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Vitamin D and skin cancer: A problem in gene regulation☆

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Abstract

The skin is the major source of Vitamin D_3 (cholecalciferol), and ultraviolet light (UV) is critical for its formation. Keratinocytes, the major cell in the epidermis, can further convert Vitamin D_3 to its hormonal form, 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] (calcitriol). $1,25(OH)_2D_3$ in turn stimulates the differentiation of keratinocytes, raising the hope that $1,25(OH)_2D_3$ may prevent the development of malignancies in these cells. Skin cancers (squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and melanomas) are the most common cancers afflicting humans. UV exposure is linked to the incidence of these cancers—UV is thus good and bad for epidermal health. Our focus is on the mechanisms by which $1,25(OH)_2D_3$ regulates the differentiation of keratinocytes, and how this regulation breaks down in transformed cells. Skin cancers produce $1,25(OH)_2D_3$, contain ample amounts of the Vitamin D receptor (VDR), and respond to $1,25(OH)_2D_3$ with respect to induction of the 24-hydroxylase, but fail to differentiate in response to $1,25(OH)_2D_3$. Why not? The explanation may lie in the overexpression of the DRIP complex, which by interfering with the normal transition from DRIP to SRC as coactivators of the VDR during differentiation, block the induction of genes required for $1,25(OH)_2D_3$-induced differentiation.

Keywords: Keratinocytes; Squamous cell carcinoma; Vitamin D; Calcium; Differentiation

1. Introduction

The Vitamin D receptor (VDR) is found in most cell types including many malignant cell types. This includes the three major types of skin cancers: basal and squamous cell carcinomas (BCC and SCC) [1,2] and melanomas [3]. These skin cancers are the most common of all malignancies. The basis for the promise of 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) (calcitriol) in the prevention and treatment of malignancy includes its antiproliferative, prodifferentiating effects on most cells. Normal keratinocytes and melanocytes respond to $1,25(OH)_2D_3$ with a reduction in proliferation and an increase in differentiation. Furthermore, these cells make their own $1,25(OH)_2D_3$ suggesting that prevention and/or treatment of such malignancies could involve providing sufficient substrate for the endogenous 25OHD-1α-hydroxylase. However, malignant transformation causes resistance to these actions of $1,25(OH)_2D_3$ for a variety of reasons. In this review, we will examine some of these mechanisms, focusing on work from our own laboratory in which an imbalance in coactivators appears to undercut the ability of $1,25(OH)_2D_3$ to initiate the sequence of gene induction required for differentiation.

2. Does Vitamin D deficiency play a role?

Epidemiologic evidence supporting the importance of adequate Vitamin D nutrition (including sunlight exposure) has been obtained for colon, breast, and prostate cancer [4–6].

Abbreviations: BCC, basal cell carcinoma; $[Ca^{2+}]_i$ and $[Ca^{2+}]_0$, intracellular and extracellular free calcium, respectively; CaR, calcium receptor; DG, diacylglycerol; 7-DHC, 7-dehydrocholesterol, Vitamin D_3 (cholecalciferol); DMBA, dimethylbenzanthracene; IP_3, inositol trisphosphate; 1OHase (P450c27B1; CYP27B1), 25OHD-1α-hydroxylase; 24OHase (P450c24; CYP24), 25-hydroxyvitamin D-24 hydroxylase; 25OHase (P450c27; CYP27), Vitamin D-25-hydroxylase; $1,25(OH)_2D_3$, 1,25-dihydroxyvitamin D_3 (calcitriol); $25\text{-}OHD_3$, 25-hydroxyvitamin D_3 (calcidiol); PLC, phospholipase C; PTH, parathyroid hormone; SCC, squamous cell carcinoma; VDR, Vitamin D receptor; VDRE, Vitamin D response element

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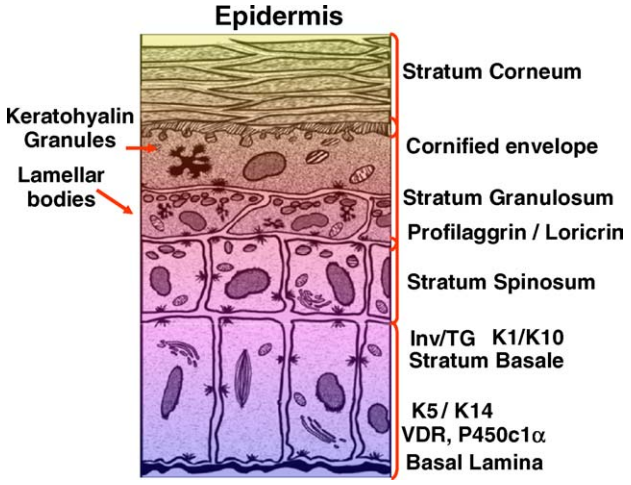

Fig. 1. A cartoon depicting the four principal layers of the epidermis and the locations where the proteins of relevance to this review are produced. Proliferation occurs in the stratum basale. The 1OHase and VDR are in highest concentration in this layer. As the cells leave the stratum basale, they begin the differentiation process with the production of early markers such as K1 and K10, involucrin (Inv), and transglutaminase (TG) starting in the stratum spinosum and late markers such as profilaggrin and loricrin in the stratum granulosum. The enucleated stratum corneum containing the cornified envelope and intercellular lipid contents of the lamellar bodies provides the barrier.

However, the results are less compelling for skin cancers. A case control study of 165 melanoma patients and 209 controls showed no association of the malignancy with Vitamin D intake [7]. van Dam et al. [8] administered a food frequency questionnaire to 43,217 males in the Health Professionals Followup Study who were then followed for 8 years. Three thousand one hundred and ninety of the participants developed basal cell carcinoma, but Vitamin D intake was not associated with the development of this malignancy. Similar results were obtained in the Nurses Health Study [9]. Associations with sunlight exposure, as have been shown for other malignancies (colon, breast, and prostate), would be complicated by the dual effect of ultraviolet (UV) light in promoting Vitamin D_3 synthesis in the skin but increasing the risk of skin cancer.

3. Epidermis: a model of differentiation in time and place

The epidermis is critical for life. It keeps what we need inside and keeps what we do not need outside—the barrier function. The primary cell in the epidermis responsible for this barrier function is the keratinocyte (Fig. 1). The epidermis is self-renewing. Proliferating keratinocytes are found only in the base of the epidermis, in the layer known as the stratum basale. Daughter cells leave the stratum basale and differentiate on their journey to the surface, where as the enucleated cells of the stratum corneum they form the permeability barrier. Along the way, genes are sequentially turned on and off to produce proteins that contribute to the fully differentiated keratinocyte. For example, basal keratinocytes produce keratins 5 and 14. As they enter the stratum spinosum, the production of keratins 1 and 10 replaces that of keratins 5 and 14. Involucrin, an important component of the cornified envelope, and transglutaminase-K, the enzyme that cross links involucrin and other substrates to form the cornified envelope, are also made in the keratinocytes of the stratum spinosum. The next higher level, the stratum granulosum, is marked by the presence of keratohyalin granules. These granules contain loricrin, a major component of the cornified envelope, and profilaggrin, a precursor of filaggrin that serves as a bundling protein for the keratin filaments. The stratum granulosum also contains lamellar bodies whose contents of lipids and lipid-processing enzymes are secreted into the junction between the stratum granulosum and stratum corneum to provide the mortar between the bricks that are the corneocytes of the stratum corneum.

The differentiation process in the epidermis is tightly regulated. A number of agents can affect the proliferation and differentiation process. Our focus has been on calcium and $1,25(OH)_2D_3$ [10] stemming from our observations nearly 20 years ago that the keratinocyte is the most prodigious producer of $1,25(OH)_2D_3$ that we have ever studied. The keratinocytes of the stratum basale contain VDR, which mediates $1,25(OH)_2D_3$ regulated proliferation and differentiation. These cells also contain ample supplies of 7-dehydrocholesterol (7-DHC) from which they make Vitamin D_3 under the influence of UV light. Since these cells also have the 25-hydroxylase (25OHase) and 25OHD-1α-hydroxylase (1OHase), they are able to produce their own supply of $1,25(OH)_2D_3$. Thus, the keratinocyte—and only the keratinocyte—has the entire metabolic machinery to produce $1,25(OH)_2D_3$ from 7-DHC and is a target for that hormone as well. However, the presence of VDR and the ability to produce $1,25(OH)_2D_3$ do not distinguish normal keratinocytes from transformed keratinocytes. All SCC lines that we have tested have both VDR [1] and the ability to produce $1,25(OH)_2D_3$ [11]. More recent studies observed increased 1OHase and VDR expression in the BCC and SCC tumors examined compared with normal epidermis, and increased 25OHase expression in the SCC tumors [2,12].

In vitro, calcium is one of the most potent means of stimulating epidermal differentiation while inhibiting proliferation. In vivo, a calcium gradient forms in the epidermis (lowest concentrations in the stratum basale, highest concentrations in the stratum granulosum) [13]. This gradient appears important for the proliferation–differentiation process in vivo. Mice lacking the ability to make $1,25(OH)_2D_3$ fail to maintain this gradient, show reduced expression of differentiation markers in their epidermis, and are slow to recover the epidermal barrier function when broken by physical means [14]. Given that $1,25(OH)_2D_3$ is a calcium regulating hormone, it should come as no surprise that the effects of calcium and $1,25(OH)_2D_3$ on keratinocyte proliferation and differentiation are interacting.