The Photobiology of Vitamins.

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KEY WORDS: Photobiology; Vitamins; Molecular Nutrition

ABSTRACT

This review explores contemporary ideas on the relationship between light exposure and vitamin biology. Nutritional biochemistry has long recognised the relationship between vitamins A and D and light exposure, but in recent years, other vitamins have also been implicated in a photo-responsive biology that influences health, wellbeing and even evolutionary origins.

Interaction between light and vitamins can modify genotype-phenotype relationships across the lifecycle, offering interesting new molecular explanations of relevance to wide aspects of human biology. This review examines both well-established and emerging ideas on vitamin photobiology in the context of: 1)'***light responsiveness***'-vitamin D (skin photosynthesis), vitamin A (vision), vitamin B3 (genomic damage response); 2)'***UV/light vulnerability***'-folate, vitamins B1, B2, B12, D (all potentially degraded); 3)'***UV filtering/protective actions***'-carotenoids, vitamins C, E (act as antioxidants and/or natural sunscreens); 4)'***Role in UV-related genomic regulation, maintenance and repair***'-folate, vitamins A, B3, C, D, E and carotenoids; 5)'***Role in a range of light signalling/transduction pathways***'-vitamins A, B2, B12, D and folate; and finally 6)'***Links to the evolution of UV/light adaptive phenotypes***'-folate, vitamin D.

INTRODUCTION

Generations of students have learnt 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

important 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 vitamins D and A, and light exposure have long been recognised,[1, 2] but in recent years, many more vitamins have also been implicated in a light responsive biology that impacts health, and even human origins.

Since the 1990s, clinical research involving vitamins has often been considered in a nutritional genetics (nutrigenetic) context, although more recently the broader exposome (totality of environmental exposures through the lifecycle) has been investigated for additional relevant factors.[3, 4] UV radiation in particular has been investigated as a factor that interacts with vitamins and their dependent genes to influence phenotype. Indeed, evidence now points to light (wavelength, duration and life stage) as a critical environmental component that interacts with nutritional agents to modify genotype-phenotype relationships across the lifecycle, offering up interesting new molecular explanations of relevance to wide aspects of human biology. This review will examine these as separate biochemical/biophysical constructs (Figure 1 provides an integrated overview of how vitamins respond to light to support the reviews narrative).

Signalling and Transduction

Typically, vitamins A (vision) and D (skin photosynthesis and VDR activation) are the vitamins most obviously linked to light mediated signal transduction pathways. However, folate in

71 the form of its reduced 5,10-methenyl coenzyme, and vitamin B_2 (in the form of flavin
72 adenine dinucleotide) are also recognised as chromophores that facilitate
73 photoreception/light transduction mechanisms.[5] These two B-vitamins have been
74 implicated in the maintenance of circadian rhythms,[4, 5] which are endogenous oscillations
75 synchronized (photo-entrained) by the natural night-day cycle which has a periodicity of
76 approximately 24 hours.[6]

77 This biological clock is regulated by input through the eye's retinal photoreceptor cells. Most
78 notably, visual holoproteins such as rhodopsin (11-*cis*-retinal and opsin) are not used in
79 circadian photoreception, but retinal cryptochromes and melanopsin are thought to
80 function as circadian photoreception pigments.[7] Cryptochromes are fascinating because
81 they contain both a flavin (FAD) and folate (5,10-methenyl-H_4folate) as light gathering
82 cofactors, and are integral to maintaining periodicity in animals and plants. They are blue-
83 light photoreceptors found in the ganglion cell layer of the retina and transduce light stimuli
84 through to the master circadian clock in the suprachiasmatic nucleus.

85 Although there is still much to learn, it has been shown that purified human cryptochrome 2
86 (hCRY2) exhibits a fluorescence profile consistent with the presence of both folate and flavin
87 cofactors,[5] although firm evidence of photoreception in mammalian cryptochromes remains
88 indirect.[8] CRY1 and CRY2 are 73% homologous in all organisms and absorb light in the 350 to
89 450 nm wavelength range. In this synergistic B-vitamin partnership, folate is effectively
90 functioning as a light gathering antenna, whilst FAD facilitates a redox reaction. The full
91 mechanism following exposure to blue-light photons proceeds by way of excitation of 5,10-
92 methenyl-H_4folate. An electron is then transferred to the reduced catalytic flavin ($FADH^-$)
93 and then on to CRY1 or CRY2.[9, 10] This system seems highly adaptive, as in the plant

kingdom, folate-containing cryptochromes regulate blue-light dependent growth; in bacteria, insects, and amphibians they stimulate the activity of enzymes that repair ultraviolet (UV)-induced DNA damage. In mammals, as indicated above, they regulate the circadian clock.

Without doubt, circadian timing is a key mechanism that regulates physiological processes like feeding behaviour and energy metabolism via dietary cues and light-activated transcription of key clock genes.[11, 12] Protein interaction network analysis for gene products linked to clock components reveals that aspects of folate metabolism, the cell cycle and hedgehog and insulin signalling are overrepresented.[13] One therefore might reasonably assume that while folate as 5,10-methenyl-H_4folate 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 pro-vitamin A carotenoid, is a chromophore required for human vision. Human visual perception is facilitated by the absorption of radiation in the 400 to 780nm region of the electromagnetic spectrum, and is a signal transduced at photoreceptors in the retina (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 a G protein-coupled receptor system in which the cognate G protein is transducin.[14, 15]

Opsins shift the absorption characteristics of 11-*cis*-retinal from the UV into the visible range of light, leading to a broad sensitivity for vision in low light via rod cells or a better refined spectral resolution to distinguish colours 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* isomerisation and a conformational change in the opsin protein; the retinal is released from its opsin binding pocket and a nerve impulse propagated via a guanine nucleotide amplification cascade leading to closing of a sodium channel.[2, 16] The released retinal is then reduced and the resulting *trans*-retinol joins a pool in the retina (retinal pigment epithelium) for reuse in the visual cycle. Several excellent review articles have recently examined the role of vitamin A in nature, and the visual cycle in particular,[2, 17-19] including new ideas on 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 greatest metabolic activity around the retinal fovea, each retinal pigment epithelium cell requires $4x10^8$ rhodopsin molecules each day, and it is likely that this high requirement explains why this is the first area to deteriorate in age related macular degeneration (AMD).[2] It also explains why a dietary shortage of vitamin A leads to impaired colour vision and dark adaptation, and an inability to see in low light, referred to as night blindness.

Interestingly, recent evidence points to a novel endocrine axis regulated by photoperiod and melatonin that utilises 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, involving 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 behaviours like hibernation and reproduction, and that nutrients, including vitamin A inform (signal) the "clock" on quality and availability of food as a stochastic environmental variable.[21]

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

The classic light-related vitamin is vitamin D.[1, 3] The established role of this "UV dependent vitamin" is discussed below (section 4), however, it also plays a role in signal transduction in a broad yet highly 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 (footnote1), has actions that can play a central role in phenotypic plasticity, altering gene expression and hence phenotypic outcomes in response to environmentally originated cues. The key role of vitamin D in signalling relates to its role as a ligand for the vitamin D receptor (VDR) protein, a transcription factor that belongs to the steroid nuclear receptor superfamily.[24] The active ligand for the VDR is the conformationally flexible secosteroid, $1,25(OH)_2D_3$, and the outcome of photosynthesised vitamin D is activation of a nuclear receptor that has high tissue specificity and regulates calcium and phosphorus homeostasis. It also underpins the growth, differentiation and

patency of many types of cell that are found in VDR dependent target tissues.[25] Such VDR action can influence gene expression including those of chromatin modifiers and remodelers, and hence can alter DNA methylation profile.[26] However, the VDR gene is itself methylated at key CpG islands, whereby genomic hyper- and hypomethylation decrease and increase expression respectively.[27] This may be one mechanism by which light signals/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 both infant bone size, height and adult bone mineral density,[28-30] indicating the importance of long term signalling 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 (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 and colleagues have shown that 2276 genomic loci are occupied by the VDR and 229 genes have altered expression profiles in response to this vitamin.[32] 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 signalling paradigm. Indeed, the idea of pleiotropic effects of vitamin D and its relation to the VDR are manifold, and ultimately are likely to shape the human phenome. It is therefore entirely reasonable to speculate that this “signalling” might have an overarching influence on our ability to adapt to changing environments (light exposure) and or geophysical cycles.

Filtering and Protection

One of the least well known attributes of vitamins is the role they play in filtering UV light and hence preventing cellular damage. Dietary carotenoids such as the pro-vitamin A nutrient, β-carotene, are long-chain polyene structures that can physically quench electronically excited molecules, and absorb UV light, hence mitigating direct damage to cellular targets, and particularly lipids, proteins and DNA. Carotenoid rich foods slowly assimilated into the skin are therefore photoprotective, although basal dermal defence against UV irradiation varies across the body's epidermis in parallel with a variable local carotenoid concentration.[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 palm of the hand. Such intervention has been shown to substantially protect against UV-induced erythema,[37, 38] and furthermore, vitamin E may also augment this protective effect of β-carotene.[39]

Although antioxidant vitamins, including pro-vitamin A carotenoids, are protective against UV challenge, this environmental agent has been shown to lower skin β-carotene in volunteers receiving a total UV dose of around 10,000 mJ/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] In the context of pro-vitamin A carotenoids, there are a number of ways in which protection from sun damage can occur. These include an increase in optical density, quenching of singlet oxygen and the formation of the retinoic acid vitamer.[43]

Further critical protective carotenoids include lutein and zeaxanthin; molecular structures that provide blue light filtration, and which bio-accumulate in the eye where they protect

the retinal fovea from damaging UV. The protective role of these dietary carotenoids is considered to be a relevant factor in the development of AMD.[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 impact risk for AMD.[44]

It is interesting that as far as the skin surface is concerned, anti-oxidative 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 hand and back have the highest carotenoid levels as these 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.[43] The bioavailability of β-carotene is actually fairly complex and dependent upon the nature of the food source, food processing, genetic variation in the carotene dioxygenase gene which at best yields an enzyme of low activity, is subject to both inhibition by other carotenoids and asymmetric cleavage of β-carotene yielding non-provitamin-A apocarotenals, and is affected by the fat content of the diet. This ineffective process yields roughly 1mg of retinol per 6mg β-carotene. However, clearly genetic variation in carotene dioxygenase might potentially reduce oxidative stress by increasing β-carotene levels in the blood and tissues.

The most abundant carotenoids in humans are α- and β-carotene, and lycopene, along with the xanthophylls; lutein, zeaxanthin, and α- and β-cryptoxanthin.[45, 46] However, overall, vitamin E is the most abundant lipophilic antioxidant in human skin, with the highest levels in the epidermis.[43] From an evolutionary perspective, it is interesting to consider whether the high levels of carotenoids/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” that took place around 1.6 million years ago in the *Homo* lineage. Certainly the loss of hair and development of significant eccrine sweat that arose at this time allowed early man to dissipate heat generated as a “consequence of” /”adaptation to” a rapidly changing climate; there was a notable shift from forest to savanna in East Africa, as this region entered a dry phase three million years ago due to global cooling. Such a change will have led *Homo ergaster* to forage further afield to maintain dietary sustenance, a practice that required a physiological adaptation to prevent overheating - one that is comfortably met in part by increased sweating and reduced hairiness.[47] This transition, leading to a significant loss of body hair in our ancestors, also likely led to the selection of a more pigmented skin as an adaptive evolutionary response to high levels of UV 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 before, 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 later.

The likely benefits of vitamin E in skin relate to protection against the cytotoxic effect of UVB via a mechanism involving inhibition of UV induced lipid peroxidation or the anti-oxidation 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 play a direct role in DNA maintenance and repair (folate, vitamin B12, niacin), an indirect role, perhaps via an anti-oxidative effect (vitamin C, E, carotenoids), or a modulatory role as a transcription factor (vitamin A, D and E). Several of these roles are important in the context of a metabolic response to UV exposure and mitigating the subsequent DNA damage that can 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 impact of UV exposure on DNA integrity.

As will be discussed later, folate is UV sensitive, but also necessary for the synthesis and expression of DNA, which is in itself, highly UV labile. The role of folate is as a carrier of various one-carbon units that can be transferred into important biosynthetic pathways. Of particular importance are the synthesis of DNA-thymidylate (dTMP) and methionine. Methionine is generated from homocysteine (Hcy) using both 5-methyltetrahydrofolate (5-methyl-H_4folate) and vitamin B12 as essential cofactors. Methyl groups derived from methionine can be utilized for both genomic [CpG] and non-genomic methylation reactions. Therefore, folate (and by association, vitamin B12) contributes to both the primary structure and expression of genes. Consequently, any factors that perturb folate metabolism including genetic variation and environmental factors (particularly dietary intake), can potentially promote uracil misincorporation into the primary DNA base sequence in place of thymine, a phenomenon associated with DNA fragility.[50] Furthermore, researchers are only now learning how critically important the epigenome is in regulating DNA expression and managing the complexities of cell biology during development and in disease.[51] To this end,

277 genomic methylation patterns orchestrate human biology and subserve wellbeing, but are
278 highly complex, and a product of multiple interactions, including dietary ones.[52]

279 Folate enzymes operate in concert to maintain dTMP synthesis. One group of metabolically
280 linked genes encodes thymidylate synthase (*TYMS*), serine hydroxymethyltransferase
281 (*SHMT1*), and dihydrofolate reductase (*DHFR*). These three genes are polymorphic and their
282 expression products operate in a tight synergy that is fundamental in maintaining the
283 fidelity of dTMP synthesis and integrity of DNA. This co-operative association makes this
284 enzyme cluster critically important during periods of rapid cell turnover and differentiation,
285 such as, for example, during early embryo development and throughout the first trimester
286 of pregnancy. Elegant mechanisms exist to post-translationally modify these folate enzymes
287 and permit nuclear translocation during S and G2/M cell cycle phases.[53, 54] However, of
288 particular interest within this gene cluster is that SHMT plays a crucial role in the repair of
289 UV-propagated DNA damage.[54] SHMT expression levels and post-translational SUMOylation
290 of TYMS increase, as does the nuclear compartmentation of SHMT and TYMS following
291 exposure to UV radiation. Interestingly, although this SHMT-related UV response does occur
292 in humans, it is absent in mice,[55] suggesting species specificity and the possibility that it may
293 have evolved as an adaptive response to protect skin from UV related DNA damage, by
294 promoting additional dTMP synthesis.

295 One idea that has recently emerged relates to whether UV-irradiance can reduce long-term
296 systemic folate levels. In this recent study,[56] it was shown that UV exposure alters folate
297 status according to C677T-*MTHFR* genotype. The authors suggest that this might be because
298 either 677TT-*MTHFR* individuals contain more 5,10-methylenetetrahydrofolate (5,10-
299 methylene-H_4folate) coenzyme, which is a UV labile form of folate, or because of increased

utilisation of folate for DNA repair (dTMP synthesis) under increased UV regimes. 5,10-methylene-H_4folate is the immediate precursor of the one-carbon unit needed for dTMP synthesis, and as a result of its metabolic location and functional change, the *MTHFR* 677TT variant is thought to help maintain the fidelity of DNA-dTMP synthesis 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 dealt with in detail in Section 5 (UV vulnerability of vitamins).

It is also relevant to note that increased use of the synthetic form of folate (pteroylmonoglutamic acid [PteGlu]) at a population level via discretionary and government mandated use might be an issue in the present context. Research has shown that PteGlu photolytic scission products (i.e. 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_4folate. However, despite these observations, the authors are unaware of any population studies that indicate fortification/supplementation with PteGlu increases DNA damage.

Another vitamin known to be light responsive in the context of DNA repair is niacin (vitamin B3). Niacin deficiency in humans lowers NAD status, resulting in sun sensitive skin. This lower NAD level actually mediates UV damage.[61]

Both of the B3 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, as well as its coenzyme role, 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 UV exposure.

Recent identification of the nicotinic acid receptor in human skin keratinocytes further supports a role for niacin as a potential pharmacologic agent in the prevention of UV induced skin cancer.[61]

This influence of niacin should be unsurprising given that the deficiency syndrome for this vitamin is Pellagra, a condition that produces a severe photo-dermatitis as part of the symptomology.

The unifying explanation for the photo-responsive 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 DNA damage response, including UV damage. This role is therefore fundamental in genomic repair, stability, signalling as a stress response in apoptosis, and gene expression.[63-66] In the latter case, PARP-1 is also a structural element of chromatin, modifying chromatin structure via its enzymatic activity (represses transcription).[67]

The involvement of PARP-1 in maintaining genomic integrity underpins the beneficial role of niacin following genotoxic stress; several labs now link the influence of this vitamin in cancer prevention.[61] Activation of PARP-1 by DNA strand breakage (including UV induced damage) leads to a complex signalling network that modifies cell survival, cell death via apoptosis, or energy loss and hence necrosis. However, from the perspective of niacin *per se*, extreme genotoxicity promotes PARP-1 over-activation and cell death through depletion of first

NAD+ and then ATP. This deprives the cell of energy dependent functions and precipitates cell death. Research has also shown that a fall 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, and so like vitamin D, niacin is not strictly speaking a vitamin, although it is conveniently classify it as such.

Antioxidant vitamins such as vitamin C, E, and carotenoids act to protect DNA from the damaging effects of free radicals that can be generated by UV exposure. These vitamins neutralise unpaired electrons in highly reactive radical species, delocalising the unpaired electron in their own molecular structure to form resonance stabilised radicals (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, and therefore act as a free radical generator. In this context, the best-known example is probably the use of high dose β-carotene to try to prevent cancer, but the outcome showed the opposite effect - increased lung cancer rates. This is despite normal levels of intake being associated with lower cancer rates.[69] Two and two does not always make four; 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 salvage of reduced folates in the stomach. The active secretion of vitamin C into the stomach lumen against a concentration gradient is considered important to prevent low pH loss of oxidised methylfolate (5-methyl-H_2folate). Vitamin C is therefore critically important

for maintaining folate bioavailability,[70, 71] and folates are arguably the most important vitamin in respect of maintaining DNA integrity.

UV Dependent Vitamins

The most obviously UV dependent micronutrient is vitamin D. The two dietary forms of this vitamin are ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). However, while vitamin D3 is a dietary component, it is also synthesised from the UVB (290-315nm) 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 isomerisation 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 ring closure to form the inactive stereoisomer metabolite, lumisterol, or isomerisation to form the inactive 6,7-trans isomer, tachysterol.[1, 72] In addition, according to Jacobs there are at least 13 toxisterols that may potentially be produced by prolonged irradiation.[73] Dauben and Bauman identified two suprasterols as products following prolonged radiation,[74] while Havinga documents four additional photoisomers of vitamin D.[75]

Vitamin D3 is itself photolabile at wavelengths between 315-335 nm, which are longer wavelengths than are required to photosynthesise 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 UVB bandwidth for optimal previtamin D synthesis is narrow (280-320 nm). This is at the short wavelength limit on the edge of the ozone absorption band, where light is first able to penetrate through 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. This means that darkly pigmented skin moderates formation of previtamin D3 after UVB exposure. As a result, deeply melanised skin can be considered as non-adaptive in circumstances where it limits vitamin D3 synthesis at higher latitudes. Indeed, melanisation interacts with altitude, latitude, time of day, and weather conditions to influence previtamin D3 biosynthesis. Of course, the use of sunscreen can equally limit the vitamins biosynthesis.[1, 77]

Once it is formed from previtamin D (around 80% conversion in 4 days), vitamin D3 is transported away from the skin, and is drawn into the capillary bed by vitamin D binding protein (DBP).[1] The main circulating and storage form of the vitamin in blood plasma is $25(OH)D_3$. $25(OH)D_3$ is metabolised from cholecalciferol in the liver and is subsequently converted into the active vitamin form of vitamin D, 1,25-dihydroxyvitamin 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 $1,25(OH)_2D_3$ (a) enhances intestinal absorption of calcium; (b) reduces urinary losses of calcium by enhanced resorption in the distal renal tubules; (c) regulates mobilization and deposition of bone mineral. For these and other reasons $1,25(OH)_2D_3$ synthesis is highly regulated: cholecalciferol undergoes two 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 are in 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: Firstly, $1,25(OH)_2D_3$ acts to reduce its own synthesis by inducing the 24-hydroxylase and repressing the 1-hydroxlase enzymes. In both these cases, modulation is via altered gene expression. Secondly, a drop in blood calcium initiates parathyroid hormone (PTH) secretion. This promotes 1-hydroxylase activity, but inhibits activity of the 24-hydroxylase. This function is countered by elevated calcium and $1,25(OH)_2D_3$ levels, which repress PTH synthesis. Thirdly, although a minor effect, calcium can act directly to inhibit the 1-hydroxylase enzyme.[3]

The solar dependency for cholecalciferol biosynthesis, and subsequently sun independent $1,25(OH)_2D_3$ synthesis, and this latter vitamers role in bone mineral homeostasis explains why the deficiency syndrome is rickets in children and osteomalacia in adults. The former condition stemming from a failure to mineralise in the first place, and the latter resulting from demineralisation.

During the mid-17th century, rachitic deformities were a distinct phenomenon arising due to the increasing urbanization of England's population, and the associated atmospheric pollution (smog and smoke) that hindered seasonal vitamin D synthesis at these northerly latitudes. By the turn of last century, industrialisation, migration, atmospheric pollution and

436 the spread of slums, poverty and overcrowding in Western Europe and the US enhanced the
437 prevalence of rickets due to the prevailing environment reducing exposure to dietary
438 vitamin D and appropriate levels of UVB.[1, 3]

439 The only other vitamin that has such a clear function linked to light exposure is vitamin A.
440 The phototransformation of the 11-cis-retinal chromophore into the 11-trans form of retinal
441 being necessary for vision as discussed above.

442 **UV Vulnerable Vitamins**

443 Several vitamins are photolabile and respond directly to different wavelengths of light by
444 degrading. However, some vitamin loss may be indirect and attributable to a UV originated
445 increase in free radicals. Although some vitamins may potentially utilise other available
446 antioxidants as a protective mechanism against radical attack.

447 Vitamin B1 (thiamine) is quickly degraded by sunlight and although flour and bread are
448 potentially good sources of this vitamin, most of this can be lost when baked products are
449 put on display in shop windows. Similarly, vitamin B2 (riboflavin) undergoes photolysis to
450 form lumiflavin under alkaline conditions or lumichrome under neutral or acidic conditions.
451 Both of these are biologically inactive meaning that dairy products, a major source of this
452 vitamin, are sensitive to sun exposure and even fluorescent light (400-550nm). Furthermore,
453 these photolysis products can cause lipid peroxidation and conversion of methionine into
454 methional, which confers a tainted “sunlight” flavour to milk.[3] Vitamin B2 is also interesting
455 because it can act as a photosensitiser for folate, enhancing UV-dependent degradation in
456 contrast to vitamin C and glutathione, which enhance folate stability.[56] Cyanocobalamin, the
457 supplementary/pharmaceutical form of vitamin B12 is the most stable B12 vitamer.

458 However, light leads to cyano group dissociation and the formation of hydroxocobalamin,
459 although this photolysis does not influence B12 activity.

460 As alluded to above, it is impossible for humans to manufacture toxic levels of vitamin D3
461 from sun exposure because of the formation of inactive lumisterol, tachysterol or a range of
462 other toxisterols after prolonged exposure,[72-75] thereby preventing hypervitaminosis D.
463 However, even vitamin D3 can be degraded by longer wavelengths than are required for its
464 synthesis (>315nm).[72]

465 Recent research has also shown strong evidence that UV exposure can destroy systemic
466 levels of folate (red cell and plasma), and that this effect is modified by C677T-*MTHFR*
467 genotype.[56] Cumulative UV-irradiance determined for 42 and 120 days pre-clinic was
468 significantly negatively associated with red cell folate. When the cohort (n=649) was
469 stratified by *MTHFR*-C677T genotype, the relationship between UV-irradiance remained
470 significant only in the cohorts containing carriers of the T allele. The authors suggest that
471 these data provide strong evidence that surface UV-irradiance reduces long-term systemic
472 folate levels, and that since this is influenced by C677T-*MTHFR* genotype, the effect may be
473 due to 677TT-*MTHFR* individuals containing more 5,10-methylene-H_4folate, a form of folate
474 that may be particularly UV labile.[56]

475 Several studies have looked at the light sensitivity of folate: In vitro studies have
476 demonstrated UV-B light at 312nm can degrade plasma/cellular 5-methyl-H_4folate, leading
477 to the formation of oxidized 5-methyl-H_2folate, with the eventual loss of all vitamin activity
478 via C9-N10 bond scission.[78] This is supported by a more recent ex vivo study that showed
479 longer UVA as well as UVB wavelengths can degrade this natural, 5-methyl-H_4folate, form of
480 folate.[79] Longer wavelengths in the UVA spectrum (315-400nm) can penetrate deeper into

481 the skin and reach the dermal circulation. For this reason it has been attributed to
482 photolytic degradation of synthetic PteGlu that remains unmetabolised in the circulation,
483 and which in this unmodified form is increasingly being linked to negative health correlates,
484 including the potential production of 6-formylpterin, which eventually oxidizes to form
485 pterin-6-carboxylic acid and which as discussed earlier may contribute to carcinogenesis.[58-60]
486 Other than the 2016 study by Lucock and colleagues,[56] the only other population study was
487 by Borradale *et al* who showed that solar UV exposure over three weeks reduces the
488 effectiveness of PteGlu supplements in a young female population of reproductive age who
489 live in a region with extreme UV exposure[80]. This was a relatively small study with 45
490 participants, and was limited to serum folate measurements that do not reflect overall
491 folate status as well as red cell folate values do.

492 Any UV-associated loss of folate status within population studies needs to be considered in
493 the context that a vitamin decline might also reflect an increased need for the vitamin to
494 maintain DNA repair processes.[56]

495 Another vitamin that is closely associated with folate is vitamin B12 (cobalamin). A 2014
496 study has suggested that deficiency in B12 is associated with geographical latitude and solar
497 radiation in an older population from Chile.[81] The research found that the prevalence of
498 vitamin B12 deficiency was associated with living closer to the Equator and solar radiation.
499 Overall, the prevalence of vitamin B12 deficiency was 11.3%, with prevalence in the North
500 of the country being significantly greater than in Central and South Chile (19.1%,10.5%, and
501 5.7%, respectively; $P < 0.001$). The authors conclude that although degradation by solar
502 radiation might explain their observation, further work is required to establish the potential
503 mechanisms involved. Although no link currently exists between solar radiation, B12 and

related redox changes, it is interesting to consider that the vitamin B12 metabolic locus may be sensitive to oxidative stress, including possibly UV induced effects. Redox changes can increase the flux of Hcy through the transsulphuration pathway to cysteine and glutathione (a major cellular antioxidant) via a regulatory role at the key enzymes, methionine synthase and cystathionine- β-synthase. It has been suggested that this may be a self-correcting response to depleted glutathione in cells facing oxidative challenge.[82] Such challenge is likely to increase following UV exposure. It is also worth noting that although not relevant to humans, micro-organisms have recently been found to use B12 as a light absorbing chromaphore to facilitate gene expression, and that the number of species and kingdoms involved suggests a B12 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 associated daily, seasonal and related geophysical cycles play a crucial role in the orchestration of the human lifecycle. Indeed, the sun is the dominant force in the human exposome, which in the broadest terms includes all wavelengths of UV and visible radiation, photoperiod, seasonality, essential and beneficial non-essential dietary nutrients, and temperature, but also includes a profusion of other environmental factors. The human exposome has therefore contributed to disease risk and the evolution of the human species.

Two vitamins that interact with light to influence human phenotype through putative evolutionary and/or evo-devo mechanisms are folate and vitamin D. Moreover, it is entirely likely that the role of UV in the degradation of folate and synthesis of vitamin D 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 opening up some interesting ideas on how seasonal/exposomal UV-R 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 select embryos with a specific vitamin-related gene variant (or variant profile) that has expression products better at utilizing lower vitamin levels.

While this has an immediate effect on embryo survival, if selected, such variants might additionally alter disease risk later in life according to an individual’s long-term nutritional habits.[84] The present authors have tested and developed this argument for the folate-related C677T-*MTHFR* variant, and this concept seems plausible given that an estimated 70% to 80% of pregnancies are lost after conception.[3, 84] Indeed, this fits perfectly with environmental and nutritional agents interacting to alter genotype–phenotype relationships across the lifecycle in a way that supports the ‘‘developmental origins of adult disease’’ model. However, it also provides a molecular explanation for the idea that UV-R photosynthesis of vitamin D and photo-degradation of folate directed the evolution of parallel but opposing phenotypic clines of skin pigmentation.

Jablonski and Chaplin have developed this idea, the “folate–vitamin D-sunlight hypothesis” of skin pigmentation in recent years[85]. The principle is relatively straightforward; The aberrant effects of folate degradation on fertility promotes protective melanisation toward equatorial latitudes, while the need for vitamin D photosynthesis and calcium balance

549 facilitates epidermal depigmentation moving away from equatorial latitudes. The authors
550 have recently published several separate articles that lend support to this hypothesis and a
551 likely involvement of both folate[56, 86] and vitamin D[3, 87] in skin pigmentation as an evolved
552 trait. This hypothesis is consistent with maximal tanning occurring during the reproductive
553 phase of the lifecycle when folate protection is most obviously required for reproductive
554 efficiency .[88] It is also consistent with the recent observation that key folate gene
555 polymorphisms exhibit a geographic distribution that points to the maintenance of
556 homeostasis between folate-dependent *de novo* thymidylate synthesis and methylation
557 pathways in environments of differing solar regimes.[86] In this study, *MTHFR*-C677T and
558 *MTHFR*-A1298C polymorphisms were positively associated with latitude, while a negative
559 association was observed between latitude and frequency of the c*SHMT*-C1420T and *TYMS*
560 28bp 2R>3R variants.[86] These findings for *MTHFR*-C677T were consistent with those of
561 previous research.[89] Overall, these findings align with solar regime selecting a cassette of
562 folate gene variants that regulate a folate "homeostat" optimised to maintain key one-
563 carbon biosynthetic reactions, particularly those destined for methyl group and DNA
564 pathways. This paradigm is additionally supported by a study in 2017 that looked at the
565 association between population prevalence of 17 variants in 9 folate-related genes (*MTRR,*
566 *MTR, MTHFR, CBS, SHMT1, MTHFD1, RFC1, BHMT, TYMS*) and the Fitzpatrick skin phototype
567 of populations.[90] The association was assessed via collation of genotypic data from ALFRED
568 (Allele Frequency Database) and 1000 Genomes databases. The study demonstrated novel
569 relationships between skin colour and folate-related genes, with trends suggesting folate
570 genotypes are selected to maintain homeostasis in the folate system under variable UVR
571 conditions. Therefore, this paradigm, based on a UV-exposome driven folate "homeostat",
572 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 polymorphisms exhibit a latitudinal gradient in allele prevalence: Hochberg and Templeton have examined the evolutionary perspective of skin colour, vitamin D, and the VDR.[91] 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 4 VDR gene polymorphisms vary according to latitude in African and several Eurasian populations.[3] Evidence is provided that VDR FokI (f), BsmI (b), ApaI (a), and TaqI (t) allele prevalence 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 colour, vitamin D, and the VDR, and is consistent with a longer-term evolutionary trend,[3] although recent studies support short-term effects as well.[92] However, a more recent detailed molecular explanation suggests the degree of VDR gene methylation acts as a molecular adaptation to light exposure. This was explored in the context of photoperiod at conception, recent UV irradiance at 305nm, and gene-latitude effects.[87] In 80 subjects, periconceptional photoperiod was positively related to VDR methylation density, explaining 17% of the variance in methylation ($p=0.001$). Within this model, photoperiod at conception and plasma 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 BsmI mutant allele, methylation density was enhanced (p=0.01), and in the presence of the TaqI or FokI mutant allele, methylation density was diminished (p=0.007 and 0.04 respectively). When multivariate modelling was performed, plasma vitamin D, photoperiod at conception, recent solar irradiance, and VDR genotype combine as independent predictors of methylation at the VDR-CpG island, explaining 34% of variance in methylation ($p<0.0001$).

The conclusions were that duration of early-life exposure and strength of recent irradiance, along with latitudinal-related genetic factors, influence VDR gene methylation in a predictable manner. This is consistent with this epigenetic phenomenon being a molecular adaptation to variation in ambient light exposure.[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 light exposure shifts according to season and latitude, with variable exposures possible at key stages in the lifecycle, it is important that humans do not retain overly rigid phenotypes, but maintain a degree of phenotypic plasticity to allow responses that are appropriate to key periods of exposure. This is particularly true during embryogenesis and foetal development, but it is also important to ensure a flexible response over the entire life course. There is much work still to be done on folate and vitamin D in this respect, but recent work on VDR gene methylation as a molecular adaptation to light exposure suggests that such endeavour will reveal new insights into human biology[87].

CONCLUSION

This article explores an aspect of vitamin biology that is often overlooked, or considered in a limited context in relation to single nutrients. With growing interest in nutritional genetics and potential interactions with the broader exposome, solar exposure is increasingly being recognised as an important factor in human biology, and is one that implicates several vitamins in highly evolved roles. The review looks at 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, and even longer term evolutionary adaptations. The goal has been to organise disparate facts into a single synthesis that will help open up further ideas and research into this fascinating and important field.

Table 1 acts as a useful summary for this review, demonstrating six light-related phenomena that show how important many vitamin-light interactions are to human wellbeing.[1-5, 9, 10, 17-19, 24, 26, 31, 32, 34-39, 41-44, 50, 51, 54, 56, 57, 59, 61-68, 72, 73, 79-81, 83-91, 93] While some of these such as vitamin D synthesis in the skin are well known, others are less well known, or poorly characterised. For example, vitamin B3 is responsive to UV induced genomic damage. Folate, vitamins B1, B2 and B12, as well as some D vitamers are vulnerable to light. Some vitamins and pro vitamins or related compounds act as protective filters in the skin (β-carotene, vitamins C and E) and eyes (lutein, zeaxanthin). Several vitamins have been shown to act as transduction intermediaries in light-related signalling. Vitamin A as retinal in the eye is best known in this respect, but vitamin D, folate and vitamins B2 and B12 have all been shown to act in light signalling pathways. The integrity of DNA in the face of UV challenge, along with genomic expression, including UV responsive expression, relies on folate, vitamins B3, A, D and E. Finally, and quite significantly, this review explores ideas and

recent data that light-vitamin (folate/vitamin D) relationships link in to the evolution of important human phenotypes.

Many questions still exist, and the goal of this review has been to focus attention on a hugely important topic that shows how connected humans are to diet and environment, and particularly how relevant solar-related geophysical cycles are to the human lifecycle.

ACKNOWLEDGEMENTS

Author Contribution

All authors read and approved the final version of the paper. Overall idea developed by ML; Clinical perspective – MV; Genetic perspective – CM, ZY, PJ, EB; Physics perspective – JF; Article crafted – ML, PJ, EB. Final form edited by all authors.

Sources of External Funding

Patrice Jones was support through an "Australian Government Research Training Program Scholarship".

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959 **TABLE**

960 Table 1: Summary of six light-related phenomena that illustrate the importance of vitamin-
961 light interactions to human biology.
962

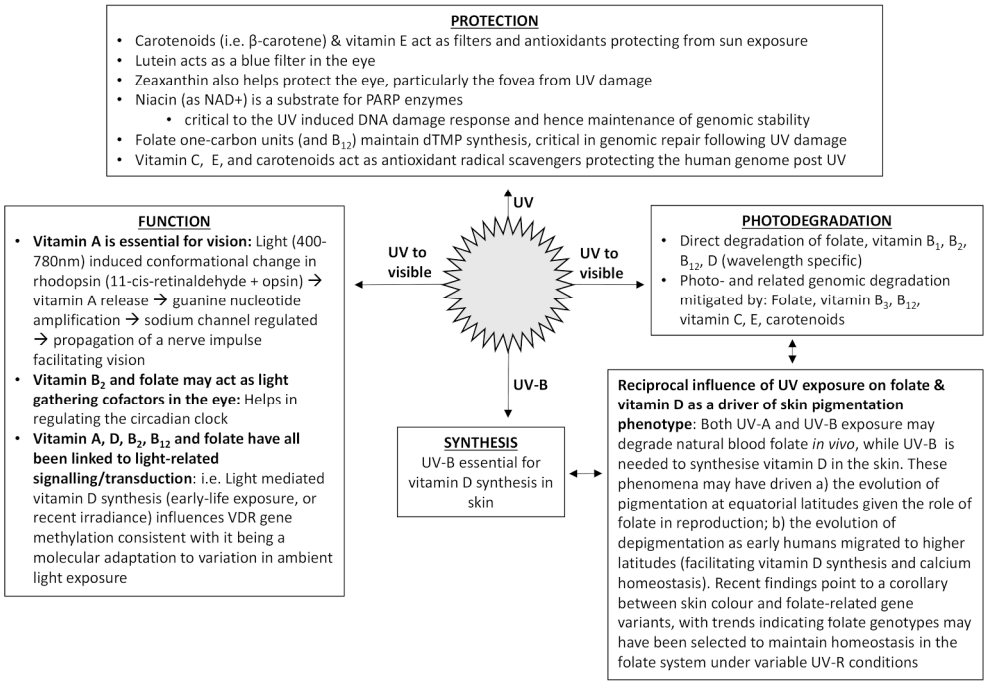
963 **FIGURE**

964 Figure 1: Integrated overview of how vitamins respond to light.
965

966 **FOOTNOTE**

967 Footnote 1: Vieth[23] points out that although the kidney acts as a classic endocrine gland,
968 producing the hormone 1,25$(OH)_2D_3$, the generic descriptor 'vitamin D' *per se*, should not be
969 linked to the term hormone, although 25$(OH)D_3$ is appropriately termed a prehormone.

Light responsive	Light vulnerable	Filtering and/or protection	UV-related DNA maintenance and repair	Light-related signalling 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 cell and serum)[4,56,79,80]	β-carotene (skin)[34-38]	Folic acid (5,10-methylene-H_4folate). Needed for dTMP and hence DNA synthesis[50,57]	Vitamin D (i.e. via VDR)[24,26,31,32]	Vitamin D (linked to evolution of skin depigmentation as humans migrated away from equator)[3,85,87,88,89,91]
Photo-transformation 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 hydroxo-cobalamin, although vitamin activity is maintained[81]	Vitamin E (tocopherols and tocotrienols) in skin[39,43]	Folic acid (5-methyl-H_4folate). 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)[56,85,86,88,89,90]
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_4folate)[5,9,10]	Vitamin-gene-UV interactions may influence embryogenesis[3,4,84]
	Wavelengths >315nm can degrade vitamin D vitamers[72]	Lutein (blue filter in eye)[44]	Antioxidant vitamins (vitamin C, E, carotenoids)[43]	*Vitamin B_{12}[83]	UV-related vitamin D formation and VDR methylation acts as molecular adaptation to light exposure[87]
		Zeaxanthin (eye)[44]	Transcription factors (vitamins A, B, D, E)[17,24,67,93]	Vitamin B_2 (FAD)[9,10]	
			SHMT expression/post-translational SUMOylation of TS (promotes dTMP synthesis in response to UV exposure)[54]		



Integrated overview of how vitamins respond to light.

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