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The potential role of vitamin D in the progression of benign and malignant melanocytic neoplasms

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Abstract

Hormonally active vitamin D₃, 1,25-(OH)₂D₃, is believed to have a role in the prevention of cancer formation and in limiting the aggressiveness of cancers that do arise. Therefore, much interest is presently being focused on 1,25-(OH)₂D₃ and its analogues as potential treatments for various cancers including melanoma. This article discusses the evidence in favour of a role for 1,25-(OH)₂D₃ in protection against the progression of melanocytic lesions and also summarizes the mechanisms by which 1,25-(OH)₂D₃ may act to protect against melanoma development and progression.

Keywords

cancer; melanocytic; melanoma; nevi; vitamin D

Introduction

Melanoma arises in activated and genetically altered melanocytes following a complex interaction between genetic and environmental factors. Cutaneous melanoma is the most dangerous form of skin cancer, causing 72% of skin cancer deaths (1). This high mortality rate has occurred as a result of the poor efficacy of established chemotherapeutic medications. While there have recently been a number of promising advances in melanoma treatment research (2), there remains a pressing need for the development of preventative and improved therapeutic treatments. One option being considered is the principal hormonally active form of vitamin D, 1,25-(OH)₂D₃, and its analogues.

1,25-(OH)₂D₃ has an important role in calcium homeostasis and is also believed to protect against cancer development (3–6). This anti-neoplastic activity results from the ability of 1,25-(OH)₂D₃ to regulate cell proliferation, differentiation, migration and apoptosis. Vitamin D receptors (VDRs) are widely expressed (6,7), including in the skin where they occur in melanocytes (8) and most other cells. Therefore, the anti-neoplastic activity of 1,25-

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(OH)₂D₃ may affect a wide variety of cells including melanocytes. This article will focus on the evidence that vitamin D, and particularly 1,25-(OH)₂D₃, has a role in preventing the progression of melanocytic neoplasms and will examine mechanisms by which 1,25-(OH)₂D₃ may exert its effects.

Vitamin D synthesis

Between 90% and 100% of vitamin D is obtained through biosynthesis following exposure to ultraviolet-B radiation (UV-B) (9). Synthesis begins in keratinocytes through UV-B-mediated photolysis of 7-dehydrocholesterol, forming previtamin D₃, with subsequent thermal isomerization to vitamin D₃ (Fig. 1) (6,10). This is then converted to 25-(OH)D₃ by the enzyme 25-hydroxylase (CYP27A1), with subsequent conversion to 1,25-(OH)₂D₃ by 1 α -hydroxylase (CYP27B1). These later two reactions occur in the liver and kidneys, respectively. In addition, both enzymes are expressed in keratinocytes (11), and 1 α -hydroxylase is expressed in many cells (12) including some melanomas (13).

Metabolism of 1,25-(OH)₂D₃ is mediated principally by the multi-catalytic enzyme 24-hydroxylase (CYP24A1). 24-Hydroxylase induction occurs in response to 1,25-(OH)₂D₃, and its cellular expression therefore mirrors that of the VDR (14).

UV exposure as a risk factor for melanoma

Sun exposure is widely accepted as a risk factor for all forms of skin cancer including melanoma (15). However, epidemiological evidence suggests that melanoma differs from other skin cancers because its development relates more to timing and severity of UV exposure than to cumulative amounts (lentigo maligna being an exception) (16). Therefore, fair-skinned people who experience occasional and intense UV exposure resulting in severe sunburn, particularly as young children, are far more likely to develop melanoma than those who are chronically exposed or exposed at an older age (17,18). Studies in transgenic mice support this view and show that early severe UV exposure results in an increased risk of melanoma-like malignancies, whereas later exposure does not (19). Further support is provided by geographical studies showing a non-linear relationship between latitude (reflecting UV exposure) and melanoma (18). Furthermore, cumulative UV exposure (assessed by solar elastosis) correlates in some studies with later onset (20) and decreased severity of melanoma (21). However, this later study (21) has proved controversial (22–25). Other researchers have not identified any protective effect from cumulative UV exposure (assessed using patient history) (25). One group (24) has suggested that the apparent decreased melanoma severity associated with cumulative UV exposure may actually reflect differing pathways of melanoma formation, with less aggressive forms developing through UV-induced mutations and more aggressive familial forms developing through endogenous instability in susceptible individuals. Actually, familial and sporadic forms of melanoma are similarly aggressive and share common mutations at CDKN2a and CDK4 (26,27). However, genetic analyses do suggest that divergent pathways of melanoma development occur at different body sites (28,29). For example, melanomas arising in intermittently sun-exposed skin more commonly harbour mutations in BRAF and NRAS, while mutations in c-KIT are more common in chronically sun-exposed skin (29). These differences may account for some of the non-linearity seen in geographical studies. Nevertheless, the studies described (17,18,20,21) do suggest that chronic UV exposure may provide some protection against melanoma, with one likely causal factor being 1,25-(OH)₂D₃ production.

VDR gene polymorphism studies

Numerous VDR gene polymorphism epidemiological studies have been undertaken examining the relationship between 1,25-(OH)₂D₃ and melanoma risk. Because of inconsistencies in the

findings from smaller studies, two large meta-analyses were recently performed (30,31). Individually, these meta-analyses identified RFLPs that were associated with either increased or reduced risk of melanoma. However, collectively the findings from these studies are contradictory and thus difficult to interpret. The variability in the results from these studies may relate to factors that include sample size and differences in the effect of VDR SNPs on VDR expression in different people; however, this remains to be determined.

The role of 1,25-(OH)₂D₃ in melanin synthesis

The importance of melanin pigment in protection against melanoma is highlighted by differences in lifetime melanoma risk in fair-skinned Americans (1 in 50) versus African Americans (1 in 1000) (32). Furthermore, when melanoma arises in African Americans, it mainly involves sites of reduced pigmentation such as mucosal surfaces and acral areas (32).

Melanocytes act as master regulators of the skin, sensing injury and maintaining homeostasis (33). One of their homeostatic mechanisms is the synthesis of melanin pigment. During sun exposure, the skin is bombarded with UV radiation that damages cells through genetic mutations. Mutagenic effects are caused principally by UV-B and to a lesser extent by UV-A (34). UV-induced epidermal stress in melanocytes and keratinocytes triggers the synthesis of proopiomelanocortin (POMC), which is subsequently converted to ACTH (35). ACTH, acting in concert with α -MSH (also derived from POMC), binds to the melanocortin 1 receptor (MC1R) on melanocytes which causes an increase in intracytoplasmic cAMP (33). This results in upregulation of microphthalmia-associated transcription factor (MITF) transcription. MITF then binds to the promoter of tyrosinase causing upregulation (36) and increased melanin synthesis.

Vitamin D is also believed to upregulate melanin synthesis (33,37), with evidence coming from both *in vitro* (38–42) and *in vivo* (43) studies. With the exception of a single study (39), in which high variability made interpretation difficult, all the *in vitro* studies described increases in tyrosinase activity in response to either vitamin D₃ or 1,25-(OH)₂D₃ treatment. An *in vivo* study (43) similarly showed increased tyrosinase activity following UV exposure in rats fed diets rich in vitamin D compared with vitamin D-deficient rats.

1,25-(OH)₂D₃ is believed to upregulate melanin synthesis through increased c-kit activity. In one study, the use of the 1,25-(OH)₂D₃ analogue, tacalcitol, caused an up-regulation of c-kit (44), and in others 1,25-(OH)₂D₃ caused increased Raf and mitogen-activated protein (MAP)-kinase activity (45,46). c-Kit acts through the Ras-Raf pathway to activate MAP-kinase, which has a minor role in upregulating MITF expression and a more important role in the phosphorylation of MITF causing an increase in its activity and its degradation (47,48).

The Ras-Raf pathway is a common site of mutation in melanoma and is thus considered to have a critical role in melanoma development. However, minor stimulation to this pathway from individual growth factors (stem-cell factor, fibroblast growth factor, etc.), acting independently, is not considered significant in melanoma formation (27). This is also likely to be true for the stimulation to this pathway from 1,25-(OH)₂D₃.

The role of 1,25-(OH)₂D₃ in protection against UV-induced melanocytic neoplasms

In addition to melanin synthesis, other important factors in skin protection from UV include endogenous DNA repair systems and possibly 1,25-(OH)₂D₃. UV exposure causes nevus formation through a poorly understood mechanism. Factors likely to be involved include proliferative responses induced in melanocytes by UV damage and UV-induced genetic

mutations (49,50). Proliferation following UV exposure occurs because of the effects of α -MSH, endothelin1 and keratinocyte-derived basic fibroblast growth factor (bFGF) (33,51–53). In addition, proliferation occurs owing to mutations in key regions of growth and cell death regulatory genes (27). More specifically, there is evidence that upregulation of the anti-apoptotic factor survivin (54) is important in nevus formation. Mutations in B-RAF (55) are also commonly identified in nevi; however, it is unclear whether these are causative or simply a late development (56). Nevertheless, the frequent identification of identical B-RAF mutations in nevi and melanomas (V600E) has led to the suggestion that these mutations may represent an important step along the pathway to melanoma development (57).

While generally benign behaving, melanocytic nevi are a recognized risk factor for melanoma when present in increased numbers. In addition, melanocytic nevi are often found associated with melanoma and may act as melanoma precursor lesions (53,58,59). 1,25-(OH) $_2$ D $_3$ regulates survivin levels in breast (60) and colon cancer cells (61) and improves the barrier function of the skin following suberythemal doses of UV-B (62). Through these mechanisms as well as its anti-proliferative and anti-mutagenic (63,64) activities, 1,25-(OH) $_2$ D $_3$ may have a role in reducing the incidence of melanocytic nevi and in decreasing their rate of progression to melanoma.

Dysplastic nevi are far more widely accepted as melanoma precursor lesions (65) than melanocytic nevi and are also associated with increased survivin levels (54). Through all of the same mechanisms described for melanocytic nevi, 1,25-(OH) $_2$ D $_3$ may also help to protect against the development and progression of other melanocytic nevi, such as dysplastic nevi.

The role of 1,25-(OH) $_2$ D $_3$ in protection against melanoma

1,25-(OH) $_2$ D $_3$ may also have an important role in protection against melanoma (see Figure S1). VDRs act as both intranuclear and intracytoplasmic receptors. Within the nucleus, the VDR forms a heterodimer with the retinoid X receptor (RXR) and then binds to the promoter of target genes containing appropriate 1,25-(OH) $_2$ D $_3$ responsive elements (VDREs), which modulates their expression (66).

The anti-proliferative effects of 1,25-(OH) $_2$ D $_3$ against melanoma and other neoplasms are believed to centre on its ability to inhibit proliferation through the G1/S checkpoint of the cell cycle. Tumor suppressor genes controlling progression through G1/S are among the most frequently inactivated genes in melanoma (27,67), and mutations in 9p21 (coding for the G1/S inhibitors p14 and p16) are believed to play an important role in early melanoma development from nevi (59). 1,25-(OH) $_2$ D $_3$ inhibits proliferation through G1/S by upregulating the p21 and p27 cell cycle inhibitors and by inhibiting cyclin D1 [reviewed in (66)].

In addition, some of the anti-neoplastic effects of 1,25-(OH) $_2$ D $_3$ result from modulation of the activity of growth factors. For example, 1,25-(OH) $_2$ D $_3$ downregulates the activity of growth factors including EGFR (68). Unregulated EGFR autocrine signalling is a feature associated with progression in melanoma (69). 1,25-(OH) $_2$ D $_3$ upregulates the activity of growth factors including TGF- β (70). TGF- β signalling shares many of the characteristic anti-neoplastic features associated with 1,25-(OH) $_2$ D $_3$ including inhibition of cell proliferation and promotion of cell differentiation and apoptosis.

1,25-(OH) $_2$ D $_3$ also increases apoptosis in melanoma (71) through various mechanisms. One of these is through downregulation of the anti-apoptotic factor survivin (60), already discussed in regard to nevi development. Survivin is strongly expressed in malignant melanoma (72, 73), and inhibitors of survivin cause melanoma regression (72,74,75). A second mechanism occurs through a vitamin D-induced increase in intra-cytoplasmic calcium leading to activation of Calpain (calcium-activated neutral protease) (76). The pro-apoptotic effects of Calpain are

mediated through proteolysis and include cleavage of Bax. The Bax cleavage product is a potent inducer of apoptosis. A further pro-apoptotic mechanism suggested for 1,25-(OH)₂D₃ is decreased expression of the secretory form of clusterin (77). In its secretory form, the clusterin glycoprotein has anti-apoptotic activity, and this molecule is expressed in a minority of melanoma cases, particularly those of the primary desmoplastic variety (78). Further discussion of 1,25-(OH)₂D₃-mediated anti-neoplastic pathways in melanoma can be found in Osborne and Hutchinson (66).

1,25-(OH)₂D₃ acting via c-Kit causes stimulation to the MAP-kinase pathway and ultimately increases MITF activity. Mutations stimulating this pathway occur commonly in melanoma, potentially raising concerns regarding the safety of 1,25-(OH)₂D₃ in melanoma prevention/treatment. As we stated earlier, we doubt that stimulation from 1,25-(OH)₂D₃ will prove physiologically significant. However, before highly potent 1,25-(OH)₂D₃ analogues gain widespread therapeutic use, the effect of this stimulation will certainly need to be evaluated.

***In vitro* (cell culture) studies**

In vitro studies have been performed by several groups examining the effect of 1,25-(OH)₂D₃ on melanocyte proliferation (71,79,80). In studies using melanoma cell lines, Seifert et al. (80) showed that some cell lines do not express VDRs and are therefore resistant to 1,25-(OH)₂D₃. By contrast, the same group showed that in melanoma cell lines expressing the VDR, 1,25-(OH)₂D₃ had a dramatic ability to inhibit proliferation. Inhibition of proliferation was also seen in the studies of Colston et al. (79) and Danielsson et al. (71) both involving melanoma cell lines. Reichrath et al. (81) examined the effect of 1,25-(OH)₂D₃ on seven melanoma cell lines and found that only three were responsive. They therefore suggested that if these findings are more widely representative of melanoma behaviour *in vivo*, then it would suggest that 1,25-(OH)₂D₃ and its analogues may have limited efficacy in treating advanced stages of melanoma.

***In vivo* studies**

The importance of 1,25-(OH)₂D₃ in the prevention of skin malignancy is perhaps best demonstrated by *in vivo* studies performed in VDR knockout mice (82,83). Zinser et al. (82) showed that mice lacking a VDR are prone to develop cutaneous malignancies following oral administration of carcinogens. The lesions mainly (80%) consisted of sebaceous, squamous or follicular papillomas, with less frequent development of melanotic foci (mice do not develop melanomas *per se*) and other lesions. The importance of 1,25-(OH)₂D₃ in limiting malignant disease progression is also highlighted by the *in vivo* studies of Chung et al. (84) which showed that prostate tumors transplanted into VDR-knockout mice grew larger than those growing in wild-type mice. The authors attributed this effect, at least in part, to the inhibitory effects of 1,25-(OH)₂D₃ on endothelial cell proliferation (84).

Effects of 25-(OH)D₃ levels and melanoma

The data regarding the effect of 25-(OH)D₃ levels on melanoma are supportive. Nurnberg et al. (85) showed that reduced 25-(OH)D₃ levels correlate with increased stage of melanoma. Similarly, Newton-Bishop et al. (86) showed that higher 25-(OH)D₃ levels are associated with both thinner tumors and better survival from melanoma. It is important to note that the flaw in these studies is that they examined 25-(OH)D₃ levels at discrete time points, whereas 25-(OH)D₃ levels constantly fluctuate owing to seasonal as well as lifestyle factors.

Effects of CYP24A1 over-expression

Changes in the levels of synthetic or degradative factors involved in 1,25-(OH)₂D₃ production would be expected to change 1,25-(OH)₂D₃ levels, and as a consequence anti-neoplastic

activity (Fig. 1). However, very few studies have examined this question in regard to melanoma. One component of the pathway that has been studied is the degradative enzyme CYP24A1. CYP24A1 amplification has been described in breast and lung cancer (87,88). An upregulation in the entire long arm of chromosome 20 (containing CYP24A1) is known to occur in melanoma (89). However, upregulation of CYP24A1 is not believed to have a significant role in the pathogenesis of melanoma (89,90).

Clinical implications

Evidence in favour of a role for 1,25-(OH)₂D₃ in the prevention of melanoma is extensive and includes epidemiological, *in vitro* and *in vivo* studies. The clinical implications of this are potentially enormous as an estimated 1 billion people worldwide are deficient (6). Given that 90% of vitamin D is derived from sunlight (9), one way to increase levels would simply be to increase sunlight exposure, which could be made at suberythemal levels to minimize the risk of skin cancer (91). However, increasing sunlight exposure is controversial and others contend that oral dosing is preferable (92).

From a chemotherapeutic standpoint, 1,25-(OH)₂D₃ may prove most useful as an adjuvant treatment (93). 1,25-(OH)₂D₃ has the advantage over other potential melanoma treatments of being a natural product. However, hypercalcemic concerns limit its effectiveness and mean that intermittent dosing schedules are required (93). As an alternative, researchers are developing non-hypercalcemic forms of 1,25-(OH)₂D₃. Various non-hypercalcemic forms are currently in various stages of clinical trials, often in combination with other agents (94). Some have shown promise in the treatment of various forms of cancer (94,95). Novel metabolites of 1,25-(OH)₂D₃ are also being developed which show great potential (96–100). Of course, because not all melanomas express VDRs (80,81), a prerequisite for the use of 1,25-(OH)₂D₃ or its analogues in melanoma treatment will be a demonstration of the expression of VDRs in the melanoma being treated.

Supplementary Material

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Figure 1.

The pathway of 1,25-(OH)₂D₃ synthesis begins in the skin with UV-B-induced previtamin D₃ production and ends with the production of the inactive end product calcitroic acid. The figure demonstrates how changes in synthetic (green) and degradative enzymes (red) might affect 1,25-(OH)₂D₃ levels.