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Achieving a Balance in Harmful and Beneficial Effects of Solar Radiation

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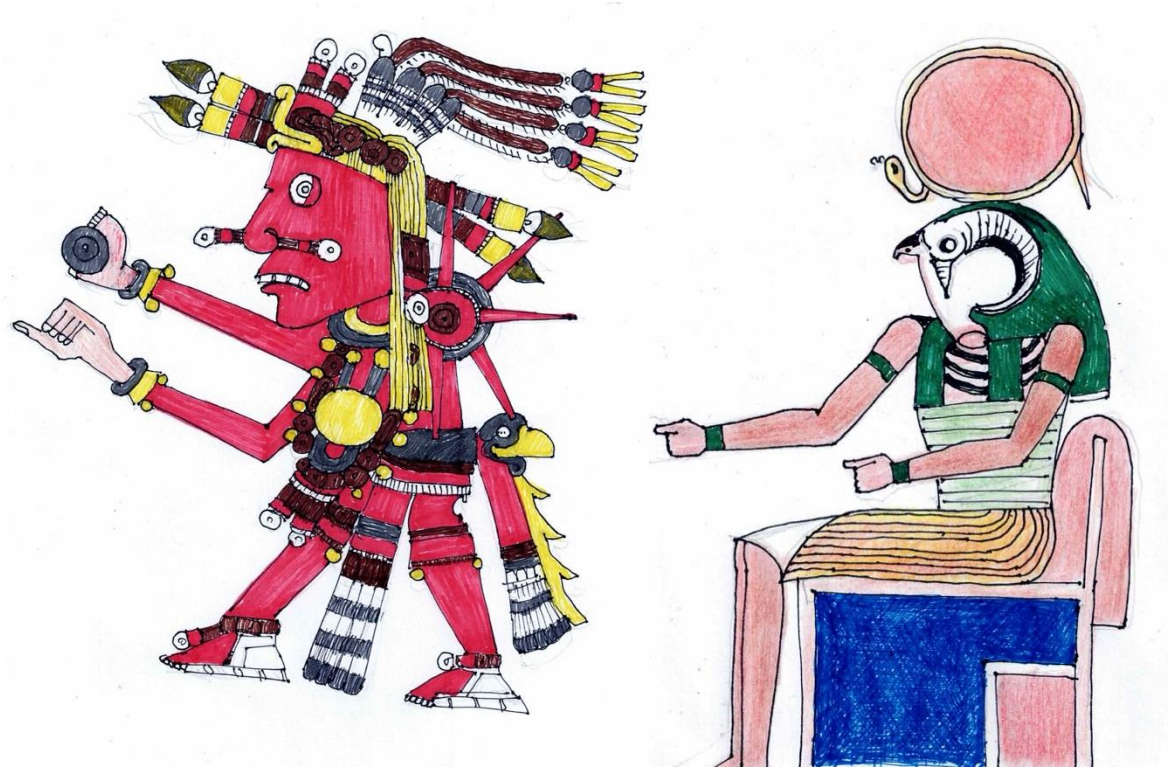
Abstract

As a skin cancer physician, I see my primary role as the prevention, identification and management of melanoma, the most dangerous solar radiation-induced skin cancer. Any pathway to reduce the load of DNA damage in melanocytes may be of relevance for the understanding of the pathogenesis of melanoma. How can we use this information to best advise our patients on protection and safest sun exposure patterns.

1. Introduction

Ancient religions believed in and worshiped many gods. Sun worship was typical of these religions. They included the ancient Egyptian Sun God Ra, believed to rule over the world as the king of the gods. The Aztecs, considered themselves 'people of the Sun', having lived through one of four 'Suns', or ages created then destroyed by their gods' struggle for control of the Sun. Only the endless repetition of ritualised human sacrifice would guarantee the Sun's reappeared to ensure life on Earth. In Hinduism, Surya (Sanskrit for 'Sun') is the solar deity and creator of the universe. The Chinese late Shang Dynasty (c.1200-1045 BCE) worshipped the Sun, to which they made sacrificial offerings, recorded as oracle bone inscriptions, some of the earliest written records found in Asia [1].

Evidence from early Chinese, Central American and Northern European cultures indicated the practice of astronomy, one of the oldest natural sciences, earliest astronomical records go back to Babylonian ~1000 BCE. Used by early cultures for timekeeping, navigation, agricultural, spiritual and religious practices. These cultures identified celestial objects with gods and spirits, a manifestation of the divine. Chief among these, the solar deity, was associated with power and strength and sun worship can be found throughout recorded history. Judaism, Christianity and Islam, which came later, shared the common tradition of the belief in one God. Belief in other Gods thought to be pagan and their worship discouraged.



Tonatiuh, an Aztec sun deity and Ra the Egyptian god of the Sun.

Celtic stone circles, including the prehistoric megalithic structure, Stonehenge, recorded the summer and winter solstices, where people came together to feast and celebrate the change of seasons marking the return of the sun and the renewal of life. The temple complexes of meso-America were constructed to record the cyclic movement of the sun, moon and Venus. Celestial events were considered the work of the Gods, harbingers of good and evil, not the least of which is the daily rising and setting of the Sun.

We seemed to have become separated from these celestial events and cycles. When did this change happen? The death of the last pagan Roman emperor, Justinian, in the 6th century saw the rise of Christianity throughout the Roman dominated Mediterranean region with suppression of Pagen beliefs. The early Roman catholic church brutally suppressing any view that questioned their doctrine. The period of European exploration saw the invasion, annexation and exploitation of foreign countries worldwide with suppression of indigenous cultures, beliefs and worship. The prudish Victorian influence favoured the body covered in clothing rather than exposed. Wealth from colonisation and slavery fuelled the industrial revolution which introduced new imperatives, work on/off replacing the movement of the sun as the daily cycle. Industrial pollution and light at night meant that a percentage of the world's population have never seen the Milky way let alone be able to follow the movement of the stars, planets and constellations. Calendars replace observation. Rural populations gravitated to cities, the centres of wealth and industry. Urbanisation resulting in the growth of cities and towns with technology becoming the new God. Artificial light sources replace the Sun making light available 24/7. Cities are proud to announce that they 'never sleep'. Is this how we want to live? Are urban life-styles good for us? Does technology provide all the answers as far as sun protection is concerned. We have evolved and adapted to be exposed to solar radiation as has the rest of the natural environment where it is the ultimate source of energy necessary for life. In modern society it now seems to be seen as the enemy, to be avoided. Why the change of

heart? Work employment and/or recreation may involve some exposure. Public heath messages and the introduction of UV-blocking creams do not seem have controlled the rising incidence of Melanoma among Caucasian populations. Are life-style practices and patterns of living playing a part? How do we achieve a balance in our exposure, as some exposure is a biological imperative.

2. Solar Radiation

The absorption of solar radiation stimulates biological systems in human skin [2]. Meaning that the UV, visible light and infrared radiation components of solar radiation can have both harmful and beneficial effects.

UV radiation is a major cause of skin photodamage. Sunburn, erythema, photodermatoses, cancer and aging [3]. UV irradiation of DNA causes mutagenic photoproducts, cyclobutene-pyrimidine dimers (CPDs) and 6-4 photoproducts [4]. This can then lead on to mutations in genes causing apoptosis and acceleration of carcinogenesis, particularly with mutations in cancer regulating genes. Weighed against this, UVB is responsible for Vitamin D biosynthesis in the skin, the most significant source of this important vitamin which has antiproliferative effects as well as being essential in bone metabolism. It is also responsible for producing several antibacterial peptides.

Solar UV rays that reach the earth's surface are a mixture of UVB (280-320 nm) and UVA (320-400nm). Even though UVB is more energetic with the ability to break covalent bonds causing direct DNA damage in epidermal cells and is the major contributor to photo carcinogenesis, UVA penetrates deeper, generating reactive oxygen species damaging the epidermis and dermis, more responsible for photo-aging effects. Visible light, less energetic again but penetrating deeper is also responsible for oxidative effects.

UVA represents the vast majority of UV reacting the earth's surface, but the UVA/UVB ratio varies with latitude, season of the year, hour of the day, local meteorology and condition of the ozone layer leading to different exposure conditions. The solar elevation angle (SEA), the angle between the horizon and the sun, greatly influences UV irradiation. The higher the sun, the greater the UVB component. Thus, exposure can be divided into extreme (zenithal) and non-extreme (non zenithal), with different effects. In everyday outdoor activity, non-extreme sun exposure, SEA <45º (for latitudes 60ºS to 60ºN), does not induce visible short-term effects but will lead to pigmentation and may have UV-induced deleterious consequences. *In vitro* simulations induced oxidative stress and alteration in expression of genes involved in several skin and stress managing functions in both compartments [5]. Production of reactive oxygen species (ROS) can induce oxidative nucleotide damage such as the formation of 8-hydroxy-2'-deoxyguanosine [6,7]. Therefore, enhancement of DNA repair processes is vital for control of solar irradiation induced skin damage.

3. Natural Skin Defense Mechanisms

The skin displays a plethora of defense mechanisms to deal with the challenges imposed by solar radiation.

- A local neuroendocrine system with local and systemic effects capable of producing biogenic amines, catecholamines, serotonin, melatonin and proopiomelanocortin (POMC) [8-10].

- A melanin-producing system for shielding protection against UVR effects [11].
- an oxidative anti-stress system [12].
- a local circadian clock to coordinate skin and body physiology as well as behavioural patterns to cyclic diurnal and seasonal changes [13].
- a complex DNA repair system [14].
- a system to shed damaged cells [15].
- The skin also produces a full range of photo-sensitive opsins and their photo-transduction cascades but is still not determined how influential is the role of these opsins in sensing and protection from solar radiation [16].

How can we best take advantage of this integrated protective system in our daily lives to minimise risk of melanoma?

4. Melanocortin

UVR is a recognised epidemiological risk factor in the incidence of melanoma related to the relative resistance of melanocytes to UVB-induced apoptosis, leading to an accumulation of UV-induced DNA mutations in melanocytes over their extended lifespan.

The skin has a complete independent neuroendocrine system. The majority of skin cell types express proopiomelanocortin (POMC). UVR stimulates synthesis of POMC, generating peptides, including α melanocyte-stimulating hormone, (αMSH), adrenocorticotrophic hormone (ACTH), and β endorphin. With release of αMSH, keratinocytes upregulate eumelanin synthesis in melanocytes and altered melanocyte morphology protects it against immune system damage, UVR-induced apoptosis and DNA damage [17]. Böhm et al showed that αMSH blocked UVB-induced apoptosis of melanocytes *in vitro* [18]. αMSH treated melanocytes enhanced capacity to repair UV-induced DNA photoproducts and inhibited UVR generated ROS [19]. The anti-apoptotic activity of αMSH, however, is not mediated by changing melanin synthesis in melanocytes, changes in cell cycle nor changes in expression of apoptosis related proteins. UVR-induced apoptosis is reduced through induction of nucleotide excision repair (NER), the genomic stability pathway responsible for clearing UV photolesions from DNA to avoid mutagenesis. αMSH increases XPC levels (damage recognition), cH2AX (assembly of repair proteins) and NR4A (colocalises with other repair enzymes to increase repair) [19]. αMSH reduces oxidative stress by increasing activity of catalase, the enzyme responsible for the reduction of H_2O_2 [20]. It also increases activity of antioxidants haem oxygenase and peroxiredoxin along with active repair of oxidative damage by elevating levels of APE1 and OGG1 in the base excision repair (BER) process.

4.1 The influence of the melanocortin 1 receptor

αMSH is also a ligand for the melanocortin 1 receptor (MC1R) on melanocytes and keratinocytes influencing constitutive pigmentation and tanning ability [21]. However, the receptor is highly polymorphic in Caucasian populations and variants can produce a fair-skinned, red-haired phenotype that has a strong association with melanoma risk. Over half the Australian population carry at least one variant allele of this gene, so whatever their Fitzgerald skin type they can be at increased risk [22].

The extrinsic mutagenic effect of UVR interacts with intrinsic skin phenotype. The balance between eumelanin and pheomelanin influencing skin, hair and eye colouration. The *MC1R* gene is intimately involved as a major regulator of

pigmentary traits [23]. The variants can result in varying degrees of loss of receptor signalling, reducing eumelanin synthesis leading to fairer skin, poorer tanning ability and increased sensitivity to UV exposure.

It is well established that pigmentation is the main photoprotective mechanism against sun-induced skin cancer. Melanoma risk is highest in individuals with low constitutive melanin content or lower eumelanin to pheomelanin ratio and poor tanning ability. Individuals with light skin colour develop more DNA photoproducts when exposed due to greater penetration of UV rays through epidermal layers. DNA damage corresponds inversely with an individual's minimal erythema dose (MED). Eumelanin is superior given its resistance to photodegeneration and ROS scavenging ability with increasing evidence that melanoma is an oxidative stress-driven tumour [24]. This is exemplified by the fact that total melanin and eumelanin correlated inversely with the extent of UVR-induced growth arrest, apoptosis and induction of CPDs but not with H_2O_2 release in melanocytes expressing functional MC1R. In comparison, melanocytes with loss-of-function MC1R, regardless of melanin content, sustained more UVR-induced apoptosis and CPDs and exhibited reduced CPD repair. Therefore, melanin content and MC1R function are independent determinant of UVR-induced DNA damage in melanocytes (FIG. 1).

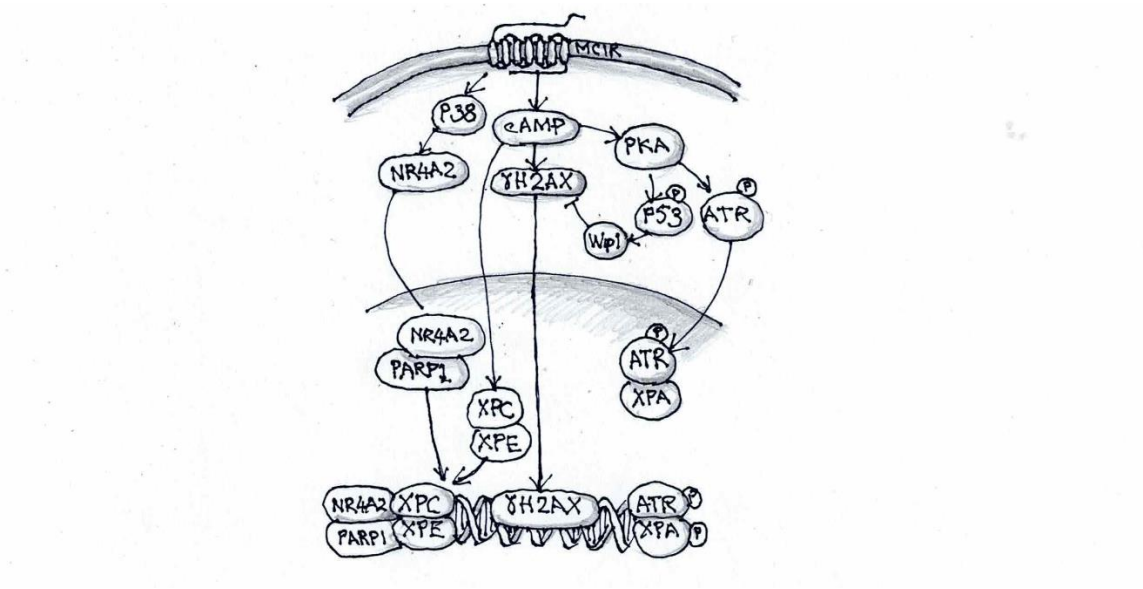


FIG. 1. **MC1R and melanocyte genomic stability.**

MC1R promotes genomic stability through multiple mechanisms. Activation induces NR4A2 translocation to the nucleus (p38/PARP1 dependent). It co-localises with XPC and XPE (damage sensing) at sites of UV-induced DNA damage. Levels of XPC and γH2Ax are also elevated promoting DNA repair complexes. PKA activation promotes phosphorylation of p53 and ATR. ATR complexes with XPA in the nucleus. The complex translocates to sites of UV-induced DNA damage to enhance Nucleotide excision repair. (Adapted from Wolf Horrell et al 2016 [25]).

5. Adaptive Changes Induced by Red Light

Considering that studies of the effects of low intensity red laser light on skin have reported adaptive changes counteracting stress-induced damage, such as UVR, including acceleration of wound healing by stimulating cell proliferation and growth of

fibroblasts [26-28], and also, accumulating evidence suggesting that beneficial effects of visible red light might be useful in photo medical applications [29,30], Kim et al undertook studies of visible-wavelength red light investigating the protective effects on UV-induced DNA damage and mechanisms of repair in human skin. Firstly, they found that visible red light produced a protective effect in fibroblasts by enhancement of growth arrest and DNA damage inducible, alpha (GADD45A)-mediated base excision repair (BER) activity [31]. They then when on to determine that these protective effects involved modulation of gene expression that enhanced the adaptive response to redox and inflammatory balancing by the differential up-regulation of genes in DNA excision repair processes [32].

Bulky photoproducts such as CPDs are induced by UVR and are traditionally considered to be repaired by a nucleotide excision repair (NER) pathway. Levels of photoproducts were examined after visible red light and UV irradiation. There was a statistical difference in the formation of photoproducts showing the protective effect of red light. However, they could find no difference in the expression of NER factors, such as XPC and G, between control and red light treated cells in their system. APE1 has been shown to be able to incise UV photolesions in XPC deficient cells [33]. In fact, Vrouwe et al showed that UV photolesions elicit ATR kinase-dependent signalling in non-cycling cells through NER-dependent and -independent pathways, processing UV photoproducts through generation of strand breaks, ultimately preventing the transition from G_1 to S phase [34]. This suggested the activity of both BER and NER on UV photolesions. Kim et al then focused on BER mechanisms in the repair of oxidative DNA lesions, UVB a known inducer of oxidative stress.

6. Base Excision Repair

Base excision repair (BER) is a major pathway for the repair of base damage caused by oxidative stress, including UVR. In the BER pathway the modified base is initially removed by DNA glycosylase, which generates apurinic/apyrimidinic sites that are recognised and incised by apurinic/apyrimidinic endonuclease (APE1) [35,36]. GADD45A interacts with APE1 [37] and interaction between GADD45A and proliferating cell nuclear antigen (PCNA), which recruits factors to DNA repair sites, affecting APE1 activity [38] (FIG. 2).

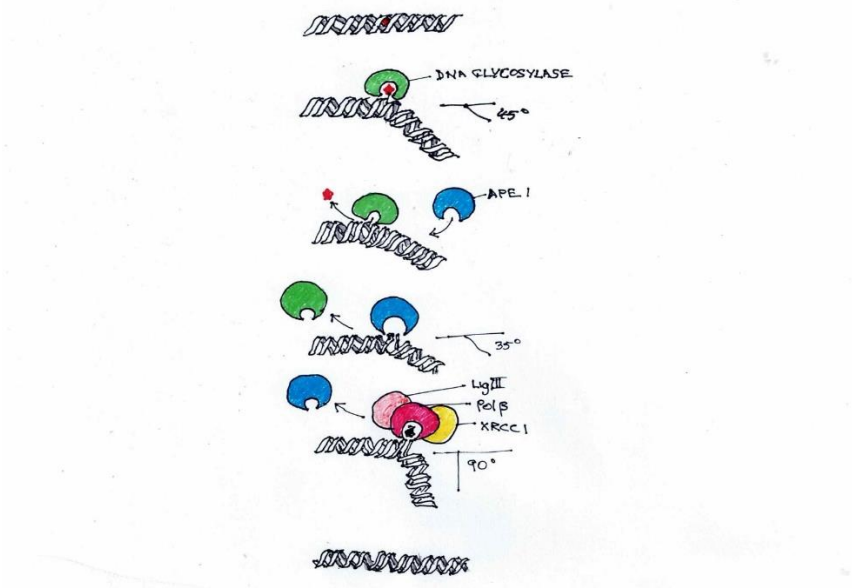


FIG. 2. **BER short-patch pathway.**

BER is initiated by a DNA glycosylase, that specifically recognises and binds the base lesion. Upon encountering a substrate base the glycosylase flips the base out of the base-stack into its catalytic site pocket where specific contacts examine the substrate base and position it for nucleophilic attack to the N-glycoside bond. Release of the substrate base results in an abasic site, which is further processed by the AP-endonuclease, APE1, that cleaves the phosphate backbone 5' to the abasic site, producing a 3'OH and a 5'deoxyribose-phosphate moiety (5'dRP). Polymeraseβ (*Polβ*) hydrolyses the 5'dRP and fills in the single nucleotide gap, which is sealed by the DNA ligase III (*LigIII*), supported by the scaffold protein XRCC1. Thus, restoring the original base sequence. The increase of DNA bending from DNA glycosylase to Polβ might support directionality of the handover from one BER factor to the next.

7. DNA Glycosylates-an Ancient Family of DNA Repair Proteins

The consideration that cells must possess an ability to remove uracil from DNA, which arises either by misincorporation of deoxyuridine monophosphate (dUMP) during DNA replication or by hydrolytic deamination of cytosine, led to the discovery of an enzyme capable of cleaving uracil deoxyribose bonds, including one of the structurally distinct mammalian glycosylases, the uracil DNA glycosylases (UDGs). Although DNA glycosylases are optimally suited for repair of damaged DNA bases, the ability to recognise and excise modified bases can be used to edit DNA at specifically marked sites. The UDG family, have additional functions in innate immunity and antibody diversification in the adaptive immune system, as well as regulation of gene expression and epigenetic maintenance [39].

8. Pre- and Post-Red-Light Treatment

Normal human dermal fibroblasts were exposed to visible red light before and after 0.1J/cm^2 UVB treatment. Kim et al found a significant decline in the level of DNA damage, assessed by decline in UV-induced apoptosis, in both pre- and post- red light treated groups. Apurinic/apyrimidinic sites where also markedly reduced. They also found that UVB-induced DNA strand breaks were decreased in an artificial 3D skin model (containing keratinocytes, fibroblasts and dermal matrix-containing fibroblasts), indicating that visible red light has a protective effect in human skin cells. They determined that visible red-light exposure affected GADD45A-mediated BER through both GADD45A/APE1 interaction and increased APE1 activity. UVB-induced DNA damage was reduced by visible red light in an APE1 dependent manner. Their results suggested that protective effects of visible red light might be mediated by activating transcription factor 2 (ATF2)-dependent DNA repair mechanisms. ATF2 has a role in stress response, cell growth and immune response by transcriptional regulation, binding to the GADD45A promoter region [31].

GADD45A expression is induced via both p53-dependent and p53-independent pathways depending on the stimulus [40]. Visible red light impaired p53 binding activity on the GADD45A promoter suggesting the independent pathway. Whereas they found that visible red light increased ATF2 binding activity on GADD45A and increased GADD45A /APE1 interaction. A tumour suppressor activity of ATF2 has been demonstrated in keratinocytes. Unlike the strong expression in normal skin, both squamous and basal cell carcinoma samples exhibited a significantly reduced nuclear staining [39]. This evidence supports a role for ATF2 modulation in GADD45A-mediated DNA repair mechanism on visible red light exposure [31].

In a subsequent study Kim et al used the same wavelength (660nm) and fluence (60J/cm^2) red light that had shown protective effects on dermal fibroblasts [31]. They observed wound healing, response to DNA damage and regulation of inflammation and oxidative stress responses were enhanced by red light irradiation. They found that red light-induced interactions among differential expressed genes of heat shock proteins, Cox2, IL-6, LIF and ATF3 were maintained despite UVB-induced changes suggesting potential pathways identifying photoprotective effects of red light. Figure 3. Heat shock proteins (HSPA1A and HSPA5) have protective functions against UV-induced skin damage [42,43]. Cox-2 modulates redox, inflammatory and anti-inflammatory responses [42]. This is linked to inflammatory activity of IL-6, LIF and ATF3. Cytokine LIF contributes to increased cell survival [45]. ATF3 modulates immune responses and is central to a cellular adaptive network [46].

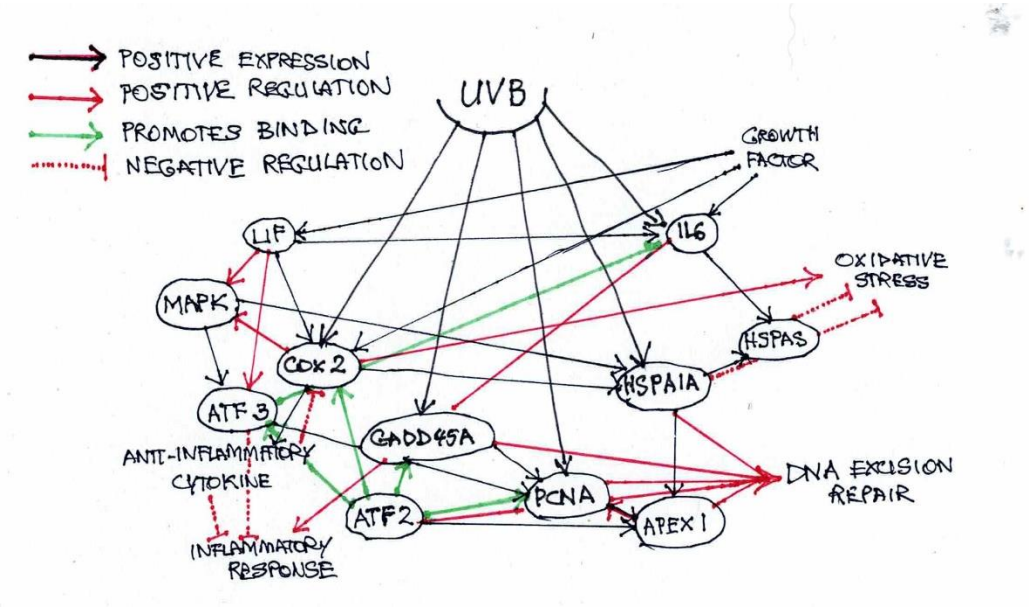


FIG. 3. **Pathway analysis of networks related to biological effects of visible red-light pretreatment against UVB.**

The GADD family of proteins play a crucial role in genomic stability protecting the epidermis against UV-induced tumorigenesis. ATF3 is a transcriptional regulator of GADD45A and helps maintain genomic stability upon UV-induced DNA damage. (Adapted from Kim et al 2019 [32]).

In particular, they found close links between visible red-light irradiation and DNA excision repair pathways. The GADD family of proteins play a crucial role in genomic stability. GADD45A regulates cell cycle and apoptosis and stimulates DNA excision repair. GADD45B interacts with PCNA and is involved in cell growth and apoptosis. ATF3, downstream of ATF2, is a transcriptional regulator of GADD45A, helping to maintain genomic stability upon UV-induced DNA damage.

UVB irradiation can causes direct physical damage to DNA and proteins leading to impairment of some cellular functions. The skin shows an early response, and their findings suggested that this was similar to the effect of red-light pretreatment on UVB irradiated skin.

9. Significance to Patterns of Solar Exposure

How do these finding have relevance to the behaviour of the diurnal human in relation to solar exposure?
Early morning solar radiation is coming in at an angle low to the horizon. This means that the irradiation is having to travel through a thicker layer of atmosphere to reach the individual. This tends to attenuate the shorter, more dangerous wavelengths of light at the UV end of the spectrum and accentuate the longer wavelengths at the red end of the visible spectrum. Even without scientific evaluation this is obvious to the observer through red highlights in the sky and reflected on clouds at this time of day. This represents a signal to arise and become active or did to our less sophisticated ancestors. This early morning exposure provided an initial boost to adaptive responses, particularly DNA repair mechanisms, pre-treating the skin prior to more intense solar exposure later in the morning. The same adaptive response is available in the evening as well, upregulating DNA repair mechanisms at twilight after daylight exposure. Our behaviour needs to be aligned with this simple circadian cycle to get the natural beneficial effects by being exposed to solar radiation at twilight, at both the start and end of the daylight phase of diurnal day. Unfortunately, this pattern seems to be lost to sophisticated urban living where the individual is separated from natural cycles by spending prolong periods indoors under artificial light, which tends to be more at the blue end of the visible spectrum, whether through overhead lighting or screens on devicies. We no longer need to hunt or forage for food so pressure to arise early is no longer there, particularly with prolonged nocturnal activity. We all appreciate the danger of UV irradiation with the sun overhead but fail to appreciate the beneficial effects of sunlight at dawn and dusk to take advantage of this protective effect.

10. Conclusion

Individuals with Fitzpatrick type 1, fair skin and poor tanning ability need to take advantage of all possible protective measures and probably best avoid high intensity solar exposure completely. Individuals with extensive freckling, high naevus counts, large or irregular naevi as well as a personal history or strong family history of melanoma also need to show some extra caution but for the rest of the population moderate sun exposure can be tolerated and extra protective measures utilised in higher risk situations.

The human body is designed for outdoor exposure and natural protective measures can be accessed by sensible exposure patterns. Regular mild to moderate sun exposure is necessary to allow for maximal photoadaptation. Recreational sun exposure is best early morning, combining sunrise exposure for circadian photoentrainment and receiving the pre-exposure boost in DNA repair through the longer wavelength red end of the visible spectrum. Evening recreational exposure is second best, although not accessing the benefits of the pre-exposure DNA repair boost. Exposure at twilight receiving both pre and post exposure DNA repair boost is beneficial particularly for occupational, longer-term exposure. Melanopsin, a light sensitive protein in the skin is considered by some investigators to be a UV sensor, so maximal skin exposure is possibly also beneficial to achieve maximum photoadaptation, particularly for normally intermittently exposed skin surfaces.

Melanoma still potentially presents a serious medical issue despite the best intentions of public health messaging and available protective clothing and creams but rather than advocate avoidance of sun exposure, I suggest sensible sun exposure taking best advantage of the body’s extensive range of natural protective mechanisms as well as its other potential beneficial effects.

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