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Review Article

Impact of Vitamin D in different skin cancer pathogenesis and treatment modalities

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Abstract

The production of vitamin D, one of the oldest hormones, dates back more than 750 million years to the earliest life forms. Most plants and animals, including phytoplankton and zooplankton, can produce vitamin D when exposed to sunlight. From birth until death, a healthy skeleton depends heavily on vitamin D for its development, growth, and maintenance. Undiagnosed vitamin D deficiency has become a significant public health issue worldwide in recent days. In addition to causing Osteomalacia and Osteoporosis in adults as well as rickets in children, vitamin D deficiency also has long-lasting effects. Chronic vitamin D deficiency may lead to detrimental consequences, such as an increased risk of hypertension, multiple sclerosis, colon, prostate, breast, and ovary cancers, type 1 diabetes, and, most significantly, skin cancer. It is very important to get a better understanding of the importance of vitamin D for overall health. Vitamin D is a hormone that has been shown in vitro to have anti-carcinogenic effects in modern research studies on different skin cancers. The available evidence is debatable, and there are no widely applicable strategies. This review aims to explain how various forms of vitamin D function at the molecular level in the human body and to make practical suggestions for prevention and treatment strategies for melanoma and non-melanoma skin cancers while maintaining adequate vitamin D levels.

Keywords - Vitamin D; Skin cancer; Oncoprotective actions.

Introduction

Low levels of 25-hydroxyvitamin D (25(OH)D) in blood have been marked as a substantial health concern since it affects approximately one billion people worldwide. Several genetic predispositions could interfere with 25-hydroxyvitamin D (25(OH)D). For instance, non-Hispanic African American Black individuals usually have lower levels of 25-hydroxyvitamin D (25(OH)D) than their white counterparts. Furthermore, skin pigmentation, malnutrition, food, season, latitude, cultural norms, religious practices, restricted awareness, illiteracy, indoor lifestyles, urban living, comorbidities such as Tuberculosis, chronic inflammatory disorders, and certain medications could contribute to vitamin D insufficiency.

Recent advances in vitamin D biology and pharmacology have opened up new and exciting opportunities in the chemo-prevention and treatment of skin cancers.[1] Melanoma is one of the most aggressive forms of skin cancer, with a steady increase in global incidence and mortality rate over the past five decades.

There is contradictory epidemiological evidence regarding vitamin D, non-melanoma skin cancer, and cutaneous melanoma, confounded by the effect of sun exposure and other factors. In patients with melanoma or at risk of cutaneous cancer, serum vitamin D checks are warranted to detect and avoid its insufficiency. Silencing the vitamin D receptor increases the propensity to develop UVB or chemically induced epidermal cancers.

We observe a remarkable sunshine-related paradox when we monitor the relationship between the dose of solar radiation and one type of skin cancer - malignant melanoma. Silencing the vitamin D receptor increases the propensity to develop UVB or chemically induced epidermal cancers. Moreover, vitamin D3 inhibits hedgehog signaling pathways implicated in many cancers. Understanding these issues will help develop more effective preventative strategies and new therapeutic approaches.

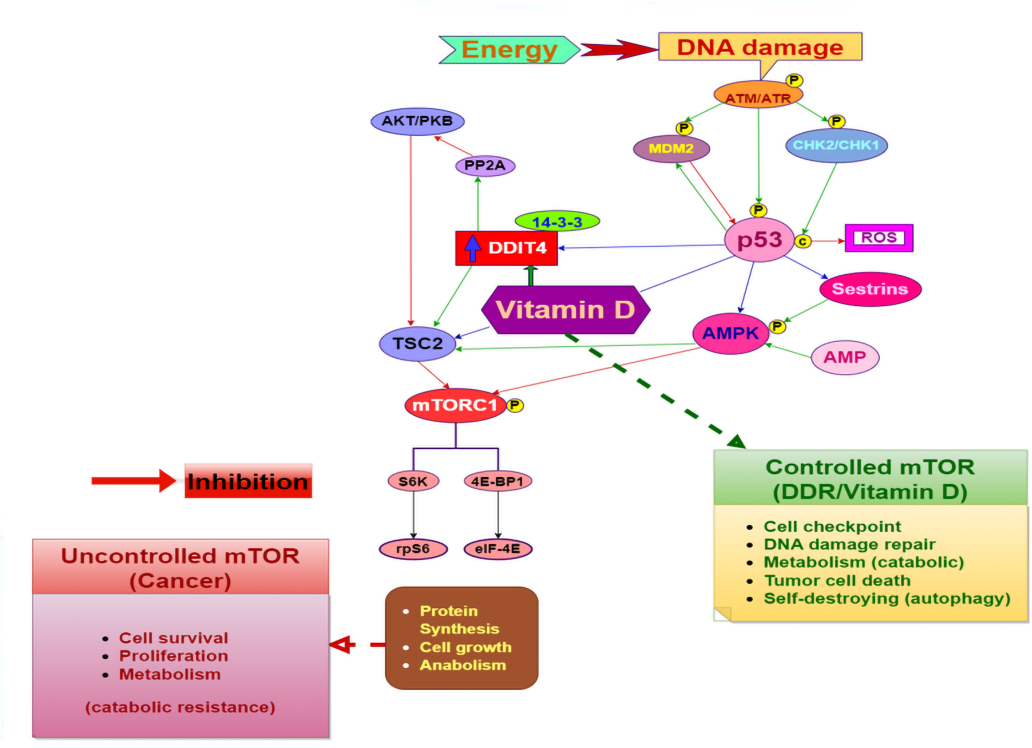

Figure 1. *Role of Vitamin D in response to DNA damage.[1]*

Exposure to UV radiation activates one key DNA damage response (DDR). UV exposure generates two types of DNA lesions: cyclobutene pyrimidine dimers (CPDs) and 6-4 photoproducts. Only UV-A and UV-B ultraviolet light from the sun may enter the Earth's atmosphere.[1] As a result, this UV radiation is the most harmful to humans, especially as the ozone layer continues to deplete, causing larger amounts of this radiation to reach the planet's surface. Figure 1 demonstrates the DNA damage response interaction between vitamin D, DDIT4, and mTORC1. When the tumor suppressor p53 is phosphorylated, stabilized, and activated by low-energy DNA damage, this event also activates the ATM/ATR and CHK1/CHK2 kinases.

Here, mTOR kinase is an important controller and hub of cellular metabolism.

As a direct transcriptional target of the vitamin D receptor (VDR), DDIT4 is essential for regulating the activity of mTORC1.p53 can also phosphorylate AMPK subunits, which then activate TSC2 to suppress mTORC1 activity. **Figure 2** depicts Vitamin D and its modulation of cancer metabolic states. Vitamin D may enhance catabolism by inhibiting mTORC1, which limits the number of cell divisions (i.e., the preservation of the life span of cells). Nevertheless, Vitamins D's ongoing regulation of mTORC1 may be a crucial first step in activating cell death-initiating mechanisms like autophagy.

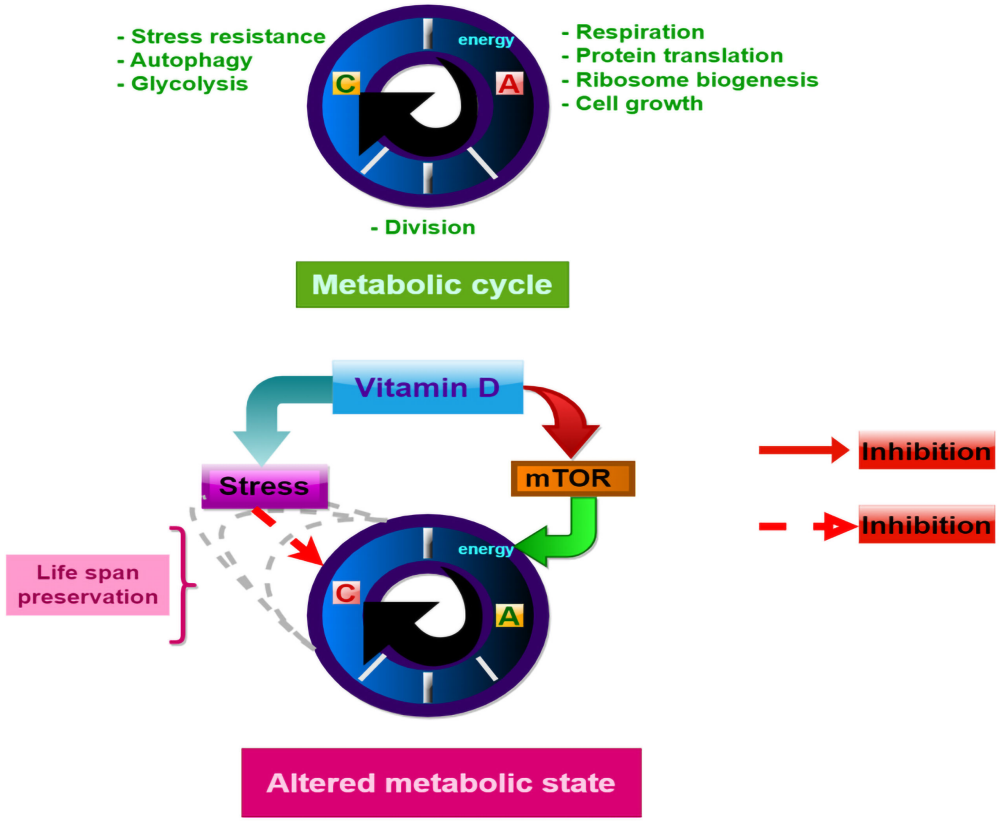

***Figure 2**. Vitamin D impacting mTOR kinase activity in altered metabolic state.[1]*

AKT (also known as protein kinase B), PP2A (protein phosphatase 2), DDIT4 (DNA damage induced transcript 4), ATM (ataxia telangiectasia mutated), ATR (ATM- and RAD3-related), MDM2 (mouse double minute 2 homolog), CHK (Checkpoint kinase), TSC (tuberous sclerosis complex), and AMPK (AMP-activated protein kinase).

Both lesions affect the structure of DNA, causing bends or kinks that impede transcription and replication. Areas of the DNA double helix that are somewhat flexible are more prone to get damaged. Both CPDs and 6-4 PPs are repaired using a technique called nucleotide excision repair (NER). Defects in several of these genes have been linked to the human illness Xeroderma Pigmentosum (XP) and other disorders that share a 1,000-fold increased risk of skin cancer. Double-strand breaks are another kind of DNA damage induced by ionizing radiation, such as gamma rays and X-rays. These breaks have been found to be quite deleterious.

The mTOR kinase is a key regulator and metabolic mode in cells. Vitamin D signaling can impact the mTOR pathway's response to DNA damage. Various DNA damage sensors alert mTOR to possible damage, causing it to transiently increase protein levels and kinase activity. Cells may be appropriately 'fixed' based on activation of repair mechanisms and resolution of mTOR activity or depending on the level of damage. They may accrue more cellular damage due to excessive, uncontrolled mTOR activation. Vitamin D may promote catabolism by decreasing mTORC1 activity, which restricts the number of cell divisions (i.e., cell life span preservation). This is a critical step in launching self-destructive processes such as autophagy, which may trigger cell death. [1]

II. Epidemiology

In the U.S., skin cancer is the most common form of cancer.[2][3] According to present estimations, one in every five Americans is in danger of developing skin cancer during their lifetime.[4][5] Approximately 9500 individuals in the U.S are diagnosed with skin cancer daily.[4][5] Squamous Cell Carcinoma (SCC) along with Basal cell carcinoma (BCC) constitute Non-melanoma skin cancer (NMSC) and are estimated to cause detrimental effects to more than 3 million Americans every year.[4][5] BCC's total incidence expanded by 145% during 1976-1984 and 2000-2010.[6] But the overall incidence of SCC grew by 263%.[6] Women experienced a higher incidence rate for both types of NMSC compared to men.[6] In the U.S., more than one million people are affected by melanoma.[7] In the U.S, the incidence of melanoma have risen over the last 30 years.[8] It more than doubled between 1982 to 2011.[8] But the rates have varied by age in the last decade.[8] Melanoma contributes to the greater majority of skin cancer mortality.[8] Furthermore, melanoma claims more than twenty American lives daily and is projected to cause 7,650 fatalities in 2022.[8][9] It is expected that 5,080 males and 2,570 females will be affected by melanoma.[8][9] Based on various studies, males suffering from melanoma were found to have a poorer prognosis than females with melanoma.[10][11] Surprisingly, melanoma fatality rates dropped by about 4% from 2014 to 2019.[8]

II. 1. Risk factors for skin cancer

According to the epidemiological data of Centers for Disease Control and Prevention (CDC), Caucasian individuals are far more prone to develop non-melanoma or melanoma skin cancers due to their lack of skin pigmentation than individuals hailing from dark-skinned ethnicities. People who are naturally dark-skinned/black, having skin types V and VI, can normally endure reasonably high amounts of sun exposure without getting sunburned or significantly raising their risk of skin cancer.[12] People with pale or freckled skin, light or red hair, and blue eyes (those having skin types I, II) are at the highest risk of developing skin cancer; people with dark hair and eyes (skin types III, IV) who do not regularly get sunburned are at medium risk. Nonetheless, prolonged sun exposure can harm all skin types, increasing the risk of eye damage and heat stroke. Besides, there are some individual risk factors for skin cancer including having fair skin, blue, green, or hazel eyes, light-colored hair, a tendency to burn rather than a suntan, a history of severe sunburns, many moles, freckles, and a family history of skin cancer. Below, **Table 1** exhibits the association of skin cancer risk with two variables - skin tone and UV light sensitivity.

Table 1: Association of skin cancer for different types of skin.[12]

Natural skin color	Very fair, pale white often freckled	Fair, white skin	Light brown	Moderate brown	Dark brown	Deeply pigmented dark brown to black
UV Sensitivity	Highly sensitive	Very sensitive	Sensitive	Less sensitive	Minimal sensitivity	Minimal sensitivity
Skin Cancer Risk	Greatest risk of skin cancer	High risk of skin cancer	High risk of skin cancer	At risk of skin cancer	Skin cancers are less common; but are often detected at a later stage	Skin cancers are less common; but are often detected at a later stage

III. Method

We have included PubMed-Indexed research studies done both in-vitro and in-vivo in humans, published from 2000 to 2022, with abstracts available in English, Spanish, or French. We used the following search query: "("Vitamin D" [Mesh] OR "Vitamin D Deficiency" [Mesh] OR Cholecalciferol [Mesh] AND ("Skin Neoplasms" [Mesh] OR "Melanoma" [Mesh] OR "Carcinoma, Basal Cell" [Mesh] OR "Carcinoma, Squamous Cell" [Mesh] AND ("Prevention and Control" [Subheading])." During our search, we also used different keywords, including anticancer properties of vitamin D, immunologic response, vitamin D receptors, and UV exposure.

We adopted an epidemiological, patient-centered approach while writing this review. From the 130 articles we screened initially, we finally selected 86 articles that address the topics elaborated in this review. The primary intention of this review is to make pragmatic suggestions regarding the best possible sources for acquiring enough vitamin D and recommendations for sun protection for individuals at risk of developing different skin cancers or patients having risk factors. In conjunction with this, we want to enlighten the effects of UV rays on vitamin D, the role of VDR and its polymorphism in Melanoma and NMSC, and the function of different cytochrome enzyme systems in the pathogenesis of Melanoma, SCC, and BCC. In this article, we have taken a deep dive into the controversial role of UV rays and vitamin D in the pathogenesis and treatment of different skin cancers. Our purpose is to connect the dots and share the current evidence on the inter-relation of vitamin D, Non-Melanocytic Skin Cancer (NMSC), and cutaneous melanoma. Thereby, we want to highlight the importance of vitamin D in treating and preventing skin cancers.

IV. Discussion

IV. 1. UV ray, geographical influence on different skin cancer

The three most common skin cancers are basal cell carcinoma (BCC), squamous cell carcinoma (SCC) (typically categorized as NMSC), and cutaneous malignant Melanoma (CMM). These malignancies are considered "sun-related" (mostly UV-related). However, NMSC is the most often diagnosed malignancy in North America, Australia, and New Zealand, while Cutaneous Melanoma is the deadliest of the three primary kinds of skin cancer.[13] Around the world, 1,042,056 new cases of NMSC were projected to have been identified in 2018;

predominantly, SCC-related deaths accounted for 65,155 deaths or about 6% of all deaths.[13] In the same year, worldwide estimated CMM cases were 287,723, resulting in up to 60,712 fatalities (21% mortality).[13] In most affluent nations, the incidence of CMM has grown, owing mostly to thinner lesions with improved prognosis. A nested case-control analysis of Swedish population-based registries indicated that patients with basal cell carcinoma (as a paradigmatic example of people with more sun exposure and vitamin D produced through it) are at increased risk of having other malignancies before BCC diagnosis.

Vitamin D insufficiency is a growing global concern, particularly among non-Caucasians, who have higher bone mass despite lower serum vitamin D levels. Female mortality in the United States is relatively consistent (1.9 deaths per 100,000 ascribed to CMM), whereas male mortality has increased over time (from 2.88 percent in 1975 to 4.44 percent in 2011-2015).[14] The solar UV index, the amount of sun-exposed and sun-protected skin, the length of time spent in the sun, the body mass index, age, and skin phototype all impact cutaneous vitamin D production as cancer pathogenesis.[15] The fairest phototypes of Caucasians often have lower vitamin D levels than others. This is partly due to their increased photosensitivity. However, there are additional variables involved in vitamin D metabolism, while certain populations show controversially higher levels of serum vitamin D in several UK-based cohort studies.[16][17] UV-A ray mostly causes DNA damage indirectly, while UV-B ray is directly responsible for premalignant and malignant skin conditions.[18] The ozone layer almost fully blocks highly energetic UVC. Given that the highly energetic shorter wavelengths are more widely distributed and more thoroughly absorbed, the depth of penetration into the epidermal layers rises with wavelength. Thus, UVB radiation primarily affects the epidermis, but UVA radiation, which is less powerful, also damages the dermal skin layers. [19]

UVB radiation (280–320 nm) is considered the most important environmental risk factor for all skin cancers. The ozone layer blocks UV wavelengths shorter than 280 nm (UVC).[17][20] UV rays attributes to various molecular and cellular signaling processes, which cause inflammation and secondary immunosuppression (apoptosis failure and abnormal differentiation).[21] UV-induced DNA alterations in oncogene and tumor suppressor genes (such as p53) are often observed in skin malignancies such as BCC, SCC, and actinic keratoses.[20] They are also often found in the promoter gene of the telomerase reverse transcriptase (TERT) in both NMSC and CMM.[22][23][24] The vitamin D receptor (VDR) is encoded by a gene on chromosome 12q13, contains polymorphisms that are hypothesized to change its function,and is increasingly being recognized as a tumor suppressor in the skin (with protective effects against UV-induced epidermal cancer development).[21][25][26] Vitamin D's involvement in cutaneous carcinogenesis is most likely connected to its effects on growth, cell death, angiogenesis, and cell differentiation.

IV. 2. Different types of skin cancer classifications

Non-melanoma skin cancers

Non-melanoma skin malignancies include basal cell carcinomas and squamous cell carcinomas. Although they are seldom fatal, surgical therapy is typically unpleasant and disfiguring. Because adequate registration of these tumors has not been established, it is impossible to evaluate the temporal trends in their occurrence. However, studies conducted in Australia, Canada, and the United States show that the frequency of non-melanoma skin malignancies increased by more than two between the 1960s and the 1980s.[12] The incidence of non-melanoma skin cancers regarding personal exposure has been studied, and the following conclusions may be drawn:

● Non-melanoma skin cancers are more common in regions of the body frequently exposed to the sun, such as the ears, face, neck, and forearms. This suggests that persistent long-term UV radiation exposure is a primary cause. [12]

● In several nations, there is a definite association between growing non-melanoma skin cancer incidence and decreasing latitude, i.e., increased UV radiation levels. [12]

Malignant Melanoma

The incidence of malignant melanoma has dramatically increased since the early 1970s, rising by an average of 4% per year in the United States.[12] Although significantly less common than non-melanoma skin cancers, malignant melanoma is the leading cause of mortality from skin cancer which is more likely to be reported and appropriately diagnosed than non-melanoma skin cancers. Several studies have found that the risk of malignant melanoma corresponds with genetic and personal traits, as well as a person's UV exposure behavior. The followings are the list of the most crucial human risk factors:

● In fair-skinned populations, the strongest risk factor for malignant melanoma is having a large number of atypical nevi (moles) is.[12]

● Malignant melanoma is more common in people with pale skin, red or fair hair, and blue eyes. Experimental studies demonstrated that a lower minimum erythema dose and more prolonged erythema in melanoma patients than in controls. [12]

● High, intermittent exposure to solar UV seems to be a significant risk factor for developing malignant melanoma. [12]

● In white populations, the incidence of malignant melanoma is generally increases with decreasing latitude and the highest recorded incidence occurring in Australia, with the ten annual rates which is 20 times the rates in Europe for men and women, respectively. [12]

● Several epidemiological studies report a positive association with the history of sunburn, particularly sunburn at an early age. [12]

● The role of cumulative sun exposure in developing malignant melanoma is equivocal. Despite, malignant melanoma risk is higher in people with a history of non-melanoma skin cancers and solar keratoses, which are indicators of cumulative UV exposure. [12]

IV. 3. Pathway of Vitamin D protection

Researchers have been trying to figure out the ideal daily vitamin D intake for cancer prevention. Vitamin D3 at 1500 international units (IU) per day has been demonstrated to reduce the mortality rate from cancer in men by 30% in the United States.[25] Numerous studies have attempted to link the prevalence of certain malignancies with blood levels of vitamin D3 (25-OH vitamin D) in recent years. These studies employed minimal levels of 30-35 ng/mL (75-87.5 nmol/l), which are thought to be ideal for maximizing the positive effects of vitamin D. These findings hold even after controlling for variables that may impact vitamin D levels, such as body mass index or age. Sufficient vitamin D serum levels can protect humans against a variety of cancers. However, there is little epidemiologic data to support vitamin D's beneficial involvement in skin cancer prevention, and there is even contradictory evidence.[25][26] Indeed, a recent meta-analysis of 13 prospective studies found that vitamin D status is related to increased risks of CMM and NMSC: every 30 nmol/L rises in 25(OH)-D3 levels were associated with a 42 percent, 30 percent, and 41 percent increase in the chances of CMM, SCC, and BCC, respectively. Sun exposure most likely confounded these findings.[25] Higher blood vitamin D3 levels are linked to NMSC (OR: 2.07, CI: 1.52-2.80),with a dose-response relationship.[20][26][27] This is most likely due to UVB's dual action of promoting vitamin D synthesis while also triggering DNA damage that leads to skin cancer.

The intracellular action of vitamin D3 (D3)- and lumisterol (L3)-hydroxyderivatives in photo protection against UVR. Signal transduction includes the activation of nuclear receptors such as vitamin D receptor (VDR), retinoic acid orphan receptor (ROR) α/γ, and aryl hydrocarbon receptor (AhR) and the direct action of D3- and L3-hydroxyderivatives on mitochondrial processes. The nuclear receptors activities are linked with the transcriptional master regulators NRF2 (nuclear factor erythroid-derived 2-like 2), p53 and NFκB (nuclear factor kappa-light-

chain-enhancer of activated B cells) to coordinate anti-oxidative, DNA repair, anti-inflammatory, and antiproliferative as well as anti-carcinogenesis mechanisms.

Even though xeroderma pigmentosum patients (who have the highest risk of NMSC) exhibit a high frequency of vitamin D insufficiency, current information surrounding vitamin D and NMSC is disputed, and it has yet to be determined if vitamin D may reduce NMSC incidence or severity. [28][21] The key tumor pathway in the development of BCC is the hedgehog pathway, which is inhibited by vitamin D. Current epidemiological research, however, is contradictory and ad hoc. Aside from the linear dose-response increase in BCC risk associated with serum levels, the previously cited meta-analysis revealed a slightly higher risk of BCC among those receiving at least 100 daily international units of either dietary or supplemental vitamin D (RR: 1.02, CI: 1.00-1.03, p = 0.03).[27] A subsequent analysis of a randomized clinical trial of vitamin D and/or calcium supplementation found no advantage in reducing BCC (HR: 0.99; 95 percent CI: 0.65-1.51).[29] Prospective human investigations are required to determine the link between vitamin D blood levels and BCC risk.[30]

Intermittent cholecalciferol supplementation, for example, has been shown to improve photodynamic treatment for squamous cell cancer. [31]. The vitamin D pathway may be involved in Melanoma since VDR expression has been found in many cancer samples and cells. Calcitriol has been found in animal models to decrease tumor invasion and angiogenesis in melanoma cell lines.[30] Although there are varied and contradicting results in different studies with different risk assessments, adequate vitamin D levels are related to a lower risk of melanoma incidence (RR 0.62 [0.42-0.94]).[26][27][30]. In terms of melanoma prognosis, lower serum vitamin D3 levels are associated with worse prognostic features, including Breslow thickness and poorer melanoma survival, even after controlling for inflammatory indicators.[32] Recent research published in this journal showed the safety of vitamin D3 supplementation (100,000 international units every 50 days) in individuals with stage II melanoma. It was also shown that Breslow thickness affects disease-free lifespan and the response to supplementation (in terms of serum vitamin D levels).[33] Lower melanoma incidence has been seen in patients who consume a vitamin D-rich diet; however, this has not been validated in case-control studies, including those who consume a vitamin D-rich diet and those who get supplements. This might be due to VDR receptor polymorphisms impacting vitamin D's anticancer activity. [34]

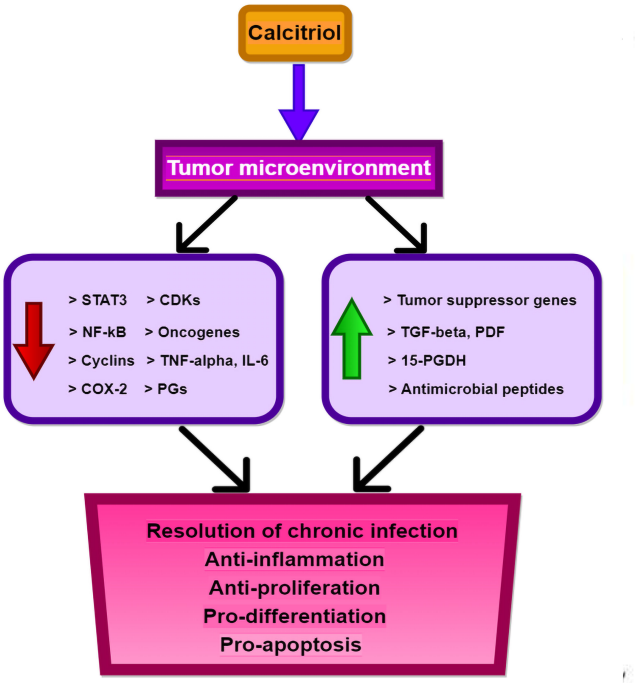

Figure 3. *The role of calcitriol in the tumor microenvironment and the effects of different tumor markers.[35]* TNF - tumor necrosis factor; IL-6 - interleukin 6; PDF - prostate deriver factor; PGs - prostaglandins; 15-PGDH - 15-hydroxyprostaglandin dehydrogenase; COX-2 - cyclooxygenase-2.

Figure 3 demonstrates how the tumor microenvironment is affected by calcitriol. Calcitriol functions to up-regulate or down-regulate (red arrow) various variables that lead to the biological consequences that are indicated, depending on whether it is triggered from 25OHD in the kidney or intratumorally. [35]

Another study found that excessive vitamin D consumption increased the incidence of melanoma in males but protected against invasive melanoma in women.[36]. In any event, it is appropriate to provide vitamin D supplementation to those with low vitamin D levels and to re-screen circulating vitamin D levels in patients with or at risk of melanoma.[37][38]

IV. 4. VDR, RORα, and ROR-γ receptors expression in human melanomas

Figure 4 illustrates receptors and mitochondria being targets of vitamin D3 and L3 that control cellular phenotypic and homeostatic processes. Microsomal or mitochondrial CYPs hydroxylate D3 and L3 precursors to produce (OH)nD3, (OH)nL3, and classical 1,25(OH)2D3. During melanoma genesis, melanocytes start to suppress the production of adhesion molecules such as E-cadherin, allowing an epithelial-mesenchymal transition that isolates melanoma cells in the process of transformation from the keratinocytes that surround them and control their activity.

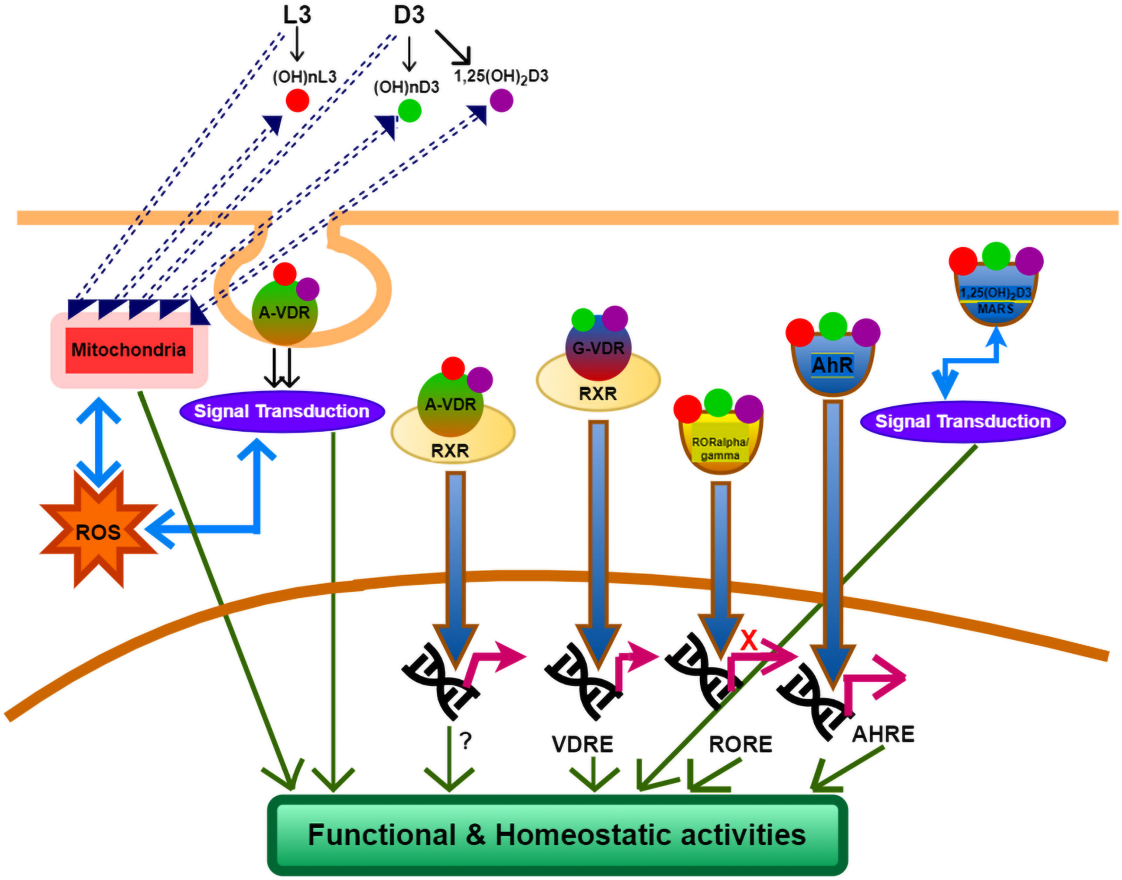

Figure 4. *Molecular mechanism of Vitamin D in melanoma prevention.[39]*

This allows the tumor to gain control of its epidermal microenvironment.[40] Wnt/-catenin signaling is recognized to be a critical regulator of melanocyte-keratinocyte adhesion and interactions, although the precise role it plays is unclear. According to several studies, Wnt/-catenin signaling activity reduces the proliferation of melanoma cells, and the absence of this signaling pathway may result in the development of melanoma.[41] Indeed, Wnt/-catenin signaling is crucial for melanocyte differentiation via MITF activation and posttranslational processing.[41][42] Others have demonstrated that Wnt/-catenin signaling is required for metastatic melanoma cell survival and that inhibiting it results in decreased proliferation, migration, and invasion.[43] Recently, data has emerged pointing to an inverse link between VDR expression and Wnt/-catenin signaling in primary melanomas, which results in decreased proliferation and immune response evasion.[44] Variations in VDR expression alter how Wnt/-catenin signaling affects melanomas. Recent discussions have also focused on the complicated alterations in vitamin D signaling and its' significance in melanoma formation, progression, and treatment.[45]

IV. 5. Role of VDR polymorphism in melanoma

Over 600 single nucleotide polymorphisms in the VDR gene have been found, including FokI (C/T-rs2228570, previously known as rs10735810) and TaqI. (rs731236).[46] These are the most widely studied in the context of melanoma, while others include Cdx2 (rs11568820) and EcoRV (rs4516035).[46] The shorter protein version is 424 amino acids long and corresponds to the C nucleotide allele or F allele. In contrast, the longer protein variant is 427 amino acids long and belongs to the F allele. For seven VDR gene polymorphisms, a meta-analysis determined the odds ratios and 95 percent confidence intervals for the dominant and recessive models. Carriers of the rarer allele f of FokI (rs2228570) (Ff + ff vs. FF) were 22% more likely to develop malignant melanoma.[47][48][49] The dominant model of Bsml (rs1544410) (Bb + BB vs. bb) exhibited a statistically significant 15% risk reduction in malignant melanoma carriers. There was no significant connection between melanoma risk and the other VDR polymorphisms studied, which included TaqI (rs731236), A-1012G (rs4516035), Cdx2 (rs11568820), and BglI.[46].

One study examined the relationship between two functional VDBP SNPs and the risk of (many) BCCs.[50] 5790 (72.5%) and 5823 (72.9%) of the 7983 individuals were genotyped for rs7041 and rs4588, respectively, and three haplotypes (Gc1s, Gc2, and Gc1f) were investigated.[46]

IV. 6. The role of Vitamin D in prevention of skin cancers in animal models

Researchers have seen that topically exposing a VDR null (VDR-/-) mouse model to the carcinogen 12-dimethyl-benz[a]anthracene (DMBA)-12-O-tetra-decanoylphorbol-13 acetate (TPA) resulted in many melanocytic growths.[50] In the same work, melanocytic growths were observed in a different mouse model with a conditional tissue-specific keratin 14 promoter-driven are-mediated epidermal RXR deletion (RXRep-/- animals).[51] This finding was investigated further in mice models in which keratinocyte RXR knockouts were paired with two melanomagenic mutational backgrounds (RXRep-/-|CDk4R24C/R24C and RXRep-/-|Tyr-NRASQ61K) and subjected to acute neonatal UVB irradiation in conjunction with adult chronic UVB dosages.

Surprisingly, strong nuclear RXR expression has been observed in epidermal keratinocytes of normal human skin. Researchers reported for the first time that its expression is reduced or lost in skin keratinocytes adjacent to melanocytic tumors during melanoma progression in humans.[52] It indicates a non-cell-autonomous role of keratinocyte RXRα in suppressing melanoma progression. On the contrary, the cytoplasmic intensity of RXR did not alter substantially across nevi and melanoma groups.

However, cytoplasmic RXRβ expression was considerably lower in human metastasis samples compared to human melanoma samples.[53] This suggests a function for RXRβ in melanoma metastasis. We also found that melanocytic VDR had

photoprotective capabilities in a separate mouse strain where melanocytic VDR was removed (VDRmel-/-).[54]

The expression of HIF-1α (hypoxia-inducible factor 1 alpha), nuclear receptors, VDR (vitamin D receptor), RORα (retinoic acid receptor-related orphan receptor alpha), and RORγ and CYP24A1 (cytochrome P450 family 24 subfamily A member 1) and CYP27B1 (cytochrome P450 family 27 subfamily B member 1), enzymes involved in vitamin D metabolism, was investigated.[54] VDR expression was inversely linked with nuclear HIF-1α expression in both primary and metastatic melanomas (r=0.2273, p=0.0302; r=0.5081, p=0.0011).[54] A comparison of immuno-stained HIF-1α, CYP27B1, and CYP24A1 levels revealed a lack of association between these parameters in both original tumors and melanoma metastases. In primary and metastatic lesions, RORα expression was linked favorably with nuclear HIF-1α expression (r=0.2438, p=0.0175; r=0.3662, p=0.0166).[54]

IV. 7. The role of Vitamin D in prevention of different skin cancers in human clinical trials

Clinical research on BCC patients in humans also suggests a possible function for vitamin D.[30][54] Men with the highest baseline serum 25(OH)D levels (>30 ng/mL) had 47% lower odds of NMSC (95% confidence interval, 0.3-0.93; P =.026; P for trend, 0.04) compared to those with the lowest baseline 25(OH)D levels in a nested case-control study of elderly men with NMSC (N = 178) or without skin cancer (N = 930) enrolled in the Osteoporotic Fractures.[55] Since adequate 25(OH)D levels cannot be determined by a diagnosis of NMSC, high 25(OH)D levels may be linked to a lower risk of NMSC. In contrast, different case-control research from the Kaiser population revealed that a slight increase in the incidence of BCC was linked to greater pre-diagnostic 25(OH)D levels.[56] A previous prospective cohort study on vitamin D consumption through dietary questionnaires, however, found no link between vitamin D and the incidence of BCC.[57] In a prospective cohort of white patients who sought guidance on the risk of osteoporosis, discovered that higher 25(OH)D levels were linked to an increased risk of NMSC.[58] Their findings may be explained by the fact that UV Exposure has a favorable connection with both vitamin D production and NMSC, and sunlight exposure is a very likely confounder. The available laboratory evidence indicates that vitamin D may reduce the growth of BCCs. However, more vitamin D levels and the risk of developing prospective human studies are required to characterize the connection more precisely between BCCs.[30]

A prospective study that included 4,641 women from the Nurses' Health Study (NHS) and the NHS II with 510 incident BCC cases and 75 incident SCC cases assessed the relationship between baseline plasma 25(OH)D levels and the risk of incident SCC and BCC.[59] After taking into account factors including age at blood collection, the season of blood collection, lab batch, hair color, inclination to burn, number of sunburns, and UV B flux of residency, it was shown that plasma 25(OH)D levels were positively related with the risk of BCC in that research. Surprisingly, women in the highest quartile of 25(OH)D had a more than 2-fold higher risk of BCC than women in the lowest quartile (OR = 2.07, 95% CI = 1.52-2.80, P for trend 0.0001).[60] After controlling for the same variables, the authors discovered a statistically positive relationship between plasma 25(OH)D levels and SCC risk (OR, highest vs. lowest quartile = 3.77, 95 percent CI = 1.70-8.36, P for trend = 0.0002).[60] Plasma 25(OH)D levels were linked with NMSC risk in this prospective analysis of women. The studies concluded that, because most circulating vitamin D is caused by sun exposure, the positive association between plasma 25(OH)D and NMSC is confounded by sun exposures.[60] The findings suggest that a single measurement of plasma vitamin D levels may reasonably reflect long-term sun exposure and predict the risk of NMSC.

A prospective study of white people in a Health Maintenance Organization cohort who sought low-bone-density or osteoporosis-related advice found that higher 25(OH)D serum concentrations (> 15 ng/ml) are associated with an increased risk of NMSC. However, the findings were not statistically significant.[58] Single nucleotide polymorphisms

(SNP) in the vitamin D-binding protein (VDBP) change 25(OH)D levels and may influence skin carcinogenesis.[56]

There is not much epidemiologic research that has looked at how vitamin D or its metabolites affect human SCC prevention or treatment. A blood 25(OH)D level of 15 ng/mL or above was related to an elevated risk of SCC but not statistically substantial.[30] Although there is mounting epidemiologic evidence linking vitamin D to a reduced risk of developing cancer in several visceral organs, there is insufficient information to evaluate this link in SCCs.

IV. 8. Expression of CYP27A1, CYP27B1, and CYP24A1 in BCC and SCC

The synthesis of 1,25(OH)2D3, the VDR's physiologically most active natural ligand is facilitated by multiple major enzymes that allow hydroxylation of vitamin D at position 25 in the liver (CYP2R1, CYP27A1) and of the resultant 25(OH)D3 at position 1 in the kidneys (CYP2R1, CYP27A1) (CYP27B1).[13][16][48] These hydroxylases are members of the cytochrome P450 mixed-function mono oxidase family. CYP27B1 has been shown to have extrarenal action in various cell types, including macrophages, keratinocytes, and prostate and colon cancer cells.[13][16][48] Modulation of these enzymes has been discovered to alter the proliferation and differentiation status of 1,25(OH)2D3-sensitive cells, whether benign or malignant.[13][16][48] It has been proposed that enhanced CYP24A1 expression owing to gene amplification may abolish vitamin D3-mediated growth regulation.[46] Higher CYP27A1 and CYP27B1 expression in NMSC represents a physiological feedback loop linked to enhanced proliferative activity in these malignancies. However, 1,25(OH)2D3 can be quickly metabolized by CYP24A1, whose expression is enhanced in both BCCs and SCCs.[61][62][63] The levels of 1,25(OH)2D3 in NMSC may grow or decrease depending on the expression levels of the CYP27A1, CYP27B1, and CYP24A1 genes.[61][62][63] As a result, the cellular and systemic effects of elevated expression of CYP27A1, CYP27B1, and CYP24A1 in skin cancers remain unknown. Nonetheless, precursors of physiologically active 1,25(OH)2D3 or CYP24A1 inhibitors may be useful in preventing or treating BCCs and SCCs.[61][62][63].

IV. 9. Role of VDR expression in SCC, BCC formation

In recent studies, researchers mostly looked at three polymorphisms in the VDR (ApaI, BsmI, and TaqI) to see if they were linked to NMSC development and demographic features.[64] The final model for predicting NMSC diagnoses included the known NMSC risk factors of older age, male sex, and light skin color; including BsmI SNP status, which significantly contributed to the model, with individuals with the SNP being twice as likely to develop NMSC, whereas ApaI and TaqI SNP status did not.[64] The connection between the two most researched VDR polymorphisms (FokI and BsmI) with cancer risk was reviewed and meta-analyzed in 67 independent studies in 2009.[60] A significant rise in skin cancer risk (SOR) was seen when comparing FokI ff with FF carriers.[60] Another study found that the Taq1 polymorphism TT was linked to an increased frequency of BCCs each year, especially when combined with skin type I and the male gender.[60].

IV. 10. P53 mutation and its role in Skin cancers

The p53 gene has a part in the early stages of pre-malignant lesions and involvement through clonal proliferation with advancement into a tumorigenic state. Mutations in the ras oncogene do not appear as relevant in developing skin cancer as mutations in the p53 tumor suppressor gene. P53 is implicated in not just NMSC but also melanoma and other malignancies. It is understandable why p53 is referred to be the "guardian of the genome".[65] In skin malignancies, p53 mutations are very frequent, and UV irradiation has been demonstrated to be a key driver of certain "signature" mutations that might lead to oncogenic transformation. There are many

'hotspots' in the p53 gene where abnormalities that result in a mutant dipyrimidine site are prevalent.[65]

Furthermore, point mutations in the p53 gene have a distinct effect on tumor susceptibility than allelic loss. Point mutations are often linked with the early stages of skin malignancies. In contrast, allelic loss promotes tumor formation at high levels of UVB exposure and accelerates skin tumor progression to greater malignancy.[65] Chronic UV exposure would decrease FasL expression and increase p53 mutations. This results in apoptosis dysregulation, mutant keratinocyte proliferation, and the onset of skin cancer. The skin's density of p53-mutated keratinocytes influences skin cancer susceptibility.[65] Therefore, these results imply that further avoiding UV exposure will only postpone the development of skin cancer, not completely prevent it. P53 mutation inhibition is a valuable early biologic goal of photo-protection against an essential beginning event in UV carcinogenesis.[65]

IV. 11. Controversy of Vit D and UV rays in the pathogenesis of different skin cancers

UV light is widely known to be a significant skin carcinogen that plays a key part in melanogenesis. However, the generation of vitamin D in the skin also depends on UVB exposure. Vitamin D insufficiency contributes to tumorigenesis and, more specifically, poor prognosis owing to multidrug resistance.[66][67] Patients with metastatic melanoma who were vitamin D deficient showed substantially worse outcomes than those who were initially deficient but saw a >20 ng/ml rise in 25-hydroxyvitamin D3 [25(OH) D3] concentration throughout treatment. The relationship between ROS levels and vitamin D analogs was explored using a hydrogen peroxide intervention. Melanoma A375 cells are ten times more susceptible to hydrogen peroxide than human immortalized HaCaT keratinocytes.[68]

At the highest doses examined, incubating melanoma A375 cells with 1,25(OH)2D3 for 24 hours resulted in a 20% reduction in cell growth. Vitamin D's suppression of melanoma cell growth should not be interpreted as a direct lethal impact but as evidence of its antiproliferative potential. Vitamin D is previously known to limit cell growth and promote differentiation.[68][69][70] Cisplatin and dacarbazine, two anticancer medicines, have similar effects on oxidative stress. The two medicines caused an initial considerable rise in oxidative stress (at one hour), but continued incubation (24 h) resulted in a decreasing trend of 2′,7′-dichlorofluorescein fluorescence. The number of cells in G0/G1 increased after pre-treatment with vitamin D analogs at a modest dose (100 nM), with this impact being seen exclusively in cells treated with these medications. Dacarbazine's possible regulatory qualities were discovered by gene expression analysis in melanoma cells.[68] This medication significantly inhibited the production of CAT, the alternative vitamin D binding protein encoded by PDIA3, and CYP27B1, which was restored by pre-treatment with 1,25(OH)2D3. In terms of cell viability and ROS generation, cells overexpressing CYP450 family member CYP24A1 were more susceptible to cisplatin treatment than cells lacking CYP2E1 expression.[71] 1,25(OH)2D3 and calcipotriol operate as biased agonists on the VDR and can act as a reverse agonist on retinoic acid orphan receptors.[71][72][73][74][75][76] In contrast, its downstream metabolite, 20,23(OH), acts as an agonist on the aryl hydrocarbon receptor.[77][78] A future objective is to pinpoint each secosteroid's particular mechanism of action. Although the tested chemotherapeutics did not significantly improve anti-melanoma activity, the findings of this study show that vitamin D analogs may be useful adjuvant medicines in chemotherapy.[68]

IV. 12. The controversial role of the vitamin D as an antioxidant

Researchers wanted to see if vitamin D receptor (VDR)-FokI polymorphisms may modify the response to vitamin D3 supplementation in a randomized control trial research by S Shab-Bidar in 2014.[79] The outcomes were changes in serum 25-hydroxyvitamin D (25(OH)D), superoxide dismutase, glutathione (GSH), total antioxidant capacity (TAC), and malondialdehyde (MDA). The FokI restriction enzyme was used to assess VDR genotypes in 140

T2D participants using FD (vitamin D3-fortified dough containing 500 IU/250 ml).[79] Nevertheless, there was no substantial link between FokI genotypes and OS biomarkers, the ff variant subgroup showed the weakest response to vitamin D. In conclusion, it is revealed that improving vitamin D intake via daily consumption of FD enhances oxidative stress/OS biomarkers in T2D individuals. The combinatorial impact of FokI genotypes cannot be ruled out. [79]

IV. 13. SCC fails to respond to 1, 25 (OH) 2D

1,25(OH)2D modulates a variety of cellular activities that contribute to its capacity to induce keratinocyte development.1,25(OH)2D increases intracellular calcium (Cai) levels in part through boosting calcium receptor expression (CaR).In the family of phospholipases C (PLC), these enzymes catalyze the breakdown of phosphatidyl inositol bisphosphate (PIP2) to generate inositol triphosphate (IP3) and diacylglycerol (DG), both of which induce calcium release from intracellular reserves and activate protein kinases C (PKC).[80] By activating the vitamin D receptor (VDR), a transcription factor, 1,25(OH)2D, controls the expression of genes by interacting with its vitamin D response elements (VDRE) in the promoters of the genes. This process is accomplished with the retinoid X receptor (RXR) or retinoid A receptor (RAR). Moreover, the VDR attaches to one of two coactivator complexes, Mediator/DRIP (VDR interacting proteins) or p160/SRC (steroid hormone receptor complex), which connect the VDR to the RNA polymerase complex.[80] Squamous cell carcinomas (SCC) fail to respond to the differentiating actions of 1,25(OH)2D because they fail to down-regulate DRIP (205) such that the p160/SRC complex fails to bind to VDR.[80] This lack of sequential binding of these coactivator complexes to the VDR maintains the cell in a state of continued proliferation. It blocks the expression of genes required for the differentiation process.

IV. 14. Antiproliferative Activity of Non-Calcemic Vitamin D Analogs on Melanoma

Various recent studies have evaluated the effect of classic vitamin D metabolites, 1,25(OH)2D3 and 25(OH)D3, as well as two low calcemic vitamin D analogs, (21(OH)p D and calcipotriol), on proliferation, mRNA expression, and vitamin D receptor (VDR) translocation in three human melanoma cell lines: WM98, A375, and SK-MEL-188b. Except for SK-MEL-188b, in which only the short side-chain vitamin D analog-21(OH)p D was effective, other investigated compounds effectively suppressed the growth of WM98 and A375 melanoma cells.[81] Therefore, 21(OH)p D was the most powerful chemical in the study's three melanoma cell lines. The insensitivity of SK-MEL-188b to 1,25(OH)2D3, 25(OH)D3, and calcipotriol is explained by a lack of specific transcripts for the VDR splicing variants and vitamin D-activating enzyme CYP27B1. VDR, its splicing variants, and other vitamin D-related genes (RXR, PDIA3, CYP3A4, CYP2R1, CYP27B1, CYP24A1, and CYP11A1) were found to be expressed in WM98 and A375 melanomas, with transcript levels regulated by vitamin D analogs. Calcipotriol significantly increased the expression of VDR isoforms in WM98 cells.[81] The antiproliferative actions of 21(OH)p D do not need VDR translocation to the nucleus, which explains its great effectiveness in SK-MEL-188b melanoma, which is VDR-/-. As a result, we believe that 21(OH)p D is a promising option for melanoma treatment, while the mechanism of action remains unknown.[81]

IV. 15. Vitamin D as nutrition in the prevention and therapy

At present, many studies have been done on melanoma and dietary factors. These studies agreed upon the useful effects of the MeD and DASH diets, weight reduction, and the harmful role of alcohol intake, particularly white wine.[82] However, the results of these studies are often controversial owing to contradictory conclusions, which poses a dilemma in formulating recommendations for or against specific

diets, foods, or supplements for melanoma prevention. Some of these retrospectives and observational studies did not consider sun exposure, skin phenotype or phototype, and the number of nevi known risk factors for melanoma development.[82] Besides, several studies present inconclusive evidence about other nutritional factors such as vitamins A, B, C, and E and food items such as vegetables, legumes, fruits, cereals, sweets, eggs, processed meat, and tea Therefore, there is a pressing need for placebo-controlled, well-designed clinical trials on the role of vitamin D in the pathogenesis of different skin cancers and treatment modalities. Additionally, at the population level, preventive campaigns should concentrate on nutritional counseling to promote healthy dietary behaviors and the maintenance of average body weight until we get our hands on more concrete evidence.

Experimental animal model studies and in vitro studies have exhibited multiple pathways involved in the effector activities of nutritional factors, such as antioxidant action with a decrease in oxygen reactive species, anti-inflammatory and immunomodulatory effects with potential immune-protective activities against UV radiation, and cytotoxic, pro-apoptotic, and sensitization effects to chemotherapy and or radiotherapy of melanoma cells.[82] These data could provide the foundation for developing well-conducted clinical trials for better comprehension of the impact of nutrition on the incidence and development of melanoma so that strategies can be optimized for disease prevention and support existing treatment options.

IV. 16. Vitamin D as a treatment with Cediranib, VEGFR inhibitors

Scientists recently discovered that vitamin D improves the efficacy of traditional cancer therapies in the human malignant melanoma A375 cell line.[46] In the current research, the influences of cediranib (AZD2171), an oral tyrosine kinase inhibitor of VEGFR1-3, PDGFR, and c-KIT, used in combination either with 1,25(OH)2D3 or the low-calcemic analog calcipotriol, were assessed on four human malignant melanoma cell lines in quest for new combination strategies and adjuvant environments to achieve better melanoma patient outcomes (A375, MNT-1, RPMI-7951, and SK-MEL-28).[46] Melanoma cells were sensitized with vitamin D before being treated with cediranib. In the laboratory systems employed, we found a substantial decline in melanoma cell proliferation (A375 and SK-MEL-28), G2/M cell cycle arrest, and a dramatic reduction in melanoma cell mobility (A375).[46] Remarkably, we observed VEGFR2 overexpression at both the protein and mRNA levels, along with a highly desired reduction in melanoma cell proliferation and motility.[46] Vitamin D did not affect MNT-1 or RPMI-7951 melanoma cells. Vitamin D compounds appear to improve cediranib effectiveness by modulating VEGFR2 expression in melanoma cells expressing VEGFR2. Experiments showed that vitamin D derivatives have potential as innovative adjuvant options to combat melanoma, particularly in individuals with vitamin D insufficiency.[46]

V. Conclusion

Vitamin D3 hydroxyderivatives can reduce UVB or chemically induced epidermal cancer genesis and decrease SCC and BCC development in studies with animal models. Besides, vitamin D3 blocks hedgehog signaling pathways, which are thought to be involved in several malignancies, and are now a target area of research to treat different skin cancers. Bufalin, known as bufo venom, with cardiotonic and local anesthetic effects, appeared to increase the ligand-dependent activation of vitamin D receptor (VDR) and upregulation of the VDR's ability to mediate the expression of endogenous target genes like CYP24. Bufalin sustained VDR expression in the nucleus of human leukemia cells in the presence of 1,25(OH)2D3, probably through decreasing the VDR breakdown or export. The results are attributed to a novel potential for cardiotonic steroids, especially bufalin, in influencing the VDR functionality and subsequent prevention and better prognosis of various skin cancers. Vitamin D's immune-modulating properties may indicate its innovative uses in participants who received immunotherapy. Research analysis affirms that individuals with higher serum vitamin D3 values had higher skin activity of the anti-inflammatory mediator arginase-1 upon therapy. Hence, early acquisition of sufficient vitamin D levels

would be imperative to prevent melanoma. Vitamin D is crucial in both direct and indirect tumor suppression mechanisms. Few meta-analyses have highlighted the relevant biological pathways and established a compelling association between normalized vitamin D levels and improved survival. Although the USPSTF does not suggest screening for vitamin D deficiency in asymptomatic individuals, we can detect it via a simple blood test. Supplementing with vitamin D may also increase the chemo- and radio-sensitivity of cancer cells resistant to these treatments. However, more study is needed to ascertain this. Historically, all association studies have been conducted using random samples. Nevertheless, if there is a hereditary relationship between cancer risk and vitamin D, then its supplementation will benefit people who lack free vitamin D and have frequent genetic deficiencies in the Vitamin D pathway. The association between genetic changes and an elevated chance of developing cancer requires further study involving more human clinical trials, including different ethnicities, to get transparent data for the future management of skin cancers.

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