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Journal
Journal of Investigative Dermatology, 137(12)

ISSN
0022-202X

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Publication Date
2017-12-01

DOI
10.1016/j.jid.2017.07.816

Peer reviewed

HHS Public Access

Author manuscript

J Invest Dermatol. Author manuscript; available in PMC 2018 December 01.

Published in final edited form as:

J Invest Dermatol. 2017 December ; 137(12): 2469–2471. doi:10.1016/j.jid.2017.07.816.

Skin-derived vitamin D3 protects against basal cell carcinoma

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Abstract

Ultraviolet radiation in sunlight causes mutations that drive basal cell carcinomas. However, the incidence of these tumors plateaus with prolonged exposure, while the incidence of other skin cancers increases. Makarova and colleagues now show that vitamin D_3 produced in the skin in response to ultraviolet radiation protects against its oncogenic effects by inhibiting Hedgehog signaling, whereas oral administration of vitamin D_3 does not.

INTRODUCTION

It is well recognized that the sun's ultraviolet radiation (UVR) is mutagenic, and thus causes various skin cancers. Exposure to sunlight and the risk of skin cancer are strongly correlated, and cancer prevention programs all urge the importance of protection from UVR. Skin cancers that arise following exposure to sunlight differ in malignant potential and medical gravity. For instance, squamous cell carcinomas (SCCs) metastasize from the primary tumor site and late stage disease is associated with poor outcome. On the other hand, basal cell carcinomas (BCCs) are relatively indolent but have a very high incidence. Moreover, BCCs often occur in the face and if left untreated can severely disfigure patients.

An interesting incongruity has become apparent between the cumulative exposure to sunlight and the incidence of SCCs and BCCs: In contrast to SCCs, the incidence of BCCs appears to plateau, at which more exposure does not result in more cases of BCC (Rosso et al., 1996). It has been suggested that the UV-driven production of vitamin D3 in the skin contributes to the protective effect of sunlight, explaining why the relative incidence of BCCs decreases compared the SCCs upon prolonged sunlight exposure. In this issue of the *Journal of Investigative Dermatology*, the Epstein group describes the use of a mouse model for UVR-driven BCCs to understand and explain this seemingly contradictory association.

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CONFLICT OF INTEREST

MFB has received research funding from Celgene. This party was not involved in drafting of the manuscript.

HEDGEHOG SIGNALING IN DEVELOPMENT AND CANCER

The developing embryo is shaped by gradients of molecules known as morphogens. The concentration, time of exposure, and combinations of the morphogens to which cells in a morphogenetic field are exposed to will determine its fate and identity and thus sculpt tissues. One of the most prominent morphogen families to shape developing organisms is that of the Hedgehog proteins. Gradients of Hedgehog pattern the digits, face, gastrointestinal organs, central nervous system and many other tissues and organs. This early role of Hedgehog signaling is complemented in its role in the maintenance of a variety of adult stem cell niches, including those in the skin and hair follicles. The widespread contribution of Hedgehog signaling to the developing embryo and stem cell niches is also reflected in the number of cancer types suspected or known to be driven by aberrantly activation Hedgehog of the Hedgehog response. These include tumors of the skin, medulla, and this forming in the derivatives of the foregut.

The Hedgehog signaling pathway is complex and large gaps exist in our understanding of its regulation. In the absence of Hedgehog ligand, the putative transporter Patched inhibits the G-protein coupled receptor, Smoothened, thus keeping the Hedgehog pathway inactive, by a still poorly understood mechanism. Soon after its identification as the main receptor for Hedgehog ligand, Patched was found not to bind directly to Smo but rather to inhibit Smoothened via a catalytic mechanism (Taipale et al., 2002). Patched is a member of a family transport proteins present in all of domains of life. As for most members of this family, the cargo of Ptch is not known. Later work from us and others demonstrated that Patched can act non-cell autonomously inhibit Smoothened by the secretion of endogenous sterol-like molecules, most notably (non-hydroxylated) vitamin D3 (Bijlsma et al., 2006; Linder et al., 2015; Roberts et al., 2016).

Vitamin D3 is synthesized in the skin from 7-dehydrocholesterol by UVR. It is then hydroxylated in the kidneys and liver to yield 1,25 OH-vitamin D3. In contrast to the classical activities of vitamin D3 like bone calcification, this hydroxylation is not required for the inhibition of Smoothened. The biological precursor to 7-dehydrocholesterol is lathosterol, the conversion of which is mediated by sterol-C5-desaturase (Sc5d). In turn, 7-dehydrocholesterol is the precursor to cholesterol, a reaction catalyzed by 7-dehydrocholesterol reductase (Dhcr7). Targeting these enzymes allows indirect manipulation of vitamin D3 levels: Ablation or inhibition of Sc5d will lead to a depletion of 7-dehydrocholesterol and thus vitamin D3, whereas inhibition of Dhcr7 leads to an accumulation of 7-dehydrocholesterol and increased levels of vitamin D3. Humans lacking *Dhcr7* display congenital abnormalities characteristic of decreased levels of Hedgehog signaling, an observation supporting the notion that (a derivative of) 7-dehydrocholesterol inhibits Smoothened.

ENDOGENOUS INHIBITORS OF HEDGEHOG SIGNALING ARE EFFECTIVE AGAINST BCC

Basal cell carcinomas are prime examples of a tumor type in which the pathway components that regulate Hedgehog signaling act as proto-oncogenes and tumor suppressors. The

oncogenic mutations responsible for BCC growth are well characterized: Mutations in Patched that impede its catalytic inhibition of Smoothened, as well as activating mutations in Smoothened that desensitize it to inhibition by Patched, are two main causes of basal cell carcinoma (Xie et al. 1998; Hahn et al., 1996). The critical role for Hedgehog pathway activation in BCC formation, and the known Hedgehog-suppressive effects of vitamin D3 imply that vitamin D3 could be effective against BCC.

Indeed, the authors had previously observed that topically applied vitamin D3 is effective against BCC, and demonstrated that at least part of this effect was mediated by the inhibitory effect of vitamin D3 on the Hedgehog pathway (Tang et al., 2011). In the current paper the authors take this observation further and prove that the same UVR exposure that drives BCC formation, is also the UVR that generates tumor-suppressive vitamin D3 (Makarova et al., 2017). They do so by making use of the fact that the female heterozygous Patched mutant mice make vitamin D3 in UVR-exposed skin, whereas their male counterparts do not. It was observed that the mice that are able synthesize vitamin D3 are protected from BCCs that typically arise in response to UVR. This was further supported by the use of conditional *Sc5d*$^{-/-}$ mice, which cannot produce vitamin D3 in their skin and had much higher incidence of BCCs after UVR exposure. In addition, the authors found that UVR-generated or topically applied (non-hydroxylated) vitamin D3 was effective against BCCs, but that dietary vitamin D3 was not. This is presumably due to the rapid hydroxylation of orally ingested vitamin D3, yielding a form of vitamin D3 that cannot inhibit Smoothened.

In summary, the authors provide evidence supporting the notion that the non-linear relationship between high cumulative sunlight exposure and the incidence of BCC is caused by the increased local availability of vitamin D3. However, the intriguing idea that the increased vitamin D3 concentration directly affects Smoothend activity remains to be answered, and differentiated from signaling by 1,25 OH-vitamin D3 through its canonical receptor (VDR), which also drives potent anti-tumor signaling. It is neverhtheless tempting to speculate that local availability of vitamin D3 inhibits BCCs through the same mechanism as the the topical application of the Smoothened inhibitors vismodegib and cyclopamine. Another question pertains to clinical applicability; if orally taken vitamin D3 does not yield high systemic levels of non-hydroxylated vitamin D3, how can we achieve concentrations that are sufficiently high to inhibit Smoothened in populations at risk of developing BCC without exposing them to the very same sunlight that is oncogenic? Topical use of pharmacological inhibitors of for instance Dhcr7 could be considered but this is of course at risk of perturbing synthesis of important downstream sterols (cholesterol). If indeed vitamin D3 synthesized in the skin due to UVR exposure is a significant tumor-suppressive mechanism, it can be hypothesized that inhibition of HMG CoA reductase by statins, thereby lowering levels of 7-dehydrocholesterol will in fact exacerbate tumor incidence but to our knowledge this has not been demonstrated.

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CLINICAL RELEVANCE

- The authors show that vitamin D3 generated in the skin by ultraviolet radiation suppresses basal cell carcinoma growth.
- Basal cell carcinomas are commonly driven by an aberrantly activated Hedgehog pathway, and the tumor-suppressive effects of skin-borne vitamin D3 are -at least in part- through inhibition of this pathway.
- These findings might provide an explanation why the incidence of basal cell carcinoma does not progress in a linear fashion with exposure to sunlight.

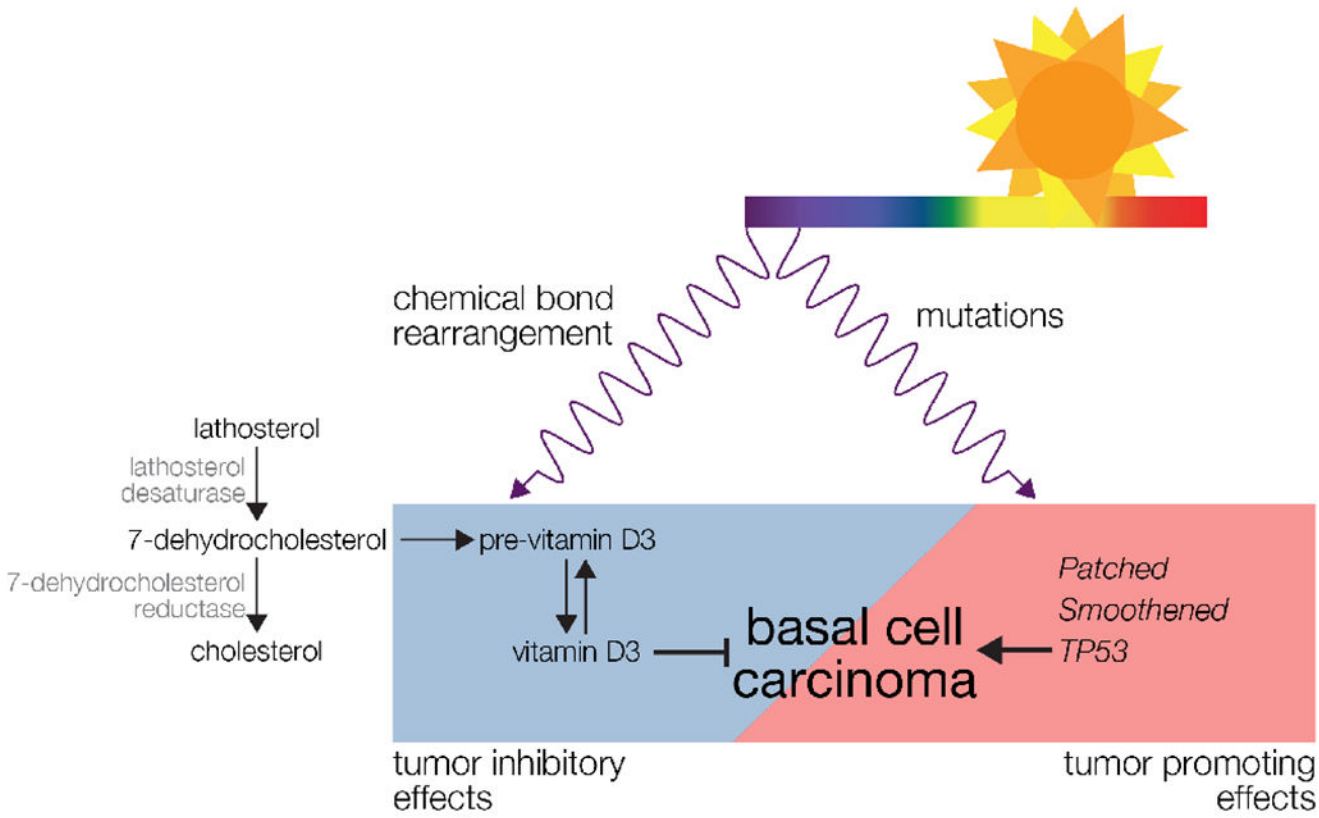

Figure 1. Schematic summary of the authors' findings.

The sun's UVR is responsible for the synthesis of vitamin D3 in the skin and the mutations that drive skin cancer. For basal cell carcinoma, these have counteracting effects on tumor progression.

It is apparent that our current understanding of the relationship between developmental signaling, cancer, and the non-canonical actions of sterol-like molecules is insufficient to translate to clinical practice. However, articles such as those discussed here provide the small steps required to get there, hopefully enabling better prevention and treatment of the most common skin cancer in the near future.