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Vitamin D Receptor, UVR, and Skin Cancer: A Potential Protective Mechanism

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Abstract

More than 1 million skin cancers occur annually in the United States—of which 80% are basal-cell carcinoma (BCC), 16% are squamous-cell carcinoma (SCC), and 4% are melanomas —making skin cancer by far the most common cancer (Greenlee *et al*., 2001). UVR is the major etiologic agent. UV wavelengths shorter than 280 nm (UVC) are absorbed by the ozone layer and do not reach the earth. UV wavelengths longer than 320 nm (UVA) have limited ability to induce the characteristic mutations in DNA seen in epidermal cancers. Thus, UVB, with a spectrum between 280 and 320 nm, is the major cause of these cancers (Freeman *et al*., 1989), but this is the same spectrum required for vitamin D production in the skin. Is there a link?

The principal genotoxic lesions induced by UVR are cyclobutane pyrimidine dimers and pyrimidine (6–4) pyrimidone photoproducts, which, if not repaired, result in C-to-T or CC-to-TT mutations, the UVB "signature" lesion (Hussein, 2005). Mutations in p53 are common (50–90%) in both BCC and SCC (Brash *et al*., 1991; Daya-Grosjean and Sarasin, 2005; Ziegler *et al*., 1993, 1994), as well as in actinic keratoses, the precursor lesions to SCC (Bito *et al*., 1995). Precursor lesions for BCC have not been identified, but BCCs are thought to arise from interfollicular basal cells, hair follicles, and sebaceous glands. Mutations in *ras* are much more common in SCC than in BCC (Reifenberger *et al*., 2005), whereas mutations in the hedgehog (Hh) signaling pathway—in particular, in patched 1 (*Ptch1*)—characterize BCC (Aszterbaum *et al*., 1998, 1999; Hahn *et al*., 1996; Johnson *et al*., 1996). However, loss of heterozygosity in the region including the *Ptch1* gene has been reported in a high percentage of both BCCs and SCCs (Danaee *et al*., 2006), and polymorphisms of the *Ptch1* gene have altered the resistance to SCC formation in mice expressing an activated *ras* oncogene (Wakabayashi *et al*., 2007). Thus, alterations in the Hh signaling pathway contribute to the formation of both SCC and BCC.

1,25-Dihydroxyvitamin D_3 (1,25 $(OH)_2D_3$) has been evaluated for its potential anticancer activity for approximately 25 years (Eisman *et al*., 1979). The list of malignant cells that express the receptor for 1,25$(OH)_2D_3$—vitamin D receptor (VDR)—is now quite extensive and for the purposes of this Commentary includes BCCs and SCCs (Kamradt *et al*., 2003;

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CONFLICT OF INTEREST

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Ratnam *et al.*, 1996), as well as melanomas (Colston *et al.*, 1981). The accepted basis for the promise of $1,25(OH)_2D_3$ in the prevention and treatment of malignancy includes its antiproliferative, prodifferentiating effects on most cell types. Epidemiologic evidence supporting the importance of adequate vitamin D nutrition (including sunlight exposure) for the prevention of a number of cancers, including those of the colon, breast, and prostate (Bostick *et al.*, 1993; Garland *et al.*, 1985, 1990; Hanchette and Schwartz, 1992; Kearney *et al.*, 1996), is strong. However, several large epidemiologic surveys have not demonstrated such a correlation with skin cancer (Hunter *et al.*, 1992; van Dam *et al.*, 2000; Weinstock *et al.*, 1992). One potential complication is that UVB radiation has the dual effect of promoting vitamin D_3 synthesis in the skin (which can be further converted to $1,25(OH)_2D_3$) and increasing DNA damage, leading to skin cancer. Thus, although UVR may be an efficient means of providing the nutritional requirement for vitamin D, the advantage to the skin may be countered by the increased risk of mutagenesis. However, recent studies indicate that the skin has evolved a vitamin D signaling mechanism whereby the harmful effects of UVR may be mitigated.

The study by Ellison *et al.* (2008) in this issue demonstrates the protective role of VDR for UVR-induced skin tumors. Earlier studies indicated that mice null for VDR were highly susceptible to epidermal tumor formation induced by either the oral administration of the carcinogen 7,12-dimethylbenzanthracene (DMBA) (Zinser *et al.*, 2002) or its topical application (Indra *et al.*, 2007). In the former study, the tumors were mostly papillomas, but several BCCs were observed. No SCCs were reported. In the latter study, only benign tumors were seen in the VDR null mice, unlike RXRα null mice, which developed both BCCs and SCCs (Indra *et al.*, 2007). Ellison *et al.* (2008) confirmed the report by Zinser *et al.* (2002) demonstrating that oral administration of DMBA induced skin tumors in all of the VDR null mice and none of the wild-type mice. Furthermore, most of the tumors that formed appeared to originate from the folliculosebaceous unit. Importantly, Ellison *et al.* (2008) did not report increased susceptibility to DMBA-induced tumor formation in mice lacking the enzyme for $1,25(OH)_2D_3$ production (CYP27B1). The authors thus concluded that, at least for DMBA induction of tumors, VDR protection does not require its principal ligand, $1,25(OH)_2D_3$.

At this point the authors turned their attention to UVR-induced skin tumors comparing VDR null mice with wild-type controls. The mice were of C57BL/6 background, a strain relatively resistant to UVR-induced skin tumors. Even at the very high doses of UVB used in these experiments, only 4 of 23 wild-type mice developed tumors by 45 weeks after the start of UVR, 1 of which was classified as an SCC. In contrast, all 22 of the VDR null mice developed tumors, and 10 of the 27 tumors analyzed were classified as SCC, although markers to document this classification were not provided. Taken at face value, therefore, it would appear that UVR-induced tumors in VDR null mice differ in type compared with DMBA-induced tumors, with SCC predominating following UVR and BCC and folliculosebaceous tumors predominating after DMBA.

Potential mechanisms were then explored. The skin of VDR null mice appeared to have greater cyclobutane pyrimidine dimer formation following UVR, suggesting a DNA repair deficiency. Previous studies with cultured keratinocytes have demonstrated that

$1,25(OH)_2D_3$ and analogs not thought to act via the nuclear configuration of the VDR were also protective against UVR-induced cyclobutane pyrimidine dimer formation (or accelerated their repair) (Dixon *et al.*, 2005; Gupta *et al.*, 2007). Ellison *et al.* (2008) did not test whether CYP27B1 null mice were also predisposed to UVR-induced tumor formation, so the results in their article are silent as to whether this is a $1,25(OH)_2D_3$-independent action of VDR. Apoptosis following a single exposure to UVR was reduced in VDR null mice, although no differences between wild-type and null mice were shown for p53 induction by UVR. These observations are discordant with earlier observations (De Haes *et al.*, 2003) that $1,25(OH)_2D_3$ increases p53 levels and protects keratinocytes from UVR-induced apoptosis (Gupta *et al.*, 2007), suggesting that VDR and $1,25(OH)_2D_3$ might have opposite effects in these responses to UVR. This possibility could be tested by comparing the responses in CYP27B1 null mice to those in VDR null mice. The proliferative response to UVR was also slightly reduced in the VDR null epidermis, which, despite the decrease in apoptosis, seems to have resulted in a thinner epidermis in the VDR null compared with wild-type mice, although UVR induced epidermal thickening compared with the nonirradiated controls of either genotype. This result is consistent with earlier studies (De Haes *et al.*, 2003; Gupta *et al.*, 2007) demonstrating that $1,25(OH)_2D_3$ enhances cell survival in keratinocytes after UVR, but it again raises the question of whether these are $1,25(OH)_2D_3$-dependent or -independent actions of VDR. The finding of the thinner epidermis in the VDR null mouse relative to controls is surprising, however, considering the higher proliferation rates in the epidermis and underlying folliculosebaceous unit of the VDR null mouse compared with controls under basal conditions (Bikle *et al.*, 2006; Xie *et al.*, 2002).

What, then, might be the underlying mechanisms? The DMBA studies producing tumors primarily of folliculosebaceous origin suggest that Hh signaling might be altered in VDR null skin. Appreciation of the pivotal role of the Hh signaling pathway in epidermal carcinogenesis began with the identification of the *Ptch1* gene as the site of mutations underlying the rare autosomal dominant heritable basal-cell nevus syndrome (Gorlin's syndrome), one cardinal feature of which is a high susceptibility to the development of BCCs (Aszterbaum *et al.*, 1998; Hahn *et al.*, 1996). The BCCs in these subjects frequently lose function of the inherited wild-type *Ptch1* allele, leaving the tumor cells functionally null of Ptch1. It has subsequently become clear that essentially all BCCs, whether arising in patients with basal cell nevus syndrome or sporadically, have mutations in *Ptch1* or other alterations in Hh signaling (Aszterbaum *et al.*, 1999). This appreciation has resulted in the development of the $Ptch1^{+/-}$ (Gorlin) mouse as the first practical model of murine BCC (Regl *et al.*, 2004a). Treatment of these mice (unlike treatment of *Ptch1* wild-type mice) with UVR or ionizing radiation produces BCC as well as SCC (Regl *et al.*, 2004a). Ptch1 is the membrane receptor for sonic hedgehog (Shh). In the absence of Shh, Ptch1 inhibits the function of another membrane protein, smoothened (Smoh). Shh reverses this inhibition, freeing Smoh to enable the activation of a family of transcription factors, Gli1 and Gli2. Gli1 and -2 overexpression in keratinocytes can increase the expression of each other as well as Ptch1, the anti-apoptotic factor bcl2, cyclins D1 and D2, E2F1, and cdc45 (all of which promote proliferation) while suppressing genes associated with keratinocyte differentiation such as *K1*, *K10*, *involucrin*, *loricrin* and *VDR* (Grachtchouk *et al.*, 2000; Nilsson *et al.*,

2000; Regl *et al.*, 2002, 2004a,b). Mice overexpressing Gli1, Gli2, or Shh in their basal keratinocytes (Grachtchouk *et al.*, 2000; Nilsson *et al.*, 2000; Oro *et al.*, 1997) or grafted with human keratinocytes overexpressing Shh (Fan *et al.*, 1997) develop BCC-like lesions. Furthermore, BCCs demonstrate overexpression of Ptch1, Smoh, Gli1, and Gli2 (Bonifas *et al.*, 2001; Tojo *et al.*, 1999). A number of the Hh pathway components, including both Gli1 and -2, have consensus vitamin D response elements in their promoters (Palmer *et al.*, 2008; Wang *et al.*, 2005). We (A. Teichert, J. Welsh, and D. Bikle, unpublished data) reported that the epidermis and epidermal portion (utricles) of the hair follicles of VDR null animals overexpress elements of the Hh signaling pathway, suggesting that one of the causes of the increased susceptibility of the epidermis to malignant transformation is a loss of VDR regulation of Hh signaling.

The wnt signaling pathway may also be involved. In a recent paper, Palmer *et al.* (2008) reported the interaction of VDR and wnt signaling in the regulation of hair follicle differentiation and tumor formation. The authors identified various combinations of putative vitamin D response elements and lymphoid-enhancing factor/T-cell factor response elements in a number of genes involved with epidermal and hair follicle differentiation, including components of the Hh signaling pathway such as *Shh*, *Ptch2*, and *Gli1* and *-2*, as well as in LEF itself, the transcriptional partner for β-catenin critical for wnt signaling. At least in colon cancer cells, $1,25(OH)_2D_3$ inhibits the tumor-promoting properties of β-catenin by inducing E-cadherin, to which β-catenin binds (Palmer *et al.*, 2001), and promoting the binding of VDR to β-catenin (Shah *et al.*, 2006), thus limiting its nuclear localization and transcriptional activity. Palmer *et al.* (2008) demonstrated in skin that lack of VDR predisposes the mouse to develop BCC when active β-catenin was overexpressed, although the link to increased Hh signaling was not explored.

In addition to suppression of Hh and wnt signaling, a third mechanism may also be at work, the DNA damage response (DDR). Many endogenous and exogenous factors, including oncogenes, tumor suppressors, radiation, chemical carcinogens, and viral infections, impact a common, but complex, set of pathways that regulate cellular survival, apoptosis, and genomic stability: DDR and the cell cycle checkpoints (Bartkova *et al.*, 2005, 2006). DDR involves a cascade of damage recognition, repair, and signal transduction that coordinates the response of the cell cycle to DNA damage. DDR activates checkpoints that delay the cell cycle, providing time for repair, and directs damaged cells into senescent or apoptotic pathways. DDR demonstrates wide variation in components, activation signals, and downstream consequences according to the cell types, species, and damaging agents. DDR is tightly controlled and highly accurate in normal primary cells such that the spontaneous mutation rate is very low and changes in copy number are negligible (Bielas *et al.*, 2006; Tlsty, 1990; Tlsty *et al.*, 1989). During malignant transformation, a DNA repair "barrier" is abrogated (Bartkova *et al.*, 2005, 2006), DDR becomes less controlled, and mutation rates and copy number changes increase by orders of magnitude (Bielas *et al.*, 2006; Tlsty *et al.*, 1989).

DDR from UV-induced photoproducts has distinct G1 and S phase responses. Nucleotide excision repair (NER) in G1, for example, excises UV photoproducts before onset of DNA replication and thereby eliminates mutagenic lesions completely (Maher *et al.*, 1979).

The main substrates for NER are the UV photoproducts between adjacent pyrimidines: cyclobutane pyrimidine dimers and pyrimidine (6–4) pyrimidone photoproducts (Cleaver *et al.*, 2005), lesions produced by UVB. Mutations in *NER* genes are associated with several human cancer and neurodegenerative diseases, especially xeroderma pigmentosum (XP) and Cockayne's syndrome (Hoeijmakers, 2001; Wood *et al.*, 2001). Damage in transcribed genes is recognized through the arrest of RNA Pol II, which is relieved through the action of two proteins, CSA and CSB. Damage in the non-transcribed or global regions of the genome is recognized by the binding of two heterodimeric XP proteins, XPE (DDB1/DDB2) and XPC/HR23B, which may act in concert to bind to damaged DNA (Hoeijmakers, 2001). These converge on a common pathway through which the damage is verified (XPA/RPA), the DNA is unwound by the XPB and XPD helicase components of the transcription factor TFIIH, cleaved by structure-specific nucleases (XPG, XPF/ERCC1), and the damage is excised and replaced. The global branch of the NER (GGR: XP-A through G) pathway is strongly influenced by transactivation of the *XPC* and *XPE* genes by p53 through DNA damage-dependent increases in p53 expression. GGR defects increase carcinogenesis (Berg *et al.*, 2000).

As noted above, recent studies have shown that vitamin D may have a strong regulatory effect on the capacity of cells and skin to carry out DDR. Treatment of the skin with $1,25(OH)_2D_3$ rapidly increased photo product excision in human and mouse cells and tissues (Dixon *et al.*, 2005; Gupta *et al.*, 2007), but the mechanism of interaction with NER remains unclear. However, when Moll *et al.* (2007) performed microarray studies of keratinocytes treated with $1,25(OH)_2D_3$ for 24 hours, they observed an upregulation of two genes important for DDR: *XPC* and *DDB2*/*XPE*. Accordingly, $1,25(OH)_2D_3$ and VDR may be protective against UVR-induced epidermal tumor formation by stimulating DDR as well as by suppressing Hh and wnt signaling.

Ellison *et al.* (2008) make the important point that VDR serves as a tumor suppressor not only for chemically induced epidermal carcinogenesis but also for the more physiologically relevant UVR-induced epidermal carcinogenesis. Although these authors have convincingly demonstrated that the former is a $1,25(OH)_2D_3$-independent action of VDR, this conclusion cannot yet be extended to UVR-induced carcinogenesis. Earlier studies indicated several mechanisms by which VDR, with or without its ligand $1,25(OH)_2D_3$, might be protective. These mechanisms include altered Hh and wnt signaling and increased DDR. Future investigations are required to determine which, if any, of these mechanisms are involved and the degree to which VDR acts through these mechanisms in a $1,25(OH)_2D_3$-dependent or -independent manner. However, this publication establishes an important fact: the skin has evolved a way of protecting itself from the deleterious actions of UVR using a key component of the pathway promoted by UVR, namely, the VDR.

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