VITAMIN D AND THE SKIN.

The keratinocytes of the skin are unique in being not only the primary source of vitamin D for the body, but also possessing the enzymatic machinery to metabolize vitamin D to active metabolites [in particular, 1,25 dihydroxyvitamin D (1,25(OH)(2)D)] and the vitamin D receptor (VDR) that enables the keratinocytes to respond to the 1,25(OH)(2)D they produce. Numerous functions of the skin are regulated by vitamin D and/or its receptor: these include inhibition of proliferation, stimulation of differentiation including formation of the permeability barrier, promotion of innate immunity, regulation of the hair follicle cycle, and suppression of tumor formation. Regulation of these actions is exerted by a number of different coregulators including the coactivators DRIP and SRC, a less well known inhibitor, hairless, and beta-catenin. Different coregulators appear to be involved in different VDR-regulated functions. This review examines the various functions of vitamin D and its receptor, and to the extent known explores the mechanisms by which these functions are regulated.

J Bone Miner Metab. 2010 Mar;28(2):117-30

VITAMIN D AND THE SKIN.

Along with other organs like prostate, bones and kidney, skin is capable of vitamin D synthesis. Primarily keratinocytes but also macrophages and fibroblasts synthesize active vitamin D from cholesterol precursors by photochemical activation. The synthesized vitamin D functions by binding to nuclear vitamin D receptors. Vitamin D deficiency usually manifests as rickets in childhood although it is today only relevant in diseases characterized by malabsorption due to today’s recommended vitamin D prophylaxis. Excessive doses of vitamin D are the usual cause of increased levels. The most common therapeutic target of vitamin D is psoriasis. Here, topical preparations are usually employed; their anti-proliferative and cell differentiation-promoting action is mediated via binding to cutaneous vitamin D receptors.

Hautarzt. 2008 Sep;59(9):737-42

VITAMIN D RECEPTOR AND COACTIVATORS SRC2 AND 3 REGULATE EPIDERMIS-SPECIFIC SPHINGOLIPID PRODUCTION AND PERMEABILITY BARRIER FORMATION.

The vitamin D receptor (VDR) is a nuclear hormone receptor that controls transcription of target genes. It exerts its biological effects through transcriptional coactivators. Previously, we identified two distinct classes of VDR coactivators, VDR-interacting protein (DRIP) and steroid receptor coactivator (SRC) at different stages of keratinocyte differentiation. Here, we determined the functions of VDR and coactivators in lipid production and permeability barrier formation. Silencing of either VDR, SRC2, or SRC3 resulted in decreases in specific glucosylceramide (GlcCer) species but not other lipids such as cholesterol and free fatty acids. Their silencing also caused decreased transcription of fatty acid elongase and ceramide glucosyltransferase, which are critical for the synthesis of epidermis-unique GlcCer species, and defects in lamellar body formation associated with decreased expression of the lipid transporter ATP-binding cassette transporter protein 12. VDR null mice exhibit abnormal barrier function with altered lipid composition in vivo. These results demonstrate that VDR and coactivators SRC2 and SRC3, which are also involved in other nuclear receptors as well, are critical for epidermis-specific sphingolipid production and barrier formation. In contrast, DRIP silencing had no apparent effect on these processes indicating that the two classes of coactivators are differentially utilized. J Invest Dermatol. 2009 Jun;129(6):1367-78

VITAMIN D: IMPORTANCE IN THE PREVENTION OF CANCERS, TYPE 1 DIABETES, HEART DISEASE, AND OSTEOPOOROSIS.

The purpose of this review is to put into perspective the many health benefits of vitamin D and the role of vitamin D deficiency in increasing the risk of many common and serious diseases, including some common cancers, type 1 diabetes, cardiovascular disease, and osteoporosis. Numerous epidemiologic studies suggest that exposure to sunlight, which enhances the production of vitamin D(3) in the skin, is important in preventing many chronic diseases. Because very few foods naturally contain vitamin D, sunlight supplies most of our vitamin D requirement. 25-hydroxyvitamin D [25(OH)D] is the metabolite that should be measured in the blood to determine vitamin D status. Vitamin D deficiency is prevalent in infants who are solely breastfed and who do not receive vitamin D supplementation and in adults of all ages who have increased skin pigmentation or who always wear sun protection or limit their outdoor activities. Vitamin D deficiency is often misdiagnosed as fibromyalgia. A new dietary source of
SUNLIGHT AND VITAMIN D FOR BONE HEALTH AND PREVENTION OF AUTOIMMUNE DISEASES, CANCERS, AND CARDIOVASCULAR DISEASE.

Most humans depend on sun exposure to satisfy their requirements for vitamin D. Solar ultraviolet B photons are absorbed by 7-dehydrocholesterol in the skin, leading to its transformation to previtamin D3, which is rapidly converted to vitamin D3. Season, latitude, time of day, skin pigmentation, aging, sunscreen use, and glass all influence the cutaneous production of vitamin D3. Once formed, vitamin D3 is metabolized in the liver to 25-hydroxyvitamin D3 and then in the kidney to its biologically active form, 1,25-dihydroxyvitamin D3. Vitamin D deficiency is an unrecognized epidemic among both children and adults in the United States. Vitamin D deficiency not only causes rickets among children but also precipitates and exacerbates osteoporosis among adults and causes the painful bone disease osteomalacia. Vitamin D deficiency has been associated with increased risks of deadly cancers, cardiovascular disease, multiple sclerosis, rheumatoid arthritis, and type 1 diabetes mellitus. Maintaining blood concentrations of 25-hydroxyvitamin D above 80 nmol/L (approximately 30 ng/mL) not only is important for maximizing intestinal calcium absorption but also may be important for providing the extrarenal 1alpha-hydroxylase that is present in most tissues to produce 1,25-dihydroxyvitamin D3. Although chronic excessive exposure to sunlight increases the risk of nonmelanoma skin cancer, the avoidance of all direct sun exposure increases the risk of vitamin D deficiency, which can have serious consequences. Monitoring serum 25-hydroxyvitamin D concentrations yearly should help reveal vitamin D deficiencies. Sensible sun exposure (usually 5-10 min of exposure of the arms and legs or the hands, arms, and face, 2 or 3 times per week) and increased dietary and supplemental vitamin D intakes are reasonable approaches to guarantee vitamin D sufficiency.

INVOLVEMENT OF ENDOGENOUSLY PRODUCED 1,25-DIHYDROXYVITAMIN D-3 IN THE GROWTH AND DIFFERENTIATION OF HUMAN KERATINOCYTES.

In this study, we investigated the possibility that cultured keratinocytes from normal human adult skin produce 1,25-dihydroxyvitamin D-3 (1,25(OH)2D3, a biologically active form of vitamin D-3) from 25-hydroxyvitamin D-3 [25(OH)D3], and that 1,25(OH)2D3 endogenously produced by keratinocytes is involved in the self regulation of their growth and differentiation. To determine whether 1,25(OH)2D3 is produced from 25(OH)D3 by skin keratinocytes, 25(OH)[3H]D3 was added to keratinocyte cultures and incubated for 1 h and 5 h. The intracellular and extracellular metabolites were analyzed by three chromatographic systems. The three chromatograms revealed that the major metabolite produced from 25(OH)D3 was 1,25(OH)2D3. Most of the 1,25(OH)2D3 endogenously produced from 25(OH)D3 remained within the cells. To determine the time course of 1,25(OH)2D3 production, the amount of 1,25(OH)[3H]D3 was measured at 15 min, 1 h, 5 h and 10 h, being at a maximum 1 h after the addition of 25(OH)D3. These data indicate that keratinocytes rapidly convert 25(OH)D3 to 1,25(OH)2D3 and that 1,25(OH)2D3 is not released into the medium. To determine whether endogenously produced 1,25(OH)2D3 is involved in the regulation of growth and differentiation of normal human keratinocytes, we examined the effects of 1,25(OH)2D3 and 25(OH)D3 on their growth and differentiation. Keratinocyte growth was inhibited to 52.6% and 23.4% by 10(-8) M and 10(-7) M 1,25(OH)2D3 and to 80.5% and 23.9% by 10(-8) M and 10(-7) M 25(OH)D3, respectively. Differentiation of these cells was evaluated by quantifying the number...
which express involucrin, a precursor protein of cornified envelope. The population of involucrin expressing cells (differentiated cells) increased from 6.2% to 14.5% by 2.5.10(-7) M 1,25(OH)2D3, and to 11.8% by 2.5.10(-7) M 25(OH)D3. These results clearly indicate that 25(OH)D3 is as effective on human keratinocytes as 1,25(OH)2D3 in inhibiting growth and inducing differentiation, although to a slightly lesser extent than 1,25(OH)2D3. The possibility that the effect of 25(OH)D3 is mediated through binding to the 1,25(OH)2D3 receptor can be excluded, since a competitive binding assay revealed that the affinity of 25(OH)D3 for the 1,25(OH)2D3 receptor in a cytosolic extract of keratinocytes was 100-times lower than that of 1,25(OH)2D3. Thus, these results suggest that 1,25(OH)2D3 endogenously produced in keratinocytes from 25(OH)D3 is involved in the regulation of their growth and differentiation in vitro.

Biochim Biophys Acta. 1991 May 17;1092(3):311-8

**INJURY ENHANCES TLR2 FUNCTION AND ANTIMICROBIAL PEPTIDE EXPRESSION THROUGH A VITAMIN D-DEPENDENT MECHANISM.**

An essential element of the innate immune response to injury is the capacity to recognize microbial invasion and stimulate production of antimicrobial peptides. We investigated how this process is controlled in the epidermis. Keratinocytes surrounding a wound increased expression of the genes coding for the microbial pattern recognition receptors CD14 and TLR2, complementing an increase in cathelicidin antimicrobial peptide expression. These genes were induced by 1,25(OH)2 vitamin D3 (1,25D3; its active form), suggesting a role for vitamin D3 in this process. How 1,25D3 could participate in the injury response was explained by findings that the levels of CYP27B1, which converts 25OH vitamin D3 (25D3) to active 1,25D3, were increased in wounds and induced in keratinocytes in response to TGF-beta1. Blocking the vitamin D receptor, inhibiting CYP27B1, or limiting 25D3 availability prevented TGF-beta1 from inducing cathelicidin, CD14, or TLR2 in human keratinocytes, while CYP27B1-deficient mice failed to increase CD14 expression following wounding. The functional consequence of these observations was confirmed by demonstrating that 1,25D3 enabled keratinocytes to recognize microbial components through TLR2 and respond by cathelicidin production. Thus, we demonstrate what we believe to be a previously unexpected role for vitamin D3 in innate immunity, enabling keratinocytes to recognize and respond to microbes and to protect wounds against infection.

J Clin Invest. 2007 Mar;117(3):803-11

**DERMAL TOXICITY AND ENVIRONMENTAL CONTAMINATION: ELECTRON TRANSFER, REACTIVE OXYGEN SPECIES, OXIDATIVE STRESS, CELL SIGNALING, AND PROTECTION BY ANTIOXIDANTS.**

Large numbers of chemicals are known to produce diverse types of skin injury, and these substances fit into a wide variety of both organic and inorganic chemical classes. Skin contact with toxins is difficult to avoid, because they are widely distributed, e.g., in industrial substances, agricultural chemicals, household products, and plants. Although various hypotheses have been advanced, there is no universal agreement as to how dermal toxins act to produce their effects. In this review, we provide evidence and numerous literature citations to support the view that oxidative stress (OS) and electron transfer (ET) comprise a portion of a key mechanism, and perhaps unifying theme that underlie the action of dermatotoxins. We apply the concept that ET and OS are key elements in the induction of dermatoxic effects to all of the main classes of toxins, and to other toxins, as well. We believe it is not coincidental that the vast majority of dermatotoxic substances incorporate recurrent ET chemical functionalities (i.e., quinone, metal complexes, ArNO2, or conjugated iminium), either per se or as metabolites; such entities potentially give rise to reactive oxygen species (ROS) by redox cycling. However, in some categories, wherein agents cause dermal damage, e.g., peroxides and radiation, it appears that ROS are generated by non-ET routes. As expected, if ET and oxidative process do constitute the mechanistic framework by which most dermal toxins act, then antioxidants (AOs), if present, should prevent or mitigate effects. This is exactly what has been discovered to occur. Because ET and OS either cause or contribute to dermal toxicity, and AOs may offer protection therefrom, policy makers and researchers may be better positioned to prevent human dermatotoxicity.

Rev Environ Contam Toxicol. 2010;203:119-38

**DELIVERY OF VITAMIN E TO THE SKIN BY A NOVEL LIQUID SKIN CLEANSER: COMPARISON OF TOPICAL VERSUS ORAL SUPPLEMENTATION.**

Topical supplementation represents an attractive approach to mitigate environmentally induced deficiencies of skin vitamin E (alpha-tocopherol). We report here the impact of natural sunlight on stratum corneum (SC) vitamin E and also compare the effectiveness of dietary supplementation to topical application as a way to increase vitamin E in the superficial layers of the SC. The effects of natural sunlight, 30 minutes of midday sunlight, were measured on two separate occasions. Vitamin E in the surface layers of the SC was measured by HPLC after ethanol extraction. Under these relevant conditions, vitamin E in the superficial SC was reduced in a dose-dependent manner by 50-65%. In a followup study, panelists entered into a randomized, double-blind, vehicle-controlled study. In this study, one group washed their skin once daily for one minute with a commercially available body wash containing 0.15% vitamin E and 0.10% vitamin E acetate, while the second group used a body wash without...
vitamin E but also supplemented their diet with 400 IU alpha-tocopherol (18 x RDI). Not surprisingly, only dietary supplementation increased serum vitamin E (approximately twofold). Although both treatment modalities increased SC vitamin E, topical delivery was significantly more effective (53-fold vs baseline) than dietary delivery (eightfold vs baseline). Moreover, only topical delivery increased SC vitamin E acetate (19-fold vs baseline). The results reported here indicate that vitamin E in the superficial layers of the SC is depleted readily by even a brief exposure to sunlight and that use of a vitamin E body wash can substantially increase the vitamin E in this superficial layer more effectively than dietary supplementation.


VITAMIN D IS A MEMBRANE ANTIOXIDANT. ABILITY TO INHIBIT IRON-DEPENDENT LIPID PEROXIDATION IN LIPOSOMES COMPARED TO ChOLESTEROL, ERGOSTEROL AND TAMOXIFEN AND RELEVANCE TO ANTICANCER ACTION.

Vitamin D is a membrane antioxidant: thus Vitamin D3 (cholecalciferol) and its active metabolite 1,25-dihydroxycholecalciferol and also Vitamin D2 (ergocalciferol) and 7-dehydrocholesterol (pro-Vitamin D3) all inhibited iron-dependent liposomal lipid peroxidation. Cholecalciferol, 1,25-dihydroxycholecalciferol and ergocalciferol were all of similar effectiveness as inhibitors of lipid peroxidation but were less effective than 7-dehydrocholesterol; this was a better inhibitor of lipid peroxidation than cholesterol, though not ergosterol. The structural basis for the antioxidant ability of these Vitamin D compounds is considered in terms of their molecular relationship to cholesterol and ergosterol. Furthermore, the antioxidant ability of Vitamin D is compared to that of the anticancer drug tamoxifen and its 4-hydroxy metabolite (structural mimics of cholesterol) and discussed in relation to the anticancer action of this vitamin.


OXIDATIVE STRESS ASSOCIATED WITH EXERCISE, PSYCHOLOGICAL STRESS AND LIFE-STYLE FACTORS.

Oxidative stress is a cellular or physiological condition of elevated concentrations of reactive oxygen species that cause molecular damage to vital structures and functions. Several factors influence the susceptibility to oxidative stress by affecting the antioxidant status or free oxygen radical generation. Here, we review the effect of alcohol, air pollution, cigarette smoke, diet, exercise, non-ionizing radiation (UV and microwaves) and psychological stress on the development of oxidative stress. Regular exercise and carbohydrate-rich diets seem to increase the resistance against oxidative stress. Air pollution, alcohol, cigarette smoke, non-ionizing radiation and psychological stress seem to increase oxidative stress. Alcohol in lower doses may act as an antioxidant on low density lipoproteins and thereby have an anti-atherosclerotic property.


THE ROLE OF REDOX REGULATION IN THE NORMAL PHYSIOLOGY AND INFLAMMATORY DISEASES OF SKIN.

Skin is the largest organ which contains complex and tightly regulated redox network of the reactive oxygen/nitrogen/lipid species producing components as well as the redox damage protective systems. This redox balancing system has evolved to regulate normal physiological processes and to protect skin and the internal organs against environmental damage. Exposure to some physical, chemical, and biological agents results in the excessive formation of free radicals and non-radical redox active species within the skin. Normally, skin reacts to this overproduction by sacrificing non-enzymatic antioxidants and by adaptive induction of both protective detoxifying and damage-eliminating systems. Thus, fast restoration of redox balance necessary to maintain normal skin structure and functioning occurs. In the case of excessive exposure or defects in the adaptive reactions, redox damage to skin components occurs. Here, we focus on the role of redox status in the acute inflammatory response to wounding and chronic inflammatory skin diseases such as psoriasis, atopic and contact dermatitis. Redox-mediated chronic inflammation and immunosuppression as risk factors for tumorigenesis are also reviewed.

Front Biosci (Elite Ed). 2009 Jun 1;1:123-41

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