**CONFIDENTIALITY**

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**Vitamin D Regulation of Cathelicidin in the Skin: Toward a Renaissance of Vitamin D in Dermatology?**

Siegfried Segaert¹

1,25-Dihydroxyvitamin D₃, the active form of vitamin D, is a major regulator of the expression of the cationic antimicrobial peptide cathelicidin, not only in monocytes but also in epidermal keratinocytes. The involvement of cathelicidin in wound healing and skin diseases as diverse as psoriasis, rosacea, and atopic dermatitis may create new opportunities for the use of vitamin D in dermatology.


With epidermal photosynthesis of vitamin D₃ as its main source, vitamin D is not a true vitamin for humans. Vitamin D₃ is biologically inert and needs successive hydroxylation by 25-hydroxylase (CYP27A1) in the liver and 1α-hydroxylase (CYP27B1) in the kidney to yield 1α,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃], also known as calcitriol. In vitamin D target cells, calcitriol subsequently activates the vitamin D receptor (VDR), resulting in altered expression of genes involved in calcium metabolism, proliferation, differentiation, apoptosis, and adaptive immunity (Reichrath, 2007). Epidermal keratinocytes occupy a unique position within the vitamin D system because they not only possess the full machinery for ultraviolet B-dependent photoproduction of 1,25(OH)₂D₃ (Vantieghem et al., 2006) but also contain VDR and respond to 1,25(OH)₂D₃ with growth arrest, differentiation, and changes in cytokine expression (Segaert et al., 1997). Almost two decades ago, this property resulted in the successful introduction of topical vitamin D analogs to treat psoriasis (Reichrath, 2007). However, other dermatologic indications for vitamin D derivatives remained largely unexplored.

The recent identification of the cationic antimicrobial peptide cathelicidin as a vitamin D target gene (Gombart et al., 2005) and of CYP27B1 and VDR upregulation in monocytes as the link between Toll-like receptor-2 (TLR-2) activation on the one hand and cathelicidin production and intracellular mycobacteria killing on the other hand (Liu et al., 2006) created a previously unknown and unexpected link between innate immunity and the vitamin D system. Vitamin D status, as determined by its cutaneous photosynthesis, promptly became a plausible explanation for increased susceptibility of African-American individuals to tuberculosis, seasonal peaking of viral infections in winter, and the therapeutic effect of phototherapy in lupus vulgaris, for which Niels Ryberg Finsen received the Nobel prize more than a century ago (Liu et al., 2006). Whether cutaneous photosynthesis of 1,25(OH)₂D₃ (Vantieghem et al., 2006) directly enhances innate immunity in the skin by induction of cathelicidin in keratinocytes (Schauber et al., 2007) or whether skin-photoproduced vitamin D₃ acts via hepatic conversion to 25-hydroxyvitamin D₃ to reach target cells, including monocytes and keratinocytes, remains to be determined (Segaert and Simonart, 2008). In addition, the mechanism of action of Finsen’s phototherapy is an

¹Department of Dermatology, University Hospital Leuven, Belgium

Correspondence: Dr Siegfried Segaert, UZ Sint-Rafael, Kapucijnenvoer 33, B-3000 Leuven, Belgium. E-mail: Siegfried.Segaert@med.kuleuven.be

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ongoing matter of debate (Segaert and Simonart, 2008).

In contrast to humans and primates, cathelicidin expression is not vitamin D–regulated in rodents (Gombart et al., 2005). The fact that the nocturnal life of these animals excludes them from vitamin D biosynthesis as an evolutionary drive may explain this intriguing finding (Liu et al., 2006). Interestingly, cats (other nocturnal animals) lack cutaneous vitamin D biosynthesis because of insufficient provitamin D stores in the skin (Morris, 1999). During evolution, the regulation of cathelicidin expression by vitamin D may have appeared in parallel with the acquisition of cutaneous vitamin D photoproduction as an adaptation to sunlight exposure.

Apart from its antimicrobial role in innate immunity, cathelicidin exhibits biological effects on cell proliferation and migration and cytokine and chemokine production, processes that are pivotal in inflammation, angiogenesis, and wound repair (Schauber and Gallo, 2007). Indeed, changes in vitamin D metabolism seen in monocytes following microbial stimulation of TLR-2 (Liu et al., 2006) were also observed in keratinocytes during wound healing (Schauber et al., 2007). Following skin injury, activation of TLR-2 and the cytokine transforming growth factor-β (TGF-β) coordinately increased keratinocyte CYP27B1 expression. This permitted 1,25(OH)2D3 biosynthesis, as shown indirectly by strong induction of 24-hydroxylase, the most vitamin D–responsive gene known (Schauber et al., 2007). Locally produced 1,25(OH)2D3 subsequently induced cathelicidin.

Furthermore, this sophisticated system is maintained by various positive-feedback loops, namely, vitamin D–dependent induction of TLR-2 and its cofactor CD14 (Schauber et al., 2007) and TGF-β (Segaert et al., 1997). The apparent pivotal role of the vitamin D–cathelicidin system during normal wound healing makes it an attractive pharmacologic target in developing vitamin D analogs to treat conditions that include compromised wound healing. Indeed, defective antimicrobial peptide expression has been observed in chronic ulcers and thermal burns (Zasloff, 2005) and may be responsible for retarded healing and susceptibility to infection.

Atopic dermatitis is another disease with decreased antimicrobial peptide expression, accounting for frequent cutaneous infections (Zasloff, 2005). However, vitamin D analogs, although poorly studied, have not been effective in atopic dermatitis. Disadvantageous vitamin D effects on adaptive immunity—specifically, the T-helper 1 to T-helper 2 lymphocyte shift caused by keratinocyte induction of thymic stromal lymphopoietin (Li et al., 2006) as well as the irritating properties of vitamin D analogs—probably outweigh the beneficial effects of antimicrobial peptide induction.

Mechanisms of vitamin D effects wound healing.

In contrast, high expression of cathelicidin and other antimicrobial peptides has been noted in psoriasis (Zasloff, 2005), an inflammatory skin disease in which superinfection is rare. It was recently demonstrated that the autoimmune response in psoriasis is initiated by cathelicidin–DNA complexes triggering interferon-α production by plasmacytoid dendritic cells (Lande et al., 2007). How can we reconcile these findings with the effectiveness of vitamin D analogs in psoriasis? The antipsoriatic effect of active vitamin D probably relies primarily on its antiproliferative properties in keratinocytes (Segaert et al., 1997) or on T-helper 1 to T-helper 2 skewing during T-helper-cell differentiation (Li et al., 2006). However, this does not exclude cathelicidin from being a potentially attractive pharmacologic target in this disease.

Intriguingly, lesional skin of rosacea patients also contains excessive cathelicidin, which is abnormally processed by serine proteases to peptides that mimic features of the disease in mice (Yamasaki et al., 2007). Oral minocycline treatment decreases cutaneous protease activity in rosacea (Yamasaki et al., 2007), making a case for the development of more specific serine protease inhibitors as topical drugs for the disease. Some other questions can be brought forward in this context. Can photogaggravation of rosacea be ascribed to (vitamin D–mediated?) induction of cathelicidin in the skin (Segaert and Simonart, 2008)? How does the poorly understood antirosacea effect of metronidazole relate to this newly identified role of cathelicidin?

In this issue of the Journal of Investigative Dermatology, Schauber et al. (2008) explore further the mechanisms by which cathelicidin and CD14 are induced by calcitriol in keratinocytes. The authors determined that these responses specifically require the vitamin D receptor coactivator SRC3 (steroid receptor coactivator 3) and its inherent histone acetylation activity (which opens up the chromatin, facilitating the access of transcription factors such as VDR to the transcription start site). Moreover, epidermal SRC3 colocalizes with cathelicidin in the differentiated superficial layers of the epidermis. The histone deacetylase inhibitors butyrate and trichostatin A markedly potentiate the vitamin D response in keratinocytes on cathelicidin, CD14, and 24-hydroxylase induction, whereas the specific VDR antagonist ZK159522 counteracts induction of the antimicrobial peptide. Translating these findings from the bench to the patient raises some interesting thoughts: can topical histone deacetylase inhibitors be combined with vitamin D analogs to increase their therapeutic potential in skin diseases such as psoriasis? Is there a rationale for the topical application of VDR antagonists in diseases with excessive cathelicidin expression such as rosacea? Because some vitamin D analogs already exist that owe their selectiveness to the recruitment of specific coactivators (Takeyama et al., 1999), can a vitamin D analog be designed that selectively recruits SRC3 to the VDR and is such an agent capable of separating effects on antimicrobial peptide induction from effects on calcium metabolism, proliferation, and differentiation? Such a drug would be a promising candidate to treat conditions with defective antimicrobial peptide activity, such as chronic wounds or atopic der-
matitis (Zasloff, 2005). Vitamin D may be making a comeback in dermatology.

**CONFLICT OF INTEREST**
The author states no conflict of interest.

**REFERENCES**


