Special Article

Photobiology of vitamins

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This review explores contemporary ideas about the relationship between light exposure and vitamin biology. Nutritional biochemistry has long recognized the relationship between vitamins A and D and light exposure, but in recent years other vitamins have also been implicated in photoresponsive biological mechanisms that influence health, well-being, and even evolutionary processes. Interactions between light and vitamins can modify genotype–phenotype relationships across the life cycle, providing a basis for interesting new explanations relevant to wide aspects of human biology. This review examines both well-established and emerging ideas about vitamin photobiology in the context of the following: (1) light responsiveness of vitamin D (photosynthesized in skin), vitamin A (linked to vision), and vitamin B_3 (needed to repair genomic damage); (2) vulnerability of folate and vitamins B_1, B_2, B_{12}, and D to ultraviolet (UV) light (all potentially degraded); (3) protective/filtering actions of carotenoids and vitamins C and E, which act as antioxidants and/or natural sunscreens, against UV light; (4) role of folate, carotenoids, and vitamins A, B_3, C, D, and E in UV-related genomic regulation, maintenance, and repair; (5) role of folate and vitamins A, B_2, B_{12}, and D in a range of light-signaling and light-transduction pathways; and (6) links between folate and vitamin D and the evolution of UV light–adaptive phenotypes.

INTRODUCTION

Generations of students have learned that vitamins are organic compounds required in small amounts for maintaining metabolic integrity, and that—with the exceptions of vitamin D and niacin—they cannot be synthesized in the body but must be provided in the diet. The predominant message has always been that overt deficiency results in specific diseases that can only be corrected by restoration of the vitamin to the diet. Today, researchers are gaining new perspectives on vitamin biology that go well beyond this traditional view.

The purpose of this review is to present contemporary paradigms on important relationships between light exposure and vitamin biology. The vital relationship between light exposure and vitamins D and A has long been recognized,[1,2] but in recent years many other vitamins have also been implicated in light-responsive biological processes that affect health and even influence human origins.

Since the 1990s, clinical research involving vitamins has often been considered in the context of nutritional genetics (nutrigenetics), although more recently the broader exposome (ie, the totality of environmental exposures throughout the life cycle) has been investigated for additional relevant factors.[3,4] Ultraviolet (UV) radiation in particular has been investigated as a factor that interacts with vitamins and their dependent genes to

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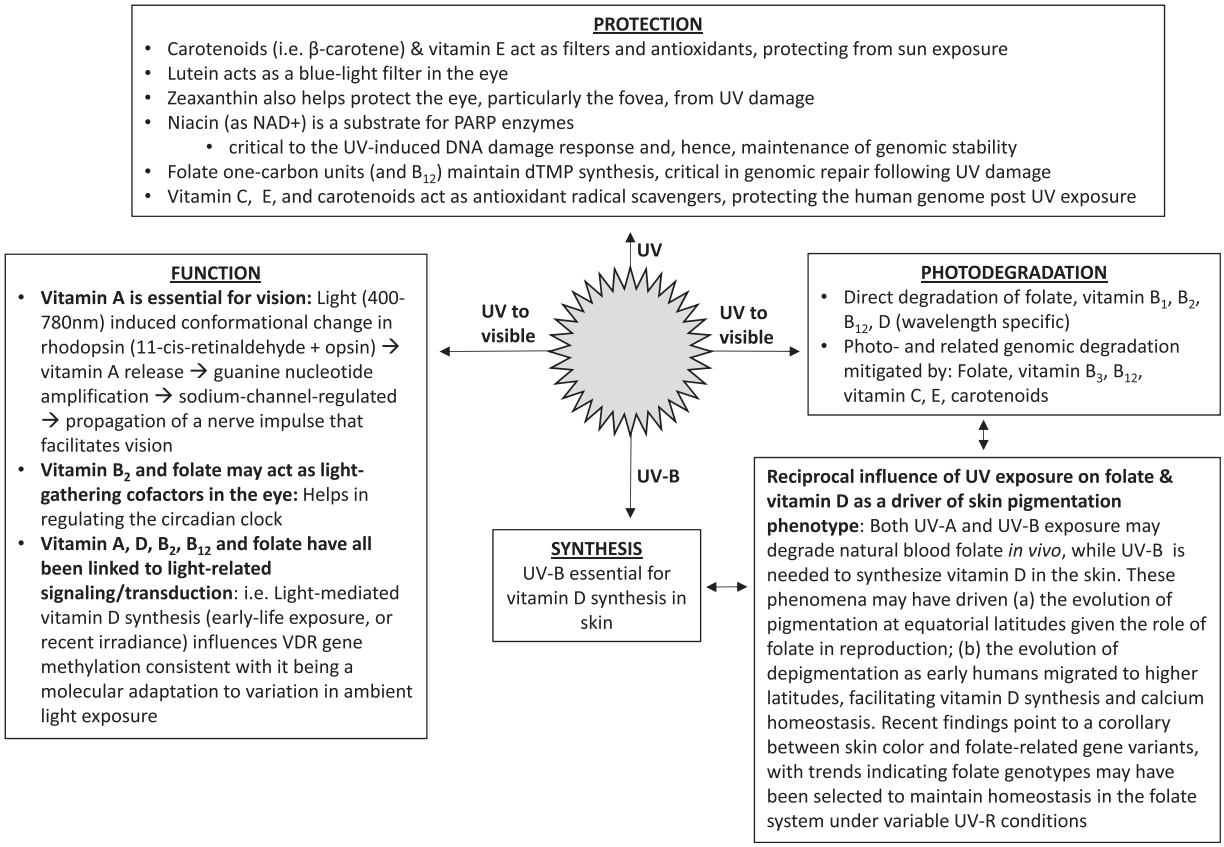

Figure 1 **Integrated overview of the manner in which vitamins respond to light.** *Abbreviations*: dTMP, DNA thymidylate; NAD, nicotinamide adenine dinucleotide; PARP, poly(ADP-ribose) polymerase; UV, ultraviolet; VDR, vitamin D receptor.

influence phenotype. Indeed, evidence now points to light (wavelength, duration of exposure, and life stage of exposure) as a critical environmental component that interacts with nutritional agents to modify genotype–phenotype relationships throughout the life cycle, offering interesting new explanations of relevance to wide aspects of human biology. This review will examine these molecular explanations as separate biochemical/biophysical constructs (see Figure 1 for an integrated overview of how vitamins respond to light).

SIGNALING AND TRANSDUCTION PATHWAYS

Typically, vitamins A (required for vision) and D (required for skin photosynthesis and activation of vitamin D receptor [VDR]) are the vitamins most obviously linked to light-mediated signal transduction pathways. However, folate, in the form of its reduced 5,10-methenyl coenzyme, and vitamin B_2, in the form of flavin adenine dinucleotide, are also recognized as chromophores that facilitate photoreception/light transduction mechanisms.[5] These two B vitamins have been implicated in the maintenance of circadian rhythms,[4,5] which are endogenous oscillations synchronized (ie, photoentrained) by the natural night-day cycle, which has a periodicity of approximately 24 hours.[6]

This biological clock is regulated by input through the eye's retinal photoreceptor cells. Most notably, visual holoproteins such as rhodopsin (formed by a complex of 11-*cis*-retinal and opsin) do not play a role in circadian photoreception; instead, retinal cryptochromes and the photopigment melanopsin are thought to function as pigments in circadian photoreception.[7] Cryptochromes are blue-light photoreceptors found in the ganglion cell layer of the retina. They transduce light stimuli to the master circadian clock in the suprachiasmatic nucleus. Cryptochromes are fascinating because they contain both a flavin and folate (5,10-methenyl-H_4 folate) as light-gathering cofactors and are integral to maintaining periodicity in animals and plants.

Although there is still much to learn, purified human cryptochrome 2 (hCRY2) exhibits a fluorescence profile consistent with the presence of both folate and flavin cofactors,[5] although evidence of photoreception in mammalian cryptochromes remains indirect.[8] The cryptochromes CRY1 and CRY2 are 73% homologous in all organisms and absorb light in the wavelength

range of 350 to 450 nm. In this synergistic B-vitamin partnership, folate is effectively functioning as a light-gathering antenna, while flavin facilitates a redox reaction. The full mechanism following exposure to blue-light photons proceeds by way of excitation of 5,10-methenyl-H_4 folate. An electron is then transferred to the reduced catalytic molecule flavin adenine dinucleotide ($FADH^-$) and then on to CRY1 or CRY2.[9,10] This system seems highly adaptive. In plants, folate-containing cryptochromes regulate blue-light–dependent growth. In bacteria, insects, and amphibians, they stimulate the activity of enzymes that repair UV-induced DNA damage. And in mammals, as indicated above, they regulate the circadian clock.

Without doubt, circadian timing is a key mechanism that regulates physiological processes like feeding behavior and energy metabolism via dietary cues and light-activated transcription of key clock genes.[11,12] Analysis of protein interaction networks for gene products linked to clock components reveals that aspects of folate metabolism, the cell cycle, and hedgehog and insulin signaling are overrepresented.[13] Therefore, one might reasonably assume that, while folate, as 5,10-methenyl-H_4 folate, plays a role in controlling the circadian clock, the clock mechanism in turn controls folate homeostasis.

Vitamin A, as 11-*cis*-retinal, be it derived as a preformed dietary vitamin or as a provitamin A carotenoid, is a chromophore required for human vision. Human visual perception is facilitated by the absorption of radiation in the 400- to 780-nm region of the electromagnetic spectrum and is a signal transduced at photoreceptors in the pigmented layer of the retina (ie, the retinal pigment epithelium).[2] A single photon of visible light converts the 11-*cis*-retinal chromophore into the 11-*trans* vitamer. This chromophore exists as a holoprotein; within the retinal pigment epithelium, all-*trans*-retinol is isomerized to 11-*cis*-retinol and subsequently is oxidized to form 11-*cis*-retinal. This reacts with a lysine residue in the opsin protein to form rhodopsin, the key holoprotein responsible for vision, sometimes referred to as *visual purple*. Rhodopsin is part of a G-protein–coupled receptor system in which the cognate G protein is transducin.[14,15]

Opsins shift the absorption spectrum of 11-*cis*-retinal from the UV wavelength into the visible range of light, leading to a broad sensitivity for vision in low light via rod cells or a more-refined spectral resolution to distinguish colors in bright light via cone cells. The absorption of light by rhodopsin over a dynamic range from a single photon to in excess of 10^8 photons leads to *trans-cis* isomerization and a conformational change in rhodopsin; the retinal is released from its opsin-binding pocket and a nerve impulse is propagated via a guanine nucleotide amplification cascade that leads to the closing of a sodium channel.[2,16] The released retinal is then reduced, and the resulting *trans*-retinol joins a pool in the retina (ie, the retinal pigment epithelium) for reuse in the visual cycle. Several excellent review articles have recently examined the role of vitamin A in nature, and of the visual cycle in particular,[2,17–19] exploring new ideas about protein-protein interactions and the biological stability of the visual cycle.[20]

Ultimately, the remarkable sensitivity of this visual process is dependent upon rod and cone cell adaptations, a dynamic pupil aperture, the rate of chromophore turnover, and processes occurring within retinal neurons. Indeed, in the area of greatest visual acuity and, hence, the area of greatest metabolic activity around the retinal fovea, each retinal pigment epithelium cell requires 4×10^8 rhodopsin molecules each day, and this high requirement likely explains why this is the first area to deteriorate in age-related macular degeneration.[2] It also explains why a dietary shortage of vitamin A leads to impaired color vision, a diminished ability to adapt to darkness, and an inability to see in low light, referred to as night blindness.

Interestingly, recent evidence points to a novel endocrine axis, which is regulated by photoperiod and melatonin, that utilizes vitamin A in its retinoic acid form to contribute to the chronobiological neuroendocrine response in rats.[21] Indeed, in mammals, this specific vitamin A vitamer is thought to regulate several rhythms in the brain and body, including both daily and seasonal cycles that are entrained by light. In this sense, it is suggested that circannual rhythms play a major function in anticipating the optimal times of year for key seasonal behaviors like hibernation and reproduction, and that nutrients, including vitamin A, inform or signal the circadian clock about the quality and availability of food as a stochastic environmental variable.[21]

In a more direct signaling role, β-carotene has been shown to interfere with UV-A–induced gene expression by multiple pathways. For example, in nonirradiated human keratinocytes, analysis of gene regulation suggests that physiological levels of β-carotene reduced stress signals and degradation of the extracellular matrix and promoted differentiation of keratinocytes.[22]

The classic light-related vitamin is vitamin D.[1,3] The established role of this UV radiation–dependent vitamin is discussed in the section *UV Radiation–Dependent Vitamins*. However, vitamin D also plays a role in signal transduction in a broad yet complex way that is not yet fully understood. This is perhaps unsurprising, given that vitamin D, in the form of 25-hydroxyvitamin D [25(OH)D_3], is a steroid prehormone[23] and

that, following its conversion into 1,25-dihydroxyvitamin D [$1,25(OH)_2D_3$], it—like many hormones—has actions that can play a central role in phenotypic plasticity by altering gene expression and, hence, phenotypic outcomes in response to environmentally originated cues (Vieth[23] points out that, although the kidney acts as a classic endocrine gland, producing the hormone $1,25(OH)_2D_3$, the generic descriptor "vitamin D" per se should not be linked to the term *hormone*, although $25(OH)D_3$ is appropriately termed a *prehormone*.). The key role of vitamin D in signaling is related to its function as a ligand for the protein VDR, a transcription factor that belongs to the nuclear receptor superfamily of steroids.[24] The active ligand for VDR is the conformationally flexible secosteroid $1,25(OH)_2D_3$, and the outcome of photosynthesis of vitamin D is the activation of a nuclear receptor that has high tissue specificity and regulates calcium and phosphorus homeostasis. This vitamin D nuclear receptor also underpins the growth, differentiation, and patency of many types of cells that are found in VDR-dependent target tissues.[25] Such VDR action can influence the expression of genes, including those that modify and remodel chromatin, and hence can alter the DNA methylation profile.[26] However, the *VDR* gene itself is methylated at key CpG islands; as a result, genomic hypermethylation and hypomethylation decrease and increase, respectively, the expression of *VDR*.[27] This may be one mechanism by which light signals or transduces vitamin D–related biological outcomes. Studies now indicate that a direct link between the early-life exposome and vitamin D-/*VDR*-/calcium-mediated end points fit a developmental origins link to bone size and height of children and to adult bone mineral density,[28–30] indicating the importance of long-term signaling potentiated by light as an early-life environmental cue.

It is now firmly established that the $1,25(OH)_2D_3$-activated VDR potentiates gene expression at the single-gene level as well as at the complex gene-network level; diet and light (as part of the exposome) as well as genetic and epigenetic mechanisms can therefore interact to modify gene expression in a way that has extremely wide pleiotropic effects.[31] Ramagopalan et al[32] have shown that 2276 genomic loci are occupied by the VDR and that 229 genes have altered expression profiles in response to vitamin D. Furthermore, over 4000 protein-coding mRNAs in adipose tissue and white blood cells exhibit seasonally derived expression profiles that invert between northern and Southern hemispheres.[33] With these findings in mind, it is easy to appreciate any potential adaptive benefits of a vitamin D signaling paradigm. Indeed, the pleiotropic effects of vitamin D and of *VDR* expression are manifold, and ultimately are likely to shape the human phenome. It is therefore reasonable to speculate that this signaling might have an overarching influence on the ability of humans to adapt to changing environments (including changes in light exposure) or geophysical cycles.

FILTERING AND PROTECTION

One of the least-known attributes of vitamins is their role in filtering UV light and, hence, in preventing cellular damage. Dietary carotenoids such as β-carotene, a provitamin A nutrient, are long-chain polyene structures that can physically quench electronically excited molecules and absorb UV light, hence mitigating direct damage to cellular targets, particularly lipids, proteins, and DNA. Carotenoid-rich foods slowly assimilated into the skin are therefore photoprotective, although basal dermal defense against UV irradiation varies across the body's epidermis in parallel with variable local carotenoid concentrations.[34–36] In one study, universally enhanced carotenoid skin levels were found following dietary supplementation with β-carotene but were most pronounced in the skin of the forehead, the back (dorsal skin), and the palm of the hand. Carotenoid supplementation has been shown to substantially protect against UV-induced erythema,[37,38] and vitamin E may augment the protective effect of β-carotene.[39]

Although antioxidant vitamins, including provitamin A carotenoids, are protective against UV challenge, environmental exposure to UV radiation has been shown to reduce cutaneous β-carotene in volunteers receiving a total UV dose of around 10 000 J/cm^2.[39,40] However, many other phytoprotectants, including other vitamins and minerals, can also protect skin from sun damage. These include vitamin E (both tocopherols and tocotrienols), vitamin C, polyphenolics (particularly flavonoids), selenium-containing structures, and polyunsaturated fatty acids.[34,41,42] Provitamin A carotenoids can protect from sun damage in several ways, eg, by increasing optical density, quenching singlet oxygen molecules, and forming retinoic acid.[43]

Other protective carotenoids include lutein and zeaxanthin, which provide blue light filtration and bioaccumulate in the eye, where they protect the retinal fovea from damaging UV light. The protective role of these dietary carotenoids is relevant to the development of age-related macular degeneration.[44] Although lutein acts as an important blue light filter and antioxidant in the retina, it also mediates immunity and inflammation elsewhere in the body, and this may further affect risk for age-related macular degeneration.[44]

Interestingly, antioxidative substances, including carotenoids and vitamin E, are secreted via eccrine sweat glands and sebaceous glands onto the epidermal

surface.[35] It is therefore unsurprising that skin on the forehead, palms of the hands, and back contains the highest levels of carotenoids, as these areas have high concentrations of sweat glands. The amount of pigment accumulated within the skin (predominantly in the upper part of the stratum corneum) correlates with dietary intake and bioavailability of carotenoids.[43] The bioavailability of β-carotene is fairly complex and depends upon the food source, food processing, fat content of the diet, and genetic variation in the carotene dioxygenase gene, which at best yields an enzyme of low activity and is subject to both inhibition by other carotenoids and asymmetric cleavage of β-carotene (yielding nonprovitamin A apocarotenals). This ineffective process yields roughly 1 mg of retinol per 6 mg of β-carotene. However, genetic variation in the carotene dioxygenase gene might reduce oxidative stress by increasing β-carotene levels in blood and tissue.

The most abundant carotenoids in humans are α-carotene, β-carotene, and lycopene, along with the xanthophylls lutein, zeaxanthin, α-cryptoxanthin, and β-cryptoxanthin.[45,46] Overall, however, vitamin E is the most abundant lipophilic antioxidant in human skin, with the highest levels found in the epidermis.[43] From an evolutionary perspective, it is interesting to consider whether the high levels of carotenoids or vitamin E in human sweat could have compensated for the increased UV exposure (and, hence, potential skin damage) that would have occurred following the transition to human nakedness (ie, loss of heavy body hair) that took place around 1.6 million years ago in the *Homo* lineage. Certainly, the loss of hair and the development of significant eccrine sweat that arose at this time allowed early humans to dissipate heat generated as a consequence of or as an adaptation to a rapidly changing climate. There was a notable shift from forest to savanna in East Africa 3 million years ago, as global cooling led to a dry phase in this region. Such a change would have led *Homo ergaster* to forage further afield to obtain dietary sustenance, a practice that required a physiological adaptation to prevent overheating—one that would be comfortably met in part by increased sweating and reduced hairiness.[47] This transition, leading to a significant loss of body hair in ancestral humans, also likely led to the selection of a more pigmented skin as an adaptive evolutionary response to high levels of UV radiation in the absence of protective hair; indeed, a specific variant of the *MC1R* gene is associated with dark pigmentation and is thought to have originated in Africa 1.2 million years ago.[48] The authors are unaware whether the idea of antioxidant vitamins within sweat has been framed in such an evolutionary context up to now, but the proposition is certainly worth considering. Indeed, other vitamins (folate and vitamin D) are now thought to have helped shape the skin phenome and are discussed in the section *Paradigms in Human Evolution Linking Vitamins to Seasonality and Geography*.

The benefits of vitamin E in skin are likely related to protection against the cytotoxic effect of UV-B via a mechanism involving inhibition of UV-induced lipid peroxidation or the antioxidative effect of the vitamin.[49] However, in truth, several potential mechanisms of action are possible in explaining the UV mitigating effects of vitamin E beyond free radical scavenging. It could act to either alter cellular response mechanisms, membrane fluidity, the eicosanoid pathway, or act as a natural sunscreen.[43]

DNA MAINTENANCE AND REPAIR

Several vitamins, including folate, vitamin B_{12}, and niacin, play a direct role in DNA maintenance and repair, while others, such as vitamin C, vitamin E, and carotenoids, play an indirect role, perhaps via an antioxidative effect. Still others, like vitamins A, D, and E, play a modulatory role as transcription factors. Several of these vitamins are important, as they are involved in the metabolic response to UV exposure and can mitigate any subsequent DNA damage that might ensue. While many of these vitamins are directly sensitive to light, they can also be indirectly light-responsive in that they can help mitigate the negative effect of UV exposure on DNA integrity.

Folate is not only UV sensitive but is also necessary for the synthesis and expression of DNA, which itself is highly UV labile. Folate serves as a carrier of various 1-carbon units that can be transferred into important biosynthetic pathways. Of particular importance is the synthesis of DNA thymidylate (dTMP) and methionine. Methionine is generated from homocysteine using both 5-methyltetrahydrofolate (5-methyl-H_4 folate) and vitamin B_{12} as essential cofactors. Methyl groups derived from methionine can be utilized for both genomic and nongenomic methylation reactions. Therefore, folate (and, by association, vitamin B_{12}) contributes to both the primary structure and the expression of genes. Consequently, any factors that perturb folate metabolism, including genetic variation and environmental factors (particularly dietary intake), can potentially promote the misincorporation of uracil—in place of thymine—into the primary DNA base sequence, a phenomenon associated with DNA fragility.[50] Furthermore, researchers are only now learning how critically important the epigenome is for regulating DNA expression and managing the complexities of cell biology during development and times of disease.[51] To this end, genomic methylation patterns orchestrate human biology and subserve well-being, but they are

highly complex and are a product of multiple interactions, including dietary ones.[52]

Folate enzymes operate in concert to maintain dTMP synthesis. Three metabolically linked genes, *TYMS*, *SHMT1*, and *DHFR*, encode the enzymes thymidylate synthase (TYMS), serine hydroxymethyltransferase (SHMT1), and dihydrofolate reductase (DHFR). These 3 genes are polymorphic, and their expression products operate in a tight synergy that is fundamental to maintaining the fidelity of dTMP synthesis and the integrity of DNA. This cooperative association makes this enzyme cluster critically important during periods of rapid cell turnover and differentiation, for example, during early embryo development and throughout the first trimester of pregnancy. Elegant mechanisms exist to modify these folate enzymes post-translationally and permit nuclear translocation during the S and G_2/M cell cycle phases.[53,54] However, of particular interest within this gene cluster is that SHMT plays a crucial role in the repair of UV-propagated DNA damage.[54] SHMT expression levels and post-translational SUMOylation of TYMS increase, as does the nuclear compartmentation of SHMT and TYMS following exposure to UV radiation. Interestingly, although this SHMT-related UV response occurs in humans, it is absent in mice,[55] suggesting species specificity and the possibility that it may have evolved as an adaptive response to protect skin from UV-related DNA damage by promoting additional dTMP synthesis.

A recent study examined whether UV irradiance can reduce systemic folate levels over the long term.[56] Exposure to UV irradiance was shown to alter folate status according to *MTHFR* C677T genotype. The authors suggest this effect might result either from higher levels of the 5,10-methylenetetrahydrofolate (5,10-methylene-H_4 folate) coenzyme, which is a UV-labile form of folate, in *MTHFR* 677TT individuals or from increased utilization of folate for DNA repair (ie, dTMP synthesis) under increased UV regimes. 5,10-methylene-H_4 folate is the immediate precursor of the 1-carbon unit needed for dTMP synthesis. Its metabolic location and variable function is thought to help the *MTHFR* 677TT variant maintain the fidelity of dTMP synthesis, a precursor of DNA elaboration, when folate levels are low.[57] While this point is germane to DNA maintenance and repair, the broader aspects of folate sensitivity to UV exposure are detailed in the section *UV Radiation–Vulnerable Vitamins*.

It is also relevant to note that increased use of the synthetic form of folate (pteroylmonoglutamic acid) at a population level via discretionary and government-mandated use might lead to unintended consequences in the present context. Research has shown that pteroylmonoglutamic acid photolytic scission products (ie, pterin-6-carboxylic acid) can lead to oxidation of 2′-deoxyguanosine 5′-monophosphate and sequence-specific DNA cleavage,[58] which represents a major risk for oncogenesis.[59,60] The same does not occur with the natural vitamer, 5-methyl-H_4 folate. However, despite these observations, the authors are unaware of any population studies indicating that fortification/supplementation with pteroylmonoglutamic acid increases DNA damage.

Another vitamin known to be light-responsive in the context of DNA repair is niacin (vitamin B_3). Niacin deficiency in humans lowers nicotinamide adenine dinucleotide (NAD) status, resulting in sun-sensitive skin. This lower level of NAD actually mediates UV damage.[61]

Both of the B_3 vitamers, nicotinic acid and nicotinamide, are required for the synthesis of nicotinamide adenine dinucleotide [NAD(H)] and nicotinamide adenine dinucleotide phosphate [NADP(H)]. Both NAD and NADP serve as coenzymes for a large number of enzymes.[62] However, besides its role as a coenzyme, oxidized NAD (NAD^+) has multiple roles as a substrate for mono-ADP-ribosylation, poly-ADP-ribosylation, and NAD-dependent protein deacetylation.[61] This is relevant to skin biology, since niacin-deficient keratinocytes, which are more sensitive to UV damage, exhibit poly(ADP-ribose) polymerase (PARP) and sirtuin inhibition due to a lack of NAD^+, resulting in unrepaired DNA damage and cell death following exposure to UV radiation.

Recent identification of the nicotinic acid receptor in human skin keratinocytes further supports a role for niacin as a potential pharmacological agent in the prevention of UV-induced skin cancer.[61] The influence of niacin in this setting should be unsurprising, given that the deficiency syndrome for this vitamin is pellagra, a condition that produces severe photodermatitis as part of the symptomology.

The unifying explanation for the photoresponsive influence of niacin in skin biology stems largely from the role of NAD^+ as a substrate for the PARP enzymes that are crucial in the response to DNA damage, including UV damage. This role is therefore fundamental in genomic repair, genomic stability, signaling as a stress response in apoptosis, and gene expression.[63–66] In the last case, PARP-1 is also a structural element of chromatin and modifies chromatin structure via enzymatic activity to repress transcription.[67]

The involvement of PARP-1 in maintaining genomic integrity underpins the beneficial role of niacin following genotoxic stress. Several laboratories have linked the influence of niacin to cancer prevention.[61] Activation of PARP-1 by DNA strand breakage (including UV-induced damage) leads to a complex signaling

network that modifies cell survival, cell death via apoptosis, or energy loss and hence necrosis. The role of niacin is important, since extreme genotoxicity promotes PARP-1 overactivation and cell death through depletion of first NAD^+ and then adenosine triphosphate. This deprives the cell of energy-dependent functions and precipitates cell death. Research has also shown that a decline in cellular NAD^+ status itself can trigger mitochondria to initiate cell apoptosis.[68] While NAD^+ is derived from dietary niacin, humans can also form this cofactor by de novo synthesis from tryptophan. Thus, like vitamin D, niacin is not a vitamin strictly speaking, although it is convenient to classify it as such.

Antioxidant vitamins such as vitamin C, vitamin E, and carotenoids act to protect DNA from the damaging effects of free radicals that can be generated by UV exposure. These vitamins neutralize unpaired electrons in highly reactive radical species, delocalizing the unpaired electron in their own molecular structure to form resonance-stabilized radicals (eg, stable radicals such as the tocopheroxyl radical for vitamin E and monodehydroascorbate for vitamin C). Specific mechanisms, both facile and enzymatic, can then salvage the stable radical form of the vitamin back to its natural antioxidative form. However, at high levels of consumption, these vitamins can behave as pro-oxidants, thereby acting as generators of free radicals. The best-known example of this is probably the use of high-dose β-carotene to try to prevent cancer. The outcome, however, showed the opposite effect: increased lung cancer rates. This was found despite normal levels of intake being associated with lower cancer rates.[69] Two and 2 does not always make 4; the problem may stem from higher antioxidant concentrations readily translocating to the nucleus.

Vitamin C may also have an indirect effect on maintaining genomic stability via its functional salvaging of reduced folates in the stomach. The active secretion of vitamin C into the stomach lumen against a concentration gradient is considered important for preventing the loss of oxidized methylfolate (5-methyl-H_2 folate) at low pH. Vitamin C is therefore critically important for maintaining folate bioavailability,[70,71] and folate is arguably the most important vitamin with respect to maintaining DNA integrity.

UV RADIATION–DEPENDENT VITAMINS

The most obviously UV radiation–dependent micronutrient is vitamin D. The 2 dietary forms of this vitamin are ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3). However, while vitamin D_3 is a dietary component, it is also synthesized from the UV-B (290–315 nm) irradiation of 7-dehydrocholesterol, a sterol that is uniquely concentrated in the skin. Following the absorption of a quantum of solar energy, 7-dehydrocholesterol opens at C9–C10 and yields the 6,7-*cis* hexatriene derivative, previtamin D. This is followed by a slower thermal-dependant isomerization that shifts the double bonds, with the resulting rotation of the single C6–C7 bond leading to a thermodynamically stable 5,6-*cis* isomer form of vitamin D (cholecalciferol).[1]

Once formed in the stratum basale and stratum spinosum, previtamin D can undergo several potential reactions: a reversible photoconversion involving either a ring closure to its parent provitamin D (cholecalciferol) or a ring closure to form the inactive stereoisomer metabolite lumisterol, or isomerization to form the inactive 6,7-*trans* isomer tachysterol.[1,72] In addition, according to Jacobs et al,[73] there are at least 13 toxisterols that may potentially be produced by prolonged irradiation. Dauben and Bauman[74] identified 2 suprasterols as products following prolonged radiation, while Havinga[75] documents 4 additional photoisomers of vitamin D.

Vitamin D_3 is itself photolabile at wavelengths between 315 and 335 nm, which are longer wavelengths than those required to photosynthesize the vitamin (< 315 nm).[72] As these wavelengths are present throughout the year, degradation may occur in every month.[72] This needs to be considered in the context that the UV-B bandwidth for optimal synthesis of previtamin D is narrow (280–320 nm). This bandwidth is at the short wavelength limit on the edge of the ozone absorption band, where light is first able to penetrate to the Earth's surface, leading to a limited, seasonal vitamin synthesis from 7-dehydrocholesterol.[72,76] It is also in the waveband absorbed by melanin, which means that darkly pigmented skin moderates the formation of previtamin D_3 after UV-B exposure. As a result, deeply melanized skin can be considered nonadaptive in circumstances where it limits vitamin D_3 synthesis at higher latitudes. Indeed, melanization interacts with altitude, latitude, time of day, and weather conditions to influence previtamin D_3 biosynthesis. Of course, the use of sunscreen can equally limit the biosynthesis of previtamin D_3.[1,77]

Once it is formed from previtamin D ($\approx 80\%$ is converted in 4 days), vitamin D_3 is transported away from the skin and is drawn into the capillary bed by vitamin D–binding protein.[1] The main circulating and storage form of vitamin D_3 in blood plasma is $25(OH)D_3$, which is metabolized from cholecalciferol in the liver and is subsequently converted into the active form of vitamin D, $1,25(OH)_2D_3$, in the proximal tubules of the kidney.[3,72]

Vitamin D underpins critical physiological processes related to calcium homeostasis. Notably, $1,25(OH)_2D_3$ enhances intestinal absorption of calcium,

reduces urinary losses of calcium by enhancing resorption in the distal renal tubules, and regulates mobilization and deposition of bone mineral. For these and other reasons, $1,25(OH)_2D_3$ synthesis is highly regulated: cholecalciferol undergoes 2 consecutive hydroxylation reactions that act to regulate both $1,25(OH)_2D_3$ synthesis and intracellular calcium levels.

Hepatic vitamin D 25-hydroxlase converts cholecalciferol into $25(OH)D_3$, and in the kidney, 25-hydroxyvitamin D-1α-hydroxylase converts $25(OH)D_3$ into $1,25(OH)_2D_3$. Both of these key regulatory enzymes belong to the cytochrome family and are encoded by *CYP2R1* and *CYP27B1*, respectively. A third enzyme (25-hydroxyvitamin D-24-hydroxylase) can also convert both $25(OH)D_3$ and $1,25(OH)_2D_3$ into apparently inactive metabolites (24,25-dihydroxyvitamin D and 1α,24R,25-trihydroxyvitamin D, respectively). Within this regulatory nexus, several feedback mechanisms are in place to regulate calcium levels. These operate at the level of the 1- and 24-hydroxylases. First, $1,25(OH)_2D_3$ acts to reduce its own synthesis by inducing the 24-hydroxylase and repressing the 1-hydroxlase enzymes. In both these cases, modulation occurs via altered gene expression. Second, a drop in blood calcium initiates the secretion of parathyroid hormone. This promotes 1-hydroxylase activity but inhibits 24-hydroxylase activity. This function is countered by elevated calcium and $1,25(OH)_2D_3$ levels, which repress parathyroid synthesis. Third, although the effect is minor, calcium can act directly to inhibit the 1-hydroxylase enzyme.[3]

The biosynthesis of cholecalciferol is solar dependent, and the subsequent synthesis of $1,25(OH)_2D_3$ is solar independent. The role of $1,25(OH)_2D_3$ in bone mineral homeostasis explains why the vitamin D deficiency syndrome is rickets in children and osteomalacia in adults. The former condition stems from a failure to mineralize in the first place, and the latter results from demineralization. During the mid-17th century, rachitic deformities in England's population were a distinct phenomenon arising from increasing urbanization and the associated atmospheric pollution (smog and smoke) that hindered seasonal vitamin D synthesis at northerly latitudes. By the turn of the 20th century, the prevalence of rickets in Western Europe and the United States had increased as industrialization, migration, atmospheric pollution, and the spread of slums, poverty, and overcrowding led to the prevailing environment in which exposure to dietary vitamin D and appropriate levels of UV-B were reduced.[1,3] The only other vitamin that has such a clear function linked to light exposure is vitamin A. The phototransformation of the 11-*cis*-retinal chromophore into the 11-*trans* form of retinal is required for vision, as discussed above in the section *Signaling and Transduction Pathways*.

UV RADIATION–VULNERABLE VITAMINS

Several vitamins are photolabile and respond directly to different wavelengths of light by degrading. Some vitamin loss, however, may be indirect and attributable to a UV-originated increase in free radicals, although some vitamins can utilize other available antioxidants as a protective mechanism against radical attack.

Vitamin B_1 (thiamine) is quickly degraded by sunlight. Although flour and bread are potentially good sources of this vitamin, most of their vitamin B_1 content can be lost when baked products are put on display in shop windows. Similarly, vitamin B_2 (riboflavin) undergoes photolysis to form lumiflavin under alkaline conditions or lumichrome under neutral or acidic conditions. Lumiflavin and lumichrome are both biologically inactive, meaning that dairy products, a major source of vitamin B_2, are sensitive to sun exposure and even fluorescent light (400–550 nm). Furthermore, they can cause lipid peroxidation and conversion of methionine into methional, which confers a tainted "sunlight" flavor to milk.[3] Vitamin B_2 is also interesting because it can act as a photosensitizer by enhancing UV radiation–dependent degradation of folate; in contrast, vitamin C and glutathione enhance folate stability.[56] Cyanocobalamin, the supplementary/pharmaceutical form of vitamin B_{12}, is the most stable B_{12} vitamer, although light leads to dissociation of the cyano group and the formation of hydroxocobalamin. This photolysis, however, does not influence B_{12} activity.

As alluded to in the section *UV Radiation–Dependent Vitamins*, it is impossible for humans to manufacture toxic levels of vitamin D_3 from sun exposure because lumisterol, tachysterol, or other toxisterols formed after prolonged exposure are inactive,[72–75] thereby preventing hypervitaminosis D. However, even vitamin D_3 can be degraded by longer wavelengths than are required for its synthesis (> 315 nm).[72]

Recent research has shown that UV exposure can reduce systemic levels of folate in red cells and plasma, an effect that is influenced by the *MTHFR* C677T genotype.[56] Cumulative UV irradiance determined for periods of 42 and 120 days prior to blood sampling was significantly negatively associated with red cell folate levels. When the cohort ($n = 649$) was stratified by *MTHFR* C677T genotype, the relationship between UV irradiance and red cell folate remained significant only in the cohorts containing carriers of the T allele. The authors suggest these data provide strong evidence that surface UV irradiance reduces long-term systemic folate levels. Moreover, since this is influenced by the *MTHFR* C677T genotype, the effect may result from higher amounts of 5,10-methylene-H_4 folate, a form of folate

that may be particularly UV labile and which may be higher in *MTHFR* 677TT individuals.[56]

Several studies have looked at the light sensitivity of folate. In vitro studies have demonstrated that UV-B light at 312 nm can degrade plasma/cellular 5-methyl-H_4 folate, leading to the formation of oxidized 5-methyl-H_2 folate, with the eventual loss of all vitamin activity via C9–N10 bond scission.[78] This is supported by a more recent ex vivo study showing that longer UV-A as well as UV-B wavelengths can degrade this natural form of folate, ie, 5-methyl-H_4 folate.[79] Longer wavelengths in the UV-A spectrum (315–400 nm) can penetrate deeper into the skin and reach the dermal circulation. For this reason, UV-A has been suggested to cause photolytic degradation of synthetic pteroylmonoglutamic acid that remains unmetabolized in the circulation and which, in this unmodified form, is increasingly being linked to negative health correlates, including the potential production of 6-formylpterin, which eventually oxidizes to form pterin-6-carboxylic acid and which, as discussed earlier, may contribute to carcinogenesis.[58–60] Other than the 2016 study by Lucock et al,[56] the only other population study was conducted by Borradale et al,[80] who showed that solar UV exposure over a 3-week period reduces the effectiveness of pteroylmonoglutamic acid supplements in a population of young females of reproductive age who live in a region with extreme UV exposure. This was a relatively small study with 45 participants, and the serum folate measurements used do not reflect overall folate status as accurately as the red cell folate values. Any UV-associated loss of folate status within a population needs to be considered alongside the possibility that a decline in vitamin status could also reflect an increased need for the vitamin to maintain DNA repair processes.[56]

Another vitamin closely associated with folate is vitamin B_{12} (cobalamin). A 2014 study suggested that B_{12} deficiency was associated with geographical latitude and solar radiation in an older population from Chile.[81] The prevalence of vitamin B_{12} deficiency was associated with solar radiation and living closer to the Equator. The overall prevalence of vitamin B_{12} deficiency was 11.3%. Prevalence was significantly greater in the northern part of the country than in the central and southern regions (19.1%, 10.5%, and 5.7%, respectively; $P < 0.001$). The authors suggested that degradation of vitamin B_{12} by solar radiation might explain their observation but added that further work is required to establish the potential mechanisms involved. Although no known link exists between solar radiation, vitamin B_{12}, and related redox changes, it is interesting to consider that the vitamin B_{12} metabolic locus may be sensitive to oxidative stress, including UV light–induced effects. Redox changes can increase the flux of homocysteine through the transsulfuration pathway to cysteine and glutathione (a major cellular antioxidant) via a regulatory role at the key enzymes methionine synthase and cystathionine β-synthase. Mosharov et al[82] suggested this may be a self-correcting response to depleted glutathione levels in cells facing oxidative challenge, which is likely to increase following UV exposure. It is also worth noting that, although not relevant to humans, microorganisms use vitamin B_{12} as a light-absorbing chromophore to facilitate gene expression; moreover, the number of species and kingdoms involved suggests a vitamin B_{12} light sensor is widespread and has a deep evolutionary history.[83]

PARADIGMS IN HUMAN EVOLUTION LINKING VITAMINS TO SEASONALITY AND GEOGRAPHY

There can be little doubt that the sun and the associated daily, seasonal, and related geophysical cycles play crucial roles in the orchestration of the human life cycle. Indeed, the sun is the dominant force in the human exposome, which in the broadest terms includes photoperiod, season, temperature, all wavelengths of UV and visible radiation, and essential and beneficial nonessential dietary nutrients as well as a profusion of other environmental factors. The human exposome has therefore contributed to disease risk and the evolution of the human species.

Folate and vitamin D interact with light to influence human phenotype through putative evolutionary and/or developmental mechanisms. Moreover, the role of UV light in the degradation of folate and the synthesis of vitamin D likely contributes to evolutionary mechanisms to influence important phenotypic traits. Both of these UV-sensitive vitamins play a crucial role in cell metabolism, with recent research suggesting interesting ideas about how seasonal/exposomal UV radiation might alter systemic levels of these vitamins that are required as cofactors/ligands for essential proteins that exhibit variable activity depending on genotype. If proteins that are potentially polymorphic are critical for early embryo development, it is conceivable that certain "UV–vitamin–genotype" combinations might lead to embryo loss. For example, low systemic levels of folate or vitamin D might result in the selection of embryos with a specific vitamin-related gene variant (or variant profile) that have expression products better able to utilize lower levels of vitamins. While this selection, if it occurs, would have an immediate effect on embryo survival, such variants might additionally alter disease risk later in life, depending an individual's long-term nutritional habits.[84] Lucock et al[3,84] tested and developed this argument for the folate-related *MTHFR* C677T variant, concluding this concept seems plausible, given that

an estimated 70% to 80% of pregnancies are lost after conception. Indeed, this fits perfectly with the idea that environmental and nutritional agents interact to alter genotype–phenotype relationships across the life cycle, thereby supporting the "developmental origins of adult disease" model. However, it also provides a molecular basis to support the idea that photosynthesis of vitamin D and photodegradation of folate, both occurring in response to UV radiation, directed the evolution of parallel, but opposing, phenotypic clines of skin pigmentation.

Jablonski and Chaplin[85] have developed the folate–vitamin D-sunlight hypothesis of skin pigmentation in recent years. This hypothesis is relatively straightforward: The aberrant effects of folate degradation on fertility promote protective melanization toward equatorial latitudes, while the need for balance between vitamin D photosynthesis and calcium facilitates epidermal depigmentation away from equatorial latitudes. Lucock et al,[3,56] Jones et al,[86] and Beckett et al[87] recently published several articles that lend support to this hypothesis, indicating a likely involvement of both folate' and vitamin D in skin pigmentation as an evolved trait. This hypothesis is consistent with maximal tanning occurring during the reproductive phase of the life cycle, when folate protection is most obviously required for reproductive efficiency.[88] It is also consistent with the recent observation that allelic variants in key folate genes exhibit a geographic distribution that points to the maintenance of homeostasis between folate-dependent de novo thymidylate synthesis and methylation pathways in environments of differing solar regimes.[86] In that study, the *MTHFR* C677T and *MTHFR* A1298C allelic variants were positively associated with latitude, while a negative association was observed between latitude and the frequency of the c*SHMT* C1420T and *TYMS* 28-bp 2R > 3R variants.[86] These findings for *MTHFR* C677T were consistent with those of previous research.[88] Overall, they align with a solar regime selecting a cassette of folate gene variants that regulate a folate homeostat optimized to maintain key 1-carbon biosynthetic reactions, particularly those destined for methyl groups and DNA pathways. This paradigm is additionally supported by a 2017 study that examined the association between the population prevalence of 17 variants in 9 folate-related genes (*MTRR*, *MTR*, *MTHFR, CBS*, *SHMT1*, *MTHFD1*, *RFC1*, *BHMT*, *TYMS*) and the Fitzpatrick skin phototype of populations.[89] The association was assessed via collation of genotypic data from the ALFRED (ALlele FREquency Database) database and the 1000 Genomes Project. Novel relationships between skin color and folate-related genes were demonstrated, with trends suggesting folate genotypes are selected to maintain homeostasis in the folate system under variable UV radiation conditions. Therefore, this paradigm, based on a UV-exposome–driven folate homeostat, merits wider investigation.

The *VDR* gene seems to be a factor in the evolutionary selection of skin depigmentation at higher latitudes to allow vitamin D synthesis. Evidence suggests that *VDR* allelic variants exhibit a latitudinal gradient in allele prevalence: Hochberg and Templeton[90] have examined the evolutionary perspective of skin color, vitamin D, and the *VDR*. They speculate that, alongside changing skin pigmentation based on *MC1R* and several other pigmentation genes, the highly variable *VDR* gene forms part of an evolutionary complex that adapts humans to an altering UV exposome. This begs the question, "Is VDR an agent of short-term adaptation, or is it a component within a cassette of genes that are altered in the longer term to adapt the human phenome to the prevailing conditions?"[3] This has been partially addressed by examining how the prevalence of 4 *VDR* gene variants change according to latitude in African and several Eurasian populations.[3] Evidence shows that the prevalence of *VDR Fok*I (*f* allele), *Bsm*I (*b* allele), *Apa*I (*a* allele), and *Taq*I (*t* allele) decreases in a significant linear fashion with respect to decreasing latitude (ie, as one approaches the equator). This fits a hypothesis that links latitude, skin color, vitamin D, and the *VDR* and is consistent with a longer-term evolutionary trend,[3] although recent studies support short-term effects as well.[91]

The results of a more recent study suggest the degree of *VDR* methylation acts as a molecular adaptation to light exposure. This was explored in the context of recent UV irradiance at 305 nm, latitudinal genetic factors, and the photoperiod at conception.[87] In 80 study participants, the periconceptional photoperiod was positively related to *VDR* methylation density, explaining 17% of the variance in methylation ($P = 0.001$). Within this model, the photoperiod at conception and the plasma concentration of vitamin D independently predicted methylation density at the VDR-CpG island. Furthermore, recent UV exposure led to a 5-fold increase in methylation density ($P = 0.02$). Again, within this model, UV exposure and plasma vitamin D independently predict methylation density at the VDR-CpG island.

In the presence of the VDR *Bsm*I variant allele, methylation density was enhanced ($P = 0.01$), and in the presence of the *Taq*I or *Fok*I mutant allele, methylation density was diminished ($P = 0.007$ and 0.04, respectively). When multivariate modeling was performed, plasma vitamin D, photoperiod at conception, recent solar irradiance, and *VDR* genotype combined as independent predictors of methylation at the *VDR*-CpG island, explaining 34% of the variance in methylation

Table 1 **Summary of 6 light-related phenomena that illustrate the importance of vitamin–light interactions to human biology**[a]

Positive responsivity to light	Vulnerability to light	Filtering of and/or protection from UV	UV-related DNA maintenance and repair	Light-related signaling and transduction	Light–vitamin links to evolution of human phenotypes
Vitamin D (UV-B required for photosynthesis of calciol/cholecalciferol in skin)[1,3,72,73]	Folic acid (red blood cells and serum)[4,56,79,80]	β-carotene (skin)[34–38]	Folic acid (5,10-methylene-H_4 folate). Needed for synthesis of dTMP and, hence, DNA[50,57]	Vitamin D (ie, via VDR)[24,26,31,32]	Vitamin D (linked to evolution of skin depigmentation as humans migrated away from equator)[3,85,87,88,90,92]
Phototransformation of 11-*cis*-retinal into 11-*trans*-retinal in vision[2,18,19]	Systemic vitamin B_{12} may be UV labile. Pharmaceutical cyanocobalamin undergoes photolysis to hydroxocobalamin, although vitamin activity is maintained[81]	Vitamin E (tocopherols and tocotrienols) in skin[39,43]	Folic acid (5-methyl-H_4-folate). Needed for de novo methionine synthesis and, hence, DNA CpG methylation[50,51]	Vitamin A (11-*cis*-retinal)[2,18,19]	Folic acid (linked to evolution of pigmentation at and approaching equatorial latitudes)[56,85,86,88,89,92]
Vitamin B_3 (NAD^+ response to genomic damage)[61–68]	Vitamin B_1 and B_2 in food[3]	Vitamin C (skin)[41–43]	Vitamin B_3 (NAD^+)[61–68]	Folic acid (5,10-methenyl-H_4 folate)[5,9,10]	Vitamin–gene–UV light interactions may influence embryogenesis[3,4,84]
	Wavelengths $>$ 315 nm can degrade vitamin D vitamers[72]	Lutein (blue-light filter in eye)[44]	Antioxidant vitamins (vitamins C and E, and carotenoids)[43]	Vitamin B_{12}[83]	UV light–related vitamin D formation and VDR methylation acts as molecular adaptation to light exposure[87]
		Zeaxanthin (eye)[44]	Transcription factors (vitamins A, B, D, and E)[17,24,67,93]	Vitamin B_2 (flavin)[9,10]	
			SHMT expression/post-translational SUMOylation of TS (promotes dTMP synthesis in response to UV exposure)[54]		

Abbreviations: dTMP, DNA thymidylate; NAD, nicotinamide adenine dinucleotide; SHMT, serine hydroxymethyltransferase; SUMOylation, post-translational modification process involving small ubiquitin-like modifiers (SUMOs); TS, thymidylate synthase; UV, ultraviolet; VDR, vitamin D receptor.

($P < 0.0001$). The conclusion was that the duration of early-life exposure to UV light, the strength of recent irradiance, and latitudinally related genetic factors all influence the methylation of the *VDR* gene in a predictable manner. This is consistent with the idea that this epigenetic phenomenon is a molecular adaptation to variation in exposure to ambient light.[87]

Ultimately, as with all organisms, the ability of humans to modify phenotype in response to an environmental challenge is a major precept in the life sciences. Since exposure to light varies according to season and latitude, and since variable exposures are possible at key stages of the life cycle, it is important that humans do not retain overly rigid phenotypes but instead maintain a degree of phenotypic plasticity to allow responses that are appropriate to key periods of exposure. This is particularly true during embryogenesis and fetal development but is also essential to ensure a flexible response over the entire life course. Much work remains to clarify the roles of folate and vitamin D in phenotypic plasticity, but recent work on *VDR* gene methylation as a molecular adaptation to light exposure has begun to reveal new insights into human biology.[87]

CONCLUSION

This review explores an aspect of vitamin biology that is often either overlooked or considered only within a limited context of single nutrients. With growing interest in nutritional genetics and potential genome–exposome interactions, solar exposure is increasingly being recognized as an important factor in human biology, one that implicates several vitamins in highly evolved roles. This review examines the broad role of light in vitamin biochemistry and offers a perspective that extends from the molecular aspects of vision to short-term epigenetic adaptations via the *VDR* gene as well as even longer-term evolutionary adaptations. The goal has been to organize disparate facts to stimulate further research in this fascinating, important field.

Table 1[1–5,9,10,17–19,23,24,26,31,32,34–39,41–44,50,51,54,56,57,61–68,72,73,79–81,83–90,92,93] summarizes this review by listing 6 light-related phenomena that demonstrate the importance of many vitamin–light interactions to the well-being of humans. While some of these interactions, such as vitamin D synthesis in the skin, are well known, others are less known or are poorly characterized. For example, vitamin B_3 is responsive to UV-induced genomic damage. Folate, vitamins B_1, B_2, and B_{12}, and some vitamin D vitamers are vulnerable to light. Some vitamins and provitamins or related compounds act as protective filters in the skin (eg, β-carotene, vitamin C, and vitamin E) and eyes (eg, lutein and zeaxanthin). Several vitamins have been shown to act as transduction intermediaries in light-related signaling. Vitamin A, as retinal in the eye, is best known in this respect, but vitamin D, folate, and vitamins B_2 and B_{12} have all been shown to act in light-signaling pathways. The integrity of DNA in the face of UV challenge, along with genomic expression, including UV-responsive expression, relies on folate and vitamins B_3, A, D, and E. Finally, and quite significantly, this review explores recent data indicating that interactions between light and vitamins (eg, folate and vitamin D) are linked to the evolution of important human phenotypes.

Many questions remain, and the goal of this review has been to focus attention on a critical topic, ie, how humans are connected to their diet and environment and, in particular, how solar-related geophysical cycles are relevant to the human life cycle.

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REFERENCES

1. Martin CE, Veysey M, Yates ZR, et al. Vitamin D: genetics, environment & health. J Food Nutr Disord. 2014;3:5. doi:10.4172/2324-9323.1000155
2. Palczewski K. Chemistry and biology of vision. J Biol Chem. 2012;287:1612–1619.
3. Lucock M, Jones P, Martin C, et al. Vitamin D: beyond metabolism. J Evid Based Complementary Altern Med. 2015;20:310–322.
4. Lucock M. Folic acid: beyond metabolism. J Evid Based Complementary Altern Med. 2011;16:102–113.
5. Ozgur S, Sancar A. Purification and properties of human blue-light photoreceptor cryptochrome 2. Biochemistry. 2003;42:2926–2932.
6. Schibler U. The daily rhythms of genes, cells and organs: biological clocks and circadian timing in cells. EMBO Rep. 2005;6(suppl 1):S9–S13.
7. Kavakli IH, Sancar A. Circadian photoreception in humans and mice. Mol Interv 2002;2:484–492.
8. Ozgur S, Sancar A. Analysis of autophosphorylating kinase activities of arabidopsis and human cryptochromes. Biochemistry. 2006;45:13369–13374.
9. Wolf G. Three vitamins are involved in regulation of the circadian rhythm. Nutr Rev. 2002;60:257–260.
10. Hsu DS, Zhao X, Zhao S, et al. Putative human blue-light photoreceptors hCRY1 and hCRY2 are flavoproteins. Biochemistry. 1996;35:13871–13877.
11. Pardini L, Kaeffer B. Feeding and circadian clocks. Reprod Nutr Dev. 2006;46:463–480.
12. Lin JD, Liu C, Li S. Integration of energy metabolism and the mammalian clock. Cell Cycle. 2008;7:453–457.
13. Zhang EE, Liu AC, Hirota T, et al. A genome-wide RNAi screen for modifiers of the circadian clock in human cells. Cell. 2009;139:199–210.

14. Palczewski K. G protein-coupled receptor rhodopsin. Annu Rev Biochem. 2006;75:743–767.
15. Hofmann KP, Scheerer P, Hildebrand PW, et al. A G protein–coupled receptor at work: the rhodopsin model. Trends Biochem Sci. 2009;34:540–552.
16. Fein A, Szuts EZ. Photoreceptors: Their Role in Vision. Cambridge, UK: Cambridge University Press; 1982.
17. McLaren DS, Kraemer K. eds. Vitamin A in nature. In: Manual on Vitamin A Deficiency Disorders (VADD). Basel, Switzerland: Karger; 2012:7–17.
18. Zhong M, Kawaguchi R, Kassai M, et al. Retina, retinol, retinal and the natural history of vitamin A as a light sensor. Nutrients. 2012;4:2069–2096.
19. Saari JC. Vitamin A metabolism in rod and cone visual cycles. Annu Rev Nutr. 2012;32:125–145.
20. Cascella M, Barfuss S, Stocker A. Cis-retinoids and the chemistry of vision. Arch Biochem Biophys. 2013;539:187–195.
21. Ransom J, Morgan PJ, McCaffery PJ, et al. The rhythm of retinoids in the brain. J Neurochem. 2014;129:366–376.
22. Wertz K, Hunziker PB, Seifert N, et al. β-Carotene interferes with ultraviolet light A-induced gene expression by multiple pathways. J Invest Dermatol. 2005;124:428–434.
23. Vieth R. Why "Vitamin D" is not a hormone, and not a synonym for 1,25-dihydroxy-vitamin D, its analogs or deltanoids. J Steroid Biochem Mol Biol. 2004;89–90:571–573. doi:10.1016/j.jsbmb.2004.03.037
24. Beckett EL, Duesing K, Martin C, et al. Relationship between methylation status of vitamin D-related genes, vitamin D levels, and methyl-donor biochemistry. J Nutr Intermed Metab. 2016;6:8–15.
25. Bouillon R, Carmeliet G, Verlinden L, et al. Vitamin D and human health: lessons from vitamin D receptor null mice. Endocr Rev. 2008;29:726–776.
26. Fetahu IS, Hobaus J, Kallay E. Vitamin D and the epigenome. Front Physiol. 2014;5:164. doi:10.3389/fphys.2014.00164
27. Deaton AM, Bird A. CpG islands and the regulation of transcription. Genes Dev. 2010;25:1010–1022.
28. Dennison EM, Arden NK, Keen RW, et al. Birthweight, vitamin D receptor genotype and the programming of osteoporosis. Paediatr Perinat Epidemiol. 2001;15:211–219.
29. Sayers A, Tobias JH. Estimated maternal ultraviolet B exposure levels in pregnancy influence skeletal development of the child. J Clin Enocrinol Metab. 2009;94:765–771.
30. Waldie KE, Poulton R, Kirk IJ, et al. The effects of pre- and post-natal sunlight exposure on human growth: evidence from the Southern Hemisphere. Early Hum Dev. 2000;60:35–42.
31. Pike JW, Meyer MB. The vitamin D receptor: new paradigms for the regulation of gene expression by 1,25-dihydroxyvitamin D3. Endocrinol Metab Clin North Am. 2010;39:255–269.
32. Ramagopalan SV, Heger A, Berlanga AJ, et al. A ChIP-seq defined genome-wide map of vitamin D receptor binding: associations with disease and evolution. Genome Res. 2010;20:1352–1360.
33. Dopico XC, Evangelou M, Ferreira RC, et al. Widespread seasonal gene expression reveals annual differences in human immunity and physiology. Nat Commun. 2015;6:7000. doi:10.1038/ncomms8000
34. Stahl W, Sies H. β-Carotene and other carotenoids in protection from sunlight. Am J Clin Nutr. 2012;96:1179S–1184S.
35. Darvin ME, Fluhr JW, Caspers P, et al. In vivo distribution of carotenoids in different anatomical locations of human skin: comparative assessment with two different Raman spectroscopy methods. Exp Dermatol. 2009;18:1060–1063.
36. Alaluf S, Heinrich U, Stahl W, et al. Dietary carotenoids contribute to normal human skin color and UV photosensitivity. J Nutr. 2002;132:399–403.
37. Lee J, Jiang S, Levine N, et al. Carotenoid supplementation reduces erythema in human skin after simulated solar radiation exposure. Proc Soc Exp Biol Med. 2000;223:170–174.
38. Stahl W, Sies H. Bioactivity and protective effects of natural carotenoids. Biochim Biophys Acta. 2005;1740:101–107.
39. Césarini JP, Michel L, Maurette JM, et al. Immediate effects of UV radiation on the skin: modification by an antioxidant complex containing carotenoids. Photoderm Photoimm Photomed. 2003;19:182–189.
40. Biesalski HK, Hemmes C, Hopfenmuller W, et al. Effects of controlled exposure of sunlight on plasma and skin levels of β-carotene. Free Radic Res. 1996;24:215–224.
41. Dinkova-Kostova AT. Phytochemicals as protectors against ultraviolet radiation: versatility of effects and mechanisms. Planta Med. 2008;74:1548–1559.
42. Sies H, Stahl W. Nutritional protection against skin damage from sunlight. Annu Rev Nutr. 2004;24:173–200.
43. Fernandez-Garcia E. Skin protection against UV light by dietary antioxidants. Food Funct. 2014;5:1994–2003.
44. Kijstra A, Tian Y, Kelly ER, et al. Lutein: more than just a filter for blue light. Prog Retin Eye Res. 2012;31:303–315.
45. Khachik F, Spangler CJ, Smith JC, et al. Identifcation, quantification, and relative concentrations of carotenoids and their metabolites in human milk and serum. Anal Chem. 1997;69:1873–1881.
46. Stahl W, Sundquist AR, Hanusch M, et al. Separation of beta-carotene and lycopene geometrical isomers in biological samples. Clin Chem. 1993;39:810–814.
47. Jablonski NG. The naked truth. Sci Amer. 2016;25:52–59.
48. Rogers AR, Iltis D, Wooding S. Genetic variation at the MCIR locus and the time since loss of human body hair. Curr Anthropol. 2004;45:105–108.
49. Packer L. Ultraviolet radiation (UVA, UVB) and skin antioxidants. In Rice Evans CA, Burdon RH, eds. Free Radical Damage and its Control. New York, NY: Elsevier Press; 1994: 234–255.
50. Lucock M. Folic acid: nutritional biochemistry, molecular biology, and role in disease processes. Mol Genet Metab. 2000;71:121–138.
51. Lucock M, Yates Z, Martin C, et al. Methylation diet and methyl group genetics in risk for adenomatous polyp occurrence. BBA Clin. 2015;3:107–112.
52. Lucock M, Leeming R. Autism, seasonality and the environmental perturbation of epigenome related vitamin levels. Med Hypotheses. 2013;80:750–755.
53. Anderson DD, Woeller CF, Stover PJ. Small ubiquitin-like modifier-1 (SUMO-1) modification of thymidylate synthase and dihydrofolate reductase. Clin Chem Lab Med. 2007;45:1760–1763.
54. Fox JT, Shin WK, Caudill MA, et al. A UV-responsive internal ribosome entry site enhances serine hydroxymethyltransferase 1 expression for DNA damage repair. J Biol Chem. 2009;284:31097–33108.
55. Woeller CF, Fox JT, Perry C, et al. A ferritin-responsive internal ribosome entry site regulates folate metabolism. J Biol Chem. 2007;282:29927–29935.
56. Lucock M, Beckett E, Martin C, et al. UV-associated decline in systemic folate: implications for human nutrigenetics, health, and evolutionary processes. Am J Hum Biol 2017;29:e22929. doi:10.1002/ajhb.22929
57. Blount BC, Mack MM, Wehr CM, et al. Folate deficiency causes uracil misincorporation into human DNA and chromosome breakage: implications for cancer and neuronal damage. Proc Natl Acad Sci USA. 1997;94:3290–3295.
58. Serrano MP, Lorente C, Vieyra FE, et al. Photosensitizing properties of biopterin and its photoproducts using 2′-deoxyguanosine 5′-monophosphate as an oxidizable target. Phys Chem Chem Phys. 2012;14:11657–11665.
59. Hirakawa K, Suzuki H, Oikawa S, et al. Sequence-specific DNA damage induced by ultraviolet A-irradiated folic acid via its photolysis product. Arch Biochem Biophys. 2003;410:261–268.
60. Ito K, Kawanishi S. Photoinduced hydroxylation of deoxyguanosine in DNA by pterins: sequence specificity and mechanism. Biochemistry. 1997;36:1774–1781.
61. Benavente CA, Jacobson MK, Jacobson EL. NAD in skin: therapeutic approaches for niacin. Curr Pharm Des. 2009;15:29–38.
62. Warburg O, Christian W, Griese A. Wasserstoffübertragendes coferment, seine zusammensetsung und wirkungsweise [in German]. Biochem Z. 1935;282:157–165.
63. Jacobson MK, Jacobson EL. Discovering new ADP-ribose polymer cycles: protecting the genome and more. Trends Biochem Sci. 1999;24:415–417.
64. Durkacz BW, Omidiji O, Gray DA, et al. $(ADP\text{-}ribose)_n$ participates in DNA excision repair. Nature. 1980;283:593–596.
65. Satoh MS, Lindahl T. Role of poly(ADP-ribose) formation in DNA repair. Nature. 1992;356:356–358.
66. Oliver FJ, Menissier-de Murcia J, de Murcia G. Poly(ADP-ribose) polymerase in the cellular response to DNA damage, apoptosis, and disease. Am J Hum Genet. 1999;64:1282–1288.
67. Kim MY, Mauro S, Gevry N, et al. NAD^+-dependent modulation of chromatin structure and transcription by nucleosome binding properties of PARP-1. Cell. 2004;119:803–814.
68. Yu SW, Wang H, Poitras MF, et al. Mediation of poly(ADP-ribose) polymerase-1-dependent cell death by apoptosis-inducing factor. Science. 2002;297:259–263.
69. Lucock M, Yates Z. Folic acid fortification: a double-edged sword. Curr Opin Clin Nutr Metab Care. 2009;12:555–564.
70. Lucock MD, Priestnall M, Daskalakis I, et al. Non-enzymatic degradation and salvage of dietary folate: physico-chemical factors likely to influence bioavailability. Biochem Mol Med. 1995;55:43–53.
71. Ng X, Lucock MD, Veysey M. Physicochemical effect of pH and antioxidants on mono- and triglutamate forms of 5-methyltetrahydrofolate, and evaluation of vitamin stability in human gastric juice: implications for folate bioavailability. Food Chem. 2008;106:200–210.
72. Webb AR, Holick MF. The role of sunlight in the cutaneous production of vitamin D3. Annu Rev Nutr. 1988;8:375–399.
73. Jacobs HJC, Boomsma F, Havinga E. The photochemistry of vitamin D and tachesterol. Recl Trav Chim Pays Bas. 1977;96:113–116.
74. Dauben WG, Bauman P. Photochemical transformations. IX. Total structure of suprasterol II. Tetrahedron Lett. 1961;2:565–572.
75. Havinga E. Vitamin D, example and challenge. Experentia. 1973;29:1181–1193.
76. Robinson N. Solar Radiation. New York, NY: Elsevier; 1966.
77. Holick MF, MacLaughlin JA, Doppelt SH. Regulation of cutaneous previtamin D3 photosynthesis in man: skin pigment is not an essential regulator. Science. 1981;211:590–593.
78. Lucock M, Yates Z, Glanville T, et al. A critical role for B-vitamin nutrition in human developmental and evolutionary biology. Nutr Res. 2003;23:1463–1475.

79. Hasoun LZ, Bailey SW, Outlaw KK, et al. Rearrangement and depletion of folate in human skin by ultraviolet radiation. Br J Dermatol 2015;173:881–1111. doi: 10.1111/bjd.13885
80. Borradale D, Isenring E, Hacker E, et al. Exposure to solar ultraviolet radiation is associated with a decreased folate status in women of childbearing age. J Photochem Photobiol B. 2014;131:90–95.
81. Cabrera S, Benavente D, Alvo M, et al. Vitamin B12 deficiency is associated with geographical latitude and solar radiation in the older population. J Photochem Photobiol B. 2014;140:8–13.
82. Mosharov E, Cranford MR, Banerjee R. The quantitatively important relationship between homocysteine metabolism and glutathione synthesis by the transsulfuration pathway and its regulation by redox changes. Biochemistry. 2000;39:13005–13011.
83. Cheng Z, Yamamoto H, Bauer CE. Cobalamin's (vitamin B_{12}) surprising function as a photoreceptor. Trends Biochem Sci. 2016;41:647–650.
84. Lucock M, Glanville T, Ovadia L, et al. Photoperiod at conception predicts C677T-MTHFR genotype: a novel gene environment interaction. Am J Hum Biol. 2010;22:484–489.
85. Jablonski NG, Chaplin G. The evolution of human skin coloration. J Hum Evol. 2000;39:57–106.
86. Jones P, Beckett E, Yates Z, et al. Converging evolutionary, environmental and clinical ideas on folate metabolism. Exp Res Hypothesis Med. 2016;1:34–41.
87. Beckett EL, Jones P, Veysey M, et al. VDR gene methylation as a molecular adaption to light exposure: historic, recent and genetic influences. Am J Hum Biol. 2017;29:e23010. doi:10.1002/ajhb.23010
88. Yafei W, Lijun P, Jinfeng W, et al. Is the prevalence of MTHFR C677T polymorphism associated with ultraviolet radiation in Eurasia? J Hum Genet. 2012;57:780–786.
89. Jones P, Lucock M, Veysey M, et al. Frequency of folate-related polymorphisms varies by skin pigmentation. Am J Hum Biol. 2018;30:e23079. doi:10.1002/ajhb.23079
90. Hochberg Z, Templeton A. Evolutionary perspective in skin color, vitamin D and its receptor. Hormones (Athens). 2010;9:307–311.
91. Lucock M, Yates Z, Martin C, et al. Vitamin D, folate, and potential early lifecycle environmental origin of significant adult phenotypes. Evol Med Public Health. 2014;2014:69–91.
92. Jablonski NG, Chaplin G. Human skin pigmentation as an adaptation to UV radiation. Proc Natl Acad Sci USA. 2010;107:8962–8968.
93. Beckett EL, Yates Z, Veysey M, et al. The role of vitamins and minerals in modulating the expression of microRNA. Nutr Res Rev. 2014;27:94–106.