to sunburn ocular melanocytosis and iris nevi

are risk factors for uveal and cutaneous melanoma (103). Chronic exposure to sunlight were not related to the risk of uveal melanoma development, but welding was identified as a risk factor (103). The majority of uveal melanomas are sporadic tumors. However recently mutations in *BAP1* were found to be related to younger age (39-50 years) at diagnosis, and higher risk of second tumors (cutaneous melanoma, renal cell carcinoma) has been identified (104).

Classical and Non-classical Vitamin D Derivatives

The main active form of vitamin D, $1,25(OH)_2D_3$ (calcitriol) acts predominantly through binding to the nuclear vitamin D receptor (VDR). VDR is activated by $1,25(OH)_2D_3$ to form a dimer with the retinoid X receptor (RXR) receptor, is translocated to the cell nucleus, and acts as a transcription factor *via* binding to VDR-responding element (VDRE) (10, 105-108). More than 1,000 target genes, varying broadly in their biological activities, regulated by vitamin D were identified depending on cell type (109-112). VDR expression was identified in many tissues and cells, including epidermal and dermal skin cells that both synthesize $1,25(OH)_2D_3$ (calcitriol) and respond to it (10, 107, 113-115). Non-canonical, noncalcemic hydroxylated vitamin D_3 forms (9, 30, 33) can also act on VDR (116-119). They can also act as inverse agonists on retinoic acid-related orphan receptors (RORs) α and γ (117, 120), which are expressed in normal and pathological skin cells, including melanoma (120, 121). Most recently, it has been shown that vitamin D_3 hydroxy-derivatives can act on arylhydrocarbone receptor (122). These alternative receptors for vitamin D_3 and its metabolites may be related to the diverse actions of vitamin D.

Vitamin D and Melanoma: Experimental and Clinical Evidence

Anticancer properties of vitamin D – An overview. Almost 40 years ago the anticancer effects of vitamin D was suggested by Garland and Garland (123) based on epidemiological studies and Colston *et al*. observed the anticancer effects of vitamin D experimentally (124). Several molecular pathways related to cancer biology, tumor development and progression have been proposed to serve as targets for active forms of vitamin D (52, 77, 125-130). Vitamin D and its derivatives have been shown to inhibit cancer-cell proliferation. p21 regulates the cell cycle by calcitriol and VDR (131-135). Vitamin D also up-regulates the cell cycle inhibitor, p27 (135-138). Vitamin D-related mechanisms regulating the cell cycle may be related to the growth factor signaling [reviewed in (108, 139)], including up-regulation of insulin-like growth factor-binding protein 3 (IGFBP3) and transforming growth factor-β (TGFβ) expression and signaling pathways (140-144), downregulation of hedgehog signaling (145-147). Cell-cycle inhibition in cancer can be accompanied by apoptosis, which is also promoted by vitamin D. This is achieved by down-regulation of phosphorylated AKT and ERK, leading to apoptosis through activation of forkhead box O 3A (FOXO3) (148), down-regulation of B-cell lymphoma 2 (BCL2) and up-regulation of BCL2-associated X protein (BAX), BCL2 antagonist/killer 1 (BAK), and BCL2-associated agonist of cell death BAD (149) [reviewed in (108, 150)]. Calcitriol induces the expression of adhesion molecules, stimulates cell maturation, and inhibits cancer progression and metastatic potential (135, 151-153). Vitamin D inhibits metastasis *via* the inhibition of vascular endothelial growth factor expression (VEGF) (154, 155).

Vitamin D can prevent cancer by protecting DNA (108, 156-158) as well as inducing the expression of superoxide dismutase, glucose-6-phosphate dehydrogenase, nuclear factor erythroid 2 (NF-E2)-related factor 2, proliferating cell nuclear antigen (PCNA) , BRCA1 and other genes (159-162).

Vitamin D can modulate immune responses by stimulating the innate immune response, while inhibiting the adaptive immunity response. Vitamin D attenuates chronic inflammation related to increased cancer risk [reviewed in (163, 164)]. Vitamin D modulates the inflammatory immune response by up-regulation of PD-1, as was observed in Crohn's disease (165) and induces the expression of programmed death-ligand 1 (PD-L1) and PD-L2 *via* VDR in experimental cell-based models (166). Immune response regulation by vitamin D is linked to the inhibition of type 1 T-helper (Th1) and promotion of Th2 phenotype, including up-regulation of interleukin 10 (IL10) and TGFβ (167, 168). The role of vitamin D in the immune response in patients with cancer appears complex (169).

$1,25(OH)_2D_3$ has antitumor properties affecting molecular pathways involved in proliferation, apoptosis and differentiation, but can also improve effectiveness of classical anticancer therapies (163, 170). Experimental cell- and animal model-based data clearly showed that vitamin D and its analogs increased the effectiveness of well-known cancer chemotherapy drugs (such as doxorubicin, cisplatinum, gemcitabine and cyclophosphamide) (171-173). $1,25(OH)_2D_3$ sensitized malignant cells to ionizing radiation (174-179) and proton beam radiation (180). These data indicate that vitamin D and its analogs alone or in combination with standard therapeutic schemes can improve the outcome of melanoma therapy.

Effects of vitamin D on melanoma cells in vitro. Since anti-melanoma properties of vitamin D and its analogs were reviewed recently (38, 130), what follows is only a short overview. Colston and co-workers showed VDR-expressing melanoma cells were inhibited by $1,25(OH)_2D_3$ (124). The anticancer properties of $1,25(OH)_2D_3$ have been shown in various melanoma cell lines. Janjetovic *et al*. reported the inhibitory effects of $1,25(OH)_2D_3$ on both pigmented and

nonpigmented SkMel-188 melanoma cells (181). A similar effect was found for $20(OH)D_3$. Both compounds stimulated VDR translocation into the nucleus, and in nonpigmented melanoma cells inhibited nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) DNA targeting by vitamin D_3. Melanin affected melanoma cell susceptibility to vitamin D_3 anticancer activity (181). $1,25(OH)_2D_3$ also inhibited colony formation by SkMel-188 cells (182, 183). The antiproliferative activity of $1,25(OH)_2D_3$, calcipotriol and $25(OH)D_3$ are related to the expression VDR and CYP27B1 (184). The growth inhibition and apoptosis inducing effects of $1,25(OH)_2D_3$ were also observed in other human melanoma cell lines, including: A375 (185), ME18 (186), MeWo (187-190), RPMI 7951 (191, 192), SM (189), SK Mel 28 (189, 192-194) and WM1341 (187, 188). The anticancer activity of calcitriol was also demonstrated against mouse B16 and hamster Bomirski melanoma cells (195). Vitamin D_3 inhibited invasiveness of malignant cells. Yudoh and co-workers reported inhibition of lysis of IV type collagen and stimulation of basement membrane reconstitution by B16 mouse melanoma cells preincubated with calcitriol for 48 h (196).

Other forms of vitamin D are biologically active and are potential anticancer agents. Vitamin D metabolites $1,24,25(OH)_3D_3$ and $1,25,26(OH)_3D_3$ inhibited the proliferation of the MM96 cell line, similarly to that found for $1,25(OH)_2D_3$ (197). It was shown that malignant cells, including pigmented melanoma cells, possess an active mechanism of metabolizing of vitamin D (198-200). In addition, several vitamin D derivatives have been developed and identified as non-calcemic or low-calcemic anticancer agents. $20(OH)D_{2/3}$, a non-calcemic vitamin D derivative, inhibited melanoma cells both *in vitro* and *in vivo* (119, 181, 183, 201-203). $20,23(OH)_2D_3$, and $1,20(OH)_2D_3$ also inhibited proliferation and colony formation of melanoma cells (183). Metabolites of $20(OH)D_3$ such as $20,24(OH)_2D_3$ and $20,25(OH)_2D_3$, produced by the action of CYP24A1, inhibited melanoma growth in soft agar more efficiently than $1,25(OH)_2D_3$ and $20(OH)D_3$ (31). A very recent report showed anti-melanoma activity of 21(OH)pD in WM98, A375 and SK-MEL-188b ($VDR^{-/-}CYP27B1^{-/-}$) lines. Only WM98 and A375 cells were sensitive to calcipotriol (184).

Effects of vitamin D and its new analogs on melanoma cells in animal models. The antitumorigenic activity of $1,25(OH)_2D_3$ in an animal model was reported for the first time by Eisman and coworkers (204), demonstrating the inhibition by $1,25(OH)_2D_3$ of the growth of human melanoma cells COLO 239F expressing VDR, which were injected into immunosuppressed mice. Another melanoma cell line, RPMI 7932, with no VDR expression, was insensitive. The VDR-positive SKMel-188 melanoma cell line, injected into immunocompromised mice, was inhibited by $20(OH)D_3$ (201). $1,25(OH)_2D_3$ reduced lung metastasis of B16 melanoma cells injected into mouse by affecting the extracellular matrix (196), and $1(OH)D_2$ reduced tumor growth in Tyr-Tag transgenic mice, which develop pigmented ocular tumors, similar to human choroidal melanoma (205). The patient-derived orthotopic xenograph (PDOX) model has been developed for melanoma in order to individualize chemotherapy for individual patients with advanced melanoma. For example, effective therapy was identified for melanoma with/without *BRAF*-V600 mutation (206-212).

Serum vitamin D level in patients with melanoma: Effects on susceptibility and survival. Garland and Garland (123) suggested that low-sun-exposure-related vitamin D insufficiency was correlated with higher colon cancer mortality rates. These results were confirmed by other epidemiological reports (213-215) and experiments in animal models treated with vitamin D, showing inhibition of tumor growth (216, 217) and higher benign and malignant tumor risk in $VDR^{-/-}$ animals (22, 27, 218, 219).

A recent case–control study showed higher vitamin D levels in serum of healthy controls than in patients at the time of melanoma diagnosis. A multivariate model revealed a negative association between vitamin D sufficiency and melanoma (220). These data confirmed previously published reports on the correlation of serum vitamin D levels and clinical outcome of patients with melanoma, including a relationship between the lower Breslow tumor thickness and higher $25(OH)D_3$ level (221). Subsequent studies confirmed that a lower vitamin D level was related to greater progression of melanoma [Breslow thickness, Clark level, the American Joint Committee on Cancer (AJCC) stage], the presence of poor prognostic markers (ulceration, higher mitotic index), shorter overall survival and increased risk for melanoma-specific death (222-226). However, some investigators (227) did not observe such relationships and found only longer disease-free survival for patients with higher vitamin D levels. Melanoma risk is related to a higher number of nevi, however Ribero and co-workers showed positive correlation of serum vitamin D level and nevi count (228). These authors suggested that melanomas associated with a low vitamin D level might be a different type from those associated with a higher nevi count, thus further studies are required to explain the association between nevi, melanoma and vitamin D level.

Correlation between vitamin D intake (supplementary or dietary) and melanoma risk is still incompletely understood (229).

Modulation of vitamin D signaling in melanoma – Clinical experimental data. Our study on clinical material showed that the reduction of VDR (both cytoplasmic and nuclear) correlated with melanoma progression, being the highest in normal skin and benign nevi, and lowest in most advanced

Table I. *Changes of vitamin D receptor (VDR, nuclear), cytochrome P450 family 27 subfamily B member 1 (CYP27B1), cytochrome P450 family 24 subfamily A member 1 (CYP24A1), retinoic acid receptor-related orphan receptor alpha (RORα, nuclear), and RORγ (nuclear) in relation to the expression in normal skin (only statistically significant change are indicated).*

Pigmented lesion	Immunoexpression				
	VDR	CYP27B1	CYP24A1	RORα	RORγ
Nevi	↓	=	↑	↓↓	↓
Melanoma – *in situ*	↓	↓	↑↑↑	↓↓↓	↓↓
Melanoma - RGP	↓↓	↓↓	↑↑	↓↓↓	↓↓
Melanoma - VGP	↓↓↓	↓↓↓	↑	↓↓↓	↓↓↓
Metastasis	↓↓↓	↓↓↓	=	↓↓↓	↓↓↓

RGP: Radial growth phase; VGP: vertical growth phase; =: no change; ↑/↑↑/↑↑↑: increase of expression; ↓/↓↓/↓↓↓: decrease of expression.

Table II. *Correlation of selected clinico-pathomorphological melanoma features and the expression of vitamin D receptor (VDR, cytoplasmic and nuclear), cytochrome P450 family 27 subfamily B member 1 (CYP27B1), cytochrome P450 family 24 subfamily A member 1 (CYP24A1), retinoic acid receptor-related orphan receptor alpha (RORα, cytoplasmic and nuclear), and RORγ (cytoplasmic and nuclear) in primary melanomas. Analysis was performed with Pearson correlation tests.*

Melanoma feature	Immunoexpression							
	VDR		CYP27B1	CYP24A1	RORα		RORγ	
	Cytoplasmic	Nuclear			Cytoplasmic	Nuclear	Cytoplasmic	Nuclear
Breslow thickness	r=–0.2860	*NS*[A]	r=–0.3796	r=–0.4035	r=–0.1924	r=–0.2914	r=–0.4108	r=–0.3109
	p=0.0056		*p*=0.0002	*p*=0.0008	*p*=0.0458	*p*=0.0048	*p*=0.0003	*p*=0.0049
Clark level	NS	r=–0.2659	r=–0.3897	r=–0.3087	r=–0.1879	r=–0.2473	r=–0.4242	r=–0.3254
		p=0.0093	*p*=0.0001	*p*=0.0087	*p*=0.0497	*p*=0.0145	*p*=0.0002	*p*=0.0034
pT	r=–0.1938	r=–0.3076	r=–0.2870	r=–0.3749	r=–0.2395	r=–0.3284	r=–0.4008	r=–0.3277
	p=0.0478	*p*=0.0036	*p*=0.0049	*p*=0.0020	*p*=0.0193	*p*=0.0020	*p*=0.0004	*p*=0.0034
pN	NS	*NS*[B]	r=–0.3159	r=–0.3705	r=–0.2580	r=–0.2802	r=–0.2773	r=–0.2863
			p=0.0022	*p*=0.0023	*p*=0.0127	*p*=0.0074	*p*=0.0115	*p*=0.0100
pM	NS	*NS*[C]	r=–0.2590	*NS*[F]	NS	NS	r=–0.2133	NS
			p=0.0102				*p*=0.0415	
TILs	*NS*[D]	NS	NS	NS	r=0.2198	r=0.3530	NS	NS
					p=0.0282	*p*=0.0009		
Overal stage	*NS*[E]	r=–0.3174	r=–0.3826	r=–0.4297	r=–0.2569	r=–0.2953	r=–0.4545	r=–0.4043
		p=0.0028	*p*=0.0002	*p*=0.0004	*p*=0.0131	*p*=0.0051	*p*<0.0001	*p*=0.0003
Presence of ulceration	r=–0.3396	r=–0.4197	r=–0.1903	r=–0.3490	r=–0.2294	r=–0.3612	r=–0.3382	r=–0.3570
	p=0.0016	*p*=0.0001	*p*=0.0475	*p*=0.0042	*p*=0.0254	*p*=0.0008	*p*=0.0029	*p*=0.0018

TILs: Tumor-infiltrating lymphocyes; NS: not statistically significant relationship. [A]Higher in melanomas with Breslow thickness <1 mm *versus* >4 mm ($p<0.05$ by ANOVA) (230). [B]Higher in pN1 *versus* pN3 melanomas ($p=0.0033$) as determined by *t*-test) (231). [C]Higher in pM0 *versus* pM1 melanomas ($p=0.0495$ by *t*-test (231). [D]Lower in melanomas without TILs or with non-brisk *versus* melanomas with brisk TILs ($p=0.0133$ by *t*-test (231). [E]Higher in overall stage 1 *versus* overall stage 4 melanomas ($p<0.01$ by ANOVA) (230). [F]Higher in pM0 *versus* pM1 melanomas ($p<0.05$ by *t*-test) (234).

melanomas (higher Breslow thickness, Clark level, pT advancement) and metastatic lesions (230, 231). High VDR expression in melanoma cells was negatively correlated with the presence of poor-prognosis markers such as nodular type, ulceration, high mitotic rate, lack of tumor infiltrating lymphocytes (TILs). In addition, VDR expression affected overall survival, with best survival for patients with a high VDR expression without ulceration (230, 231). Del Puerto and co-workers observed higher cytoplasmic VDR levels in nevi than in melanomas, which inversely correlated with Clark level and pTNM staging. However, in their study, nuclear VDR expression was higher in melanomas (232). This surprising pattern might have been secondary to the specificity of the antibodies used in the study (in contrast to our study, the authors used polyclonal antibodies, and did not verify specificity) and use of a different assay method.

In addition, we also observed modulation of the expression of enzymes involved in vitamin D metabolism. CYP27B1 expression, as well VDR, was reduced in melanomas, showing the lowest level in most advanced primary tumors and metastatic melanomas (233). However, there was a lack of correlation between the presence of an ulceration or lack of TILs and CYP27B1 expression. However, CYP27B1 expression was accompanied by a lower proliferation index and better overall and disease-free survival (233). VDR and CYP27B1 expression were also negatively correlated to pigmentation in melanoma (230, 233). The correlation of CYP24A1 and melanoma progression is complex. CYP24A1 expression was lowest in metastatic lesions, and highest in benign nevi and localized melanomas (pT1-2, Clark level 1-2, Breslow thickness <2 mm, stage 1-2, pN0). Additionally, patients with melanoma showing poor prognostic markers such as nodular type, high mitotic index, ulceration and necrosis had low CYP24A1 expression. CYP24A1 expression was positively correlated to pigmentation in clinical samples of melanoma, which was in contrast to VDR and CYP27B1 expression (234).

Similar to VDR, RORα and RORγ expression decreased with melanoma progression, with the lowest expression being observed in metastatic melanomas, and the highest in benign melanocytic tumors. The substratification of melanomas according to Breslow thickness, Clark level, and overall stage revealed that more advanced primary tumors had reduced ROR expression. Non-metastasizing melanomas (pN0) had higher ROR levels and ulceration, nodular type, lack of TILS and had lower ROR expression. ROR expression was highest in amelanotic lesions (121). The summary of changes in the expression of these markers is presented in Table I. Correlation of selected clinico-pathomorphological melanoma features and the expression of VDR, CYP27B1, CYP24A1, RORa and RORg in primary melanomas is presented in Table II. Most recently, we reported on the complex relationship between expression of VDR, RORα and RORγ receptors with hypoxia-indicuble factor 1α levels in human melanomas (235).

In summary, alterations in vitamin D activation, its local and systemic levels, and vitamin D-regulated signaling pathways can result in loss of anticancer protection provided by vitamin D and promote melanoma development. This suggests that impairment of the vitamin D endocrine system operation in melanoma cells is related to melanoma progression and poor prognosis.

Clinical trials

Clinical trials are currently investigating the effects of vitamin D therapy on patients with melanoma. Italian MelaViD (ClinicalTrials.gov Identifier: NCT01264874), registered in 2010 (236), is a randomized, double blind phase II clinical trial on vitamin D supplementation for patients after resection of stage II melanoma (n=150), treated with 100,000 IU of vitamin D_3 every 50 days for 3 years. Disease-free survival has been defined as a primary end-point of efficacy. Overall survival, Breslow thickness and VDR were also measured. A Belgian-Hungarian ViDMe randomized controlled trial (ClinicalTrials.gov Identifier: NCT01748448) (237) is a multicenter randomized double blind placebo-controlled phase III trial, registered in 2012, with monthly administration of 100,000 units of vitamin D or placebo (Arachidis oleum raffinatum) to 500 patients with melanoma. This study examines the relationship between disease-free survival, melanoma subtype, anatomic site and vitamin D receptor, the vitamin D pathway and vitamin D level at the time of diagnosis and at 6 months intervals during the study. The duration of this trial is 3.5 years or until relapse. An Australian-New Zealand Clinical Mel-D pilot placebo-controlled randomized phase II trial (Australia and New Zealand Clinical Trials Registry ACTRN12609000351213) (238) is determining the efficacy of oral administration of high-dose vitamin D (loading dose of vitamin D of 500,000 IU followed by a dose of 50,000 IU of vitamin D monthly for 2 years) *versus* placebo in 75 patients with surgically resected stage IIb, IIc, IIIa (N1a, N2a) or IIIb (N1a, N2a) melanoma. A Danish retrospective trial (registered in 2017) on serum vitamin D effects on plasma levels of sPD-1 in 40 patients with melanoma patients at baseline, 3 and 6 weeks after treatment initiation with pembrolizumab (anti-PD1 therapy) was approved for the treatment of advanced melanoma followed by 3 years of follow-up (ClinicalTrials.gov Identifier: NCT03197636) (239). We are awaiting the results of this trial.

Conclusion

Published reports presenting the association between melanoma risk and serum vitamin D level and vitamin D intake have shown inconsistent results. The role of calcitriol in the modulation of immune response needs to be clarified, since it was suggested that tumor resistance to $1,25(OH)_2D_3$ and its derivatives might be related to suppression of antitumor immunity. However, both experimental- and clinical-based studies clearly suggest that disturbances in vitamin D signaling may be related to melanoma development, progression and disease-free and overall survival of patients. Disruption of local vitamin D level might result from altered vitamin D metabolism in melanoma cells. The anti-melanoma efficacy of vitamin D requires proper function of both VDR and metabolizing enzymes. Since VDR, CYP27B1, CYP24A and ROR expression are related to the prognosis of patients with melanoma, they can be considered as potential biomarkers, similar to the serum vitamin D level. In addition, vitamin D and its new derivatives are promising candidates in the prevention and treatment of melanoma (Figure 1).

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

AAB conceptualized and wrote the article, RMH wrote the subchapter and corrected the article, ATS conceptualized, wrote and corrected the final version of the article.

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