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The Circadian Control of Skin and Cutaneous Photodamage†

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Abstract

Biologically, light including ultraviolet (UV) radiations is vital for life. However, UV exposure does not come without risk, as it is a major factor in the development of skin cancer. Natural protections against UV damage may have been affected by lifestyle changes over the past century, including changes in our sun exposure due to working environments, and the use of sunscreens. In addition, extended 'day time' through the use of artificial light may contribute to the disruption of our circadian rhythms; the daily cycles of changes in critical bio-factors including gene expression. Circadian disruption has been implicated in many health conditions, including cardiovascular, metabolic, and psychiatric diseases, as well as many cancers. Interestingly, the pineal hormone melatonin plays a role in both circadian regulation, as well as protection from UV skin damage, and is therefore an important factor to consider when studying the impact of UV light. This review discusses the beneficial and deleterious effects of solar exposure, including UV skin damage, Vitamin D production, circadian rhythm disruption, and the impact of melatonin. Understanding of these benefits and risks is critical for the development of protective strategies against solar radiation.

Introduction

The electromagnetic solar spectrum, which includes visible light and ultraviolet (UV) radiations among other radiations, plays a significant role in a variety of biological functions within a living system. In earth's natural environment, we are exposed to the solar radiations in a regular 24 hour cycle which varies according to the season. These radiations may have beneficial as well as harmful effects to living organisms. For example, UV radiation has many effects on the environment and the organisms inhabiting the planet. The most beneficial impact of UV light in humans is its essential role in the production of Vitamin D_3 in the skin. Calcitriol, the active form of vitamin D_3, participates in a variety of the body's protective functions, including DNA damage repair and immune function. However, excessive exposure to UV radiation can have a variety of adverse effects on the skin, including cancers of the skin. Studies have suggested that solar radiations are important regulators of 'Circadian Rhythms', which by definition are physical, mental and behavioral changes that follow an approximately 24 hours cycle that primarily responds to light and dark in an organism's environment.

Unfortunately, the lifestyle factors of the modern era such as the widespread use of artificial lights to extend our 'daylight' time, contribute adversely to the biological processes leading to unwanted conditions and responses. For example, excessive UV exposure to skin can cause skin aging, pre-cancerous skin conditions, and melanoma and non-melanoma skin

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cancers. The modern research is suggesting that circadian rhythms may be involved in the development and/or progression of cancer because it is believed that approximately 10% of the genes oscillate according to the body's circadian clock. Their functions are widely varied but are connected with the normal cell cycle, metabolic functions, and DNA damage repair. Normal circadian rhythms are therefore essential for the body's natural defense against diseases such as cancer. It is believed that a deregulation of oscillatory expression and function of circadian rhythm regulatory genes over the 24 hour period enhances the risk of carcinogenesis. Light and dark cycles influence the circadian clock and the daily oscillations of the genes controlled by the circadian rhythms. Although artificial light can also contribute to the circadian network, the solar light is its major regulator. With increased exposure to artificial light, there is an increase in the probability of disrupting these rhythms, since circadian rhythm gene expression has been shown to be lower in artificial light relative to natural light.

Altered circadian rhythm disrupts the DNA damage responses and cell cycle regulations as well as the expression of the pineal hormone melatonin. Like other circadian factors, the circadian control of melatonin secretion is regulated by the circadian clock machinery which depends on a network of genes and their rhythmic oscillations driven by the circadian timing system located in the suprachiasmatic nucleus (SCN) of the hypothalamus as well as peripheral oscillators located in cells. Dysregulated circadian control of melatonin can contribute to the adverse effects of UV radiation on the skin, as melatonin has been shown to have a protective role against UVB skin damage. Further, melatonin is a strong anti-oxidant and can attenuate UV radiation mediated oxidative stress. Indeed, low levels of melatonin have been associated with increased risk or shown to play a role in the development of several cancers (1–5).

Light Spectrum, UV Radiation and Skin Cancer

The Earth is continuously exposed to a solar electromagnetic spectrum, irradiated by light protons ranging from infrared light at 780–5000nm, to visible light at 400–780nm, and UV light at 200–400nm. Radiation from the UV end of the solar electromagnetic spectrum provides energy that is essential for biological life, but it does not come without risk. Approximately 5% of the radiant energy from the sun is in the UV range, which consists of wavelengths that are shorter than those of the visible spectrum and longer than X-rays. There are notably 3 major subtypes of UV rays, UVA (320–400 nm), UVB (290–320 nm), and UVC (200–290 nm) (6, 7). The energy transfer of UV radiation is invaluable to life on the planet; however, it does not come without risk as this very energy is also responsible for damage to DNA and other unwanted effects (8). UV radiation is a potent mutagen which is currently accepted as being the major cause of human skin cancers (9). Both solar and indoor UVR exposures contribute to carcinogenesis of the skin. The cellular effects of UV radiation are induced primarily through a chain of events that lead to the induction of DNA lesions. The chemical nature and efficiency of the formation of DNA lesions is largely dependent on the type of UV radiation and its wavelength, along with the base composition of the DNA at the lesion site (10, 11). Different wavelengths of UV irradiance display different levels of skin penetration, resulting in a diverse set of effects (12). The absorption spectra of DNA for wavelengths greater than 300 nm increases with the number of guanine-cytosine bases, demonstrating the relationship of the DNA content and the susceptibility to UV absorption (13).

Skin, the first line of defense against environmental toxicants, is continuously exposed to the sunlight and consequently suffers directly from the deleterious effects of UV radiation (14–16). Solar UV radiation is the primary source for the development of cutaneous cancers which affect the Caucasian population more frequently. The estimated incidence rate for these cancers is approximately 1 million new cases diagnosed every year within the United

States alone (17). Most skin cancers diagnosed are non-melanoma skin cancers consisting of squamous cell carcinomas (SCCs) and basal cell carcinomas (BCCs) accounting for ~96% of all skin cancers, while melanoma accounts for the remaining 4% (14, 17). Most skin cancers develop on sun-exposed areas of the skin. The non-melanoma skin cancers are more easily treatable whereas melanoma, the least common form of skin cancer, is often lethal. UV radiation-induced skin cancer involves three distinct stages identified as initiation, promotion, and progression, which are mediated by alterations to cellular, molecular, and biochemical mechanisms. Initiation is the first step in the photocarcinogenesis process, involving genetic alterations which lead to DNA translational changes. Once these mutations occur, they are thought to be irreversible. These DNA mutations lead to alterations in signal transduction pathways, which in turn cause clonal expansion of initiated cells, but the clonal expansion is still considered to be reversible. If the initiated cells go through clonal expansion and the carcinogenesis processes is not halted, tumor progression begins with the malignant transformation of papillomas to carcinomas (18, 19).

It has been suggested that modern lifestyle choices such as increasing outdoor activities and sun-tanning are responsible for increasing cases of skin cancers, which has led to increased use of sunscreens. Outdoor workers get 3–9 times the amount of UV exposure compared to that of the average indoor worker (20–22). Surprisingly, although outdoor workers are much more exposed to solar UV, it is the indoor workers' incidence of cutaneous malignant melanoma (CMM) that has increased at an exponential rate since before 1940. The lifetime risk assessments demonstrate that those with lower exposures rates have an increased risk for developing CMM (23, 24). It has also been established that outdoor workers have lower incidence rates of CMM (25–27). This does not follow the same patterns as squamous cell carcinoma (SCC) where it is the accumulated UV exposure that determines the risk for development. The difference in incidence numbers between the two groups has brought about speculation regarding the benefits of sunscreens. Most sunscreens block UVB but allow for increased penetration of UVA, leading to a reduction of cutaneous vitamin D levels with a possible inverse correlation to the increase in the incidence of melanoma (28).

Of the UV radiation emitted by the sun, UVC is effectively absorbed in the upper atmosphere preventing it from reaching the earth. On the other hand, UVA and UVB reach the earth and penetrate the skin, causing a variety of adverse effects (29, 30). UVA makes up approximately 95% of the total UV energy that reaches the surface of the Earth, while UVB makes up the remaining 5%. While UVB only makes up about 5% of the UV radiation that makes it to the earth, it is thought to be most responsible for skin cancers. UVB has been shown to have less penetrating power than UVA and mainly acts on the epidermal basal layer of the skin. It is the typical source of sunburns, inflammation, DNA damage, oxidative stress, free radical production, immunosuppression, photoaging and skin cancer (31–35). In addition to these negative effects, UVB also has an important and extremely beneficial function in the production of vitamin D_3.

UV Radiation and Vitamin D

Vitamin D_3 is generated in humans from photo-initiation by the action and energy supplied by UVB (36). The UVB acts on subcutaneous 7-dehydrocholestral (7-DHC) to convert it into pre-vitamin D_3, after which it is thermally converted into 25-hydroxycholecalciferol ($25(OH)D_3$) (calcifediol) (37, 38). Vitamin D_3 is then converted primarily in the kidneys and liver into its most hormonally active form, 1α,25-dihydroxvitamin D_3 or calcitriol, which has been shown to have an anti-tumor effect *in vitro* (39, 40). Calcitriol has also been shown to be formed in melanoma cells and keratinocytes where it inhibits the growth of tumors (41, 42). Calcitriol controls or eliminates melanoma cells through signaling pathways for either apoptosis or cell growth inhibition after binding to the vitamin D_3 receptor on the nuclear membrane but does not affect normal melanocytes (43–47). Many types of cancers

exhibit these effects when exposed to calcitriol such as melanoma, leukemia, prostate, colon, and breast (48–50). Calcitriol may regulate nearly 60 genes (49) through which it can down-regulate proto-oncogenes such as c-myc, c-fos and c-jun, as well as upregulate gene responsible for cell cycle arrest, DNA repair and affect the immune system (49, 51–53). This demonstrates the beneficial effects of UVB, but UVA can only break down vitamin D_3 and do so while it is bound to vitamin D binding protein (54). This break down of vitamin D_3 can also occur within the circulating plasma as UVA can penetrate to the dermal layer of the skin and reach the capillaries (55). This may be of significant interest when evaluating exposures and protection from UV radiation with indoor workers as the limited amount of vitamin D_3 production they have during the workweek and UVA from window exposure is able to break down existing serum bound or newly formed vitamin D_3 in the skin. Beyond the breakdown of vitamin D_3, solar UVA exposure, while indoors from window penetrance, has further detrimental biological effects. Some of these include oxidative stress (56–59), damage to organelles, red blood cell lyses (57), humoral immune suppression (60) and photoaging. UVA is capable of causing DNA damage and mutations, which has led to SCC development in mice (61–64). This suggests that UVA exposure without UVB exposure will cause mutations and deplete vitamin D_3 in the skin. The lack of UV exposure leaves the skin with inadequate amounts of cutaneous vitamin D_3, and together these environmental stressors promote CMM (28).

In summary, UVB exposure is necessary for maintaining a healthy lifestyle due to its important role in the synthesis of vitamin D_3. However, in excess, it is well known that UVB light causes a number of adverse health effects ranging from sunburn to cancer.

Effect of UV on Circadian Rhythms

Despite the fact that sunlight is a major regulator of circadian rhythms, limited information is available on the effects of UV radiation on circadian rhythms. A study on the effects of UV light on keratinocytes shows that UVB is capable of suppressing several of the genes involved in circadian rhythm regulation for a period of up to 24 hours (65). While this mechanism requires further study, it suggests that light may have more than one route of action in the maintenance of these rhythms.

A very recent study has shown that circadian rhythms may also have an impact on the skin's ability to cope with UVB damage (66). The xeroderma pigmentosum group A (XPA) protein is critical to the body's DNA damage repair mechanism, as it is one of several proteins which carry out DNA excision repair. Gaddameedhi and colleagues have shown that XPA oscillates in the skin with circadian rhythmicity, peaking in mice in the early evening, and reaching its lowest point of expression in the early morning. Mice subjected to UVB light in the early morning showed five-fold higher frequency and a faster growth rate of skin cancers than mice subjected to the same level of UVB light in the early evening (66). This shows that normal circadian oscillation is important in the body's natural defense against UV-induced skin cancer, and should be considered when studying UV exposure and cancer. Based on this study, the authors suggested that the circadian rhythm could be exploited to reduce skin cancer incidence in humans. Since the core circadian clock and their outputs exhibit opposite phases in mice (being nocturnal species) versus humans (being diurnal species), the authors of this study predicted that humans will have a higher rate of repair in the morning and would be less prone to the carcinogenic effect of UV radiations early in the day. The authors further advised for humans to restrict their occupational, therapeutic, recreational, and cosmetic UVR exposure to the morning hours. However, further in-depth studies are needed in this direction.

Regulation of Circadian Rhythm

Since as many as 10% of the genes in the body are believed to have circadian oscillation, circadian rhythms impact a wide variety of physiological functions. This is important when considering the effects of UV light on the body, since the group of genes under circadian control includes those involved in the DNA damage repair response, cell proliferation, cell cycle and cell-cycle arrest, and apoptosis [reviewed in (67)]. Light also plays an important role in regulating the circadian rhythms within the body. Circadian rhythms are entrained by a central pacemaker in the SCN region of the brain when light is sensed by the retina [reviewed in (68)]. In this way, the body is able to adjust its own clock to the light/dark cycles in the environment.

The molecular circuitry behind the oscillation of circadian rhythms is complex. However, at a basic level, several genes/proteins have been recognized as being essential to the function of the core clock mechanism in mammals (Figure 1). These proteins function in a transcriptional-translational feedback loop, the positive limb of which includes the protein CLOCK (69–71) and the aryl-hydrocarbon receptor nuclear translocator-like protein (ARNTL), also known as BMAL1(71). Both CLOCK and BMAL1 are members of the bHLH-PAS-containing family of transcription factors, containing the basic helix-loop-helix domain, which binds DNA, as well as the ligand-binding PAS domain. They begin the circadian cycle when they form a heterodimer through binding at their PAS domains (72). As a heterodimer, they bind to E-box elements in the promoters of their target genes, inducing transcription (71). Several of these target genes then function in the negative limb of the transcriptional-translational feedback loop. They are Cryptochrome 1 and 2, (CRY1 and CRY2) (73), and Period 1, 2, and 3 (PER1, PER2, and PER3) (74). During the positive phase of the circadian cycle, PER1 and PER2 are primarily cytoplasmic proteins, and require binding to the cryptochromes (73) or to PER3 (75) for nuclear translocation. Once in the nucleus, the Period/Cryptochrome complex interferes with the CLOCK/BMAL1 induced transcription (76), modulating expression of the target circadian proteins, thereby completing the cycle.

It is known that the expression level of BMAL1 is regulated by REV-ERB α and β, and ROR α, β, and γ, with the REV-ERBs repressing BMAL1 transcription and the RORs activating it (77, 78). Thus, the available levels of BMAL1 in the cell provide for a regulatory mechanism for the positive limb of the circadian mechanism. It is also clear that post-translational modifications play an important role in regulating this system. The phosphorylation states of PER1, PER2, and CLOCK are important for their nuclear localization. PER1 contains a nuclear localization signal (NLS) adjacent to a binding site for casein kinase 1 epsilon (CKIε). PER1 export to the cytoplasm is dependent on masking of the NLS through phosphorylation by CKIε.(79) In addition, both PER1 and PER2 have a nuclear export signal (NES) located near their PAS domains, facilitating export to the cytoplasm.(80) CLOCK's nuclear localization oscillates with circadian rhythmicity and depends on its heterodimerization with BMAL1 and subsequent phosphorylation.(72) A second post-translational modification which plays a role in regulation of the core clock circuitry is the acetylation of BMAL1. In the normal cycle, after the formation of the CLOCK/BMAL1 heterodimer and initiation of the transcription of its target genes, CLOCK acetylates BMAL1 at its Lys537 residue, allowing for recruitment of CRY1 and subsequent repression of BMAL1-CLOCK activity (81). It has been shown that the class III histone deacetylase (HDAC) SIRT1 is responsible for de-acetylation of BMAL1 during the opposite phase of the circadian cycle, resetting the system to its original state in preparation for a new cycle (82).

Circadian Rhythms in the Skin

While the circadian rhythms within the body are thought to be synchronized through the central pacemaker in the SCN, peripheral cells have also been shown to display rhythmic oscillation on their own, both in the body and when isolated in *in vitro* cell culture systems (74, 83–85). This is especially important when assessing the effects of light, both visible and UV, on skin cells. The circadian genes *Clock* and *Period 1* have been shown to be expressed in various human skin cells, including keratinocytes, melanocytes, and dermal fibroblasts (86). In addition, the core clock genes are transcribed in human skin tissue with normal circadian frequency, with *Per1*, *Cry1*, and *Bmal1* levels peaking in the early morning, late afternoon, and night, respectively (87). There is some evidence that the normal levels of circadian rhythm gene expression in the skin can be suppressed by UVB radiation, as demonstrated for *Per1*, *Clock*, and *Bmal1* in human keratinocytes (65). As discussed above, Gaddameedhi et al have shown that the time of UVB light exposure may dictate the tumorigenic potential and frequency of skin tumorigenesis *in vivo* (66). Since skin is continuously exposed to solar radiation, the regulation of cutaneous circadian rhythm *in vivo* needs to be carefully studied, as its disruption can lead to a variety of skin health issues.

Dysregulation of Circadian Rhythms and Health Effects

Since light has a direct and substantial impact on the entrainment of circadian rhythms, disturbances in natural light patterns, such as the increased use of artificial light at night, could potentially lead to the dysregulation of circadian rhythms. Even before the circadian molecular mechanism was elucidated, it was shown through serum cortisol and temperature measurements that light applied in irregular patterns could shift, amplify, or greatly suppress circadian oscillations in humans (88, 89). Prior to the discovery of the circadian clock network, the pineal hormone melatonin was also frequently used to study circadian rhythms, as its oscillation in response to light was known relatively early (90). Using melatonin as an output measurement, it was shown that shifting the normal light cycle by 8 hours results in a shift in circadian rhythm patterns as well. This shift also differs in length in albino rats compared to pigmented rats, as does the normal amount of time required to re-entrain the rhythms after disruption (91). This suggests that in addition to light, the degree of skin pigmentation also has significant impact on circadian rhythms. In addition, rats subjected to normal light/dark cycles in natural light expressed a higher amplitude of oscillation in their melatonin expression than rats exposed to artificial light (92), suggesting that natural light is more effective at maintaining normal circadian rhythms than artificial light, even when the light/dark cycle is not altered.

Dysregulated circadian rhythms may contribute to a variety of adverse health effects. Obesity, diabetes, and cardiovascular disease may be influenced by circadian rhythm disruptions. Shifts in eating and sleeping patterns result in increased postprandial glucose, insulin, and mean arterial pressure, as well as decreased leptin levels and inverted cortisol expression patterns (93). In addition, disruption of circadian rhythms through the shifting of normal light patterns results in an accelerated development of diabetes in diabetes-prone HIP rats (94). Epidemiologic studies also show an increased risk of metabolic disease for night shift and rotating shift workers relative to their daytime counterparts (95, 96). Studies have also suggested that many psychiatric disorders, including depression, bipolar disorder, and Alzheimer's disease are associated with circadian disruption (97–99). However, circadian abnormalities in cardiovascular diseases and psychiatric disorders have not been well studied.

The regulation of circadian clock network in cancer is being actively investigated at present. Dysregulated expression of the core clock proteins has been shown to occur in certain cancers (100–113). The specific clock proteins that are affected have been found to vary

with the type of cancer. In cancers where the expression levels of the Periods and Cryptochromes are aberrant, they have been found to be consistently down-regulated compared to normal tissues (100–104, 106, 109–111, 113). Per1 has been shown to be down-regulated in non-small cell lung cancer tissues (NSCLC) (102), colorectal cancer (106), and endometrial carcinomas (113). Lower expression of Per1 and Per2 has been shown in human gliomas (111), hepatocellular carcinomas (104), ovarian cancer (109), breast cancer (101, 110), and prostate cancer (100, 103). In addition, low expression levels of Cry2 have been demonstrated in ovarian cancer (109) and hepatocellular carcinomas (104). Per1 down-regulation could have a significant impact on tumor development, as decreased Per1 levels in breast cancer cells has been shown to result in increased cell growth *in vitro* and tumor growth *in vivo* (112). Further, forced expression of Per1 in both NSCLC and prostate cancer cell lines results in significant tumor growth reduction, and lowered survival of the cancer cells (100, 102).

In contrast to the consistently lower levels of components of the negative limb of the circadian clock, the expression levels of BMAL1 and CLOCK seem to be cancer type specific. BMAL1 has been shown to be overexpressed in ovarian and prostate cancers, whereas its expression was found to be suppressed in hematologic malignancies (103, 108, 109). The expression pattern of BMAL1 is found to be inconsistent in colorectal cancer; however, high BMAL1 coupled with low Per1 levels is shown to be associated with liver metastasis (106). CLOCK expression levels appear to be opposite of BMAL1 in at least two of these cancers, as it is down-regulated in both ovarian and prostate cancer, and up-regulated in colorectal cancer (103, 106, 109).

Circadian Rhythms and Melatonin

It is becoming clear that dysregulation of circadian rhythms can have a deleterious impact on health. Therefore, it is important to understand the mechanism of circadian rhythms' regulation. As previously mentioned, light plays an important role in the regulation of circadian rhythms through its impact on the central pacemaker in the SCN. Interestingly, light may play a secondary role in the maintenance of circadian rhythms through its regulation of the pineal hormone melatonin. Melatonin is a phylogenetically conserved methoxyindole that was identified over five decades ago as the main secretory product of the pineal gland (114–116). Historically, melatonin has been used extensively in the study of circadian day-night rhythms and seasonal biorhythms (117, 118), as it is often considered to be a regulator of these oscillatory patterns. Melatonin is known to oscillate with circadian rhythmicity (90). It is highly expressed at night, with lower levels of expression during the daytime hours (119). As with all circadian proteins, this oscillation is sensitive to light, and any change in the normal light/dark cycle leads to consequent disturbances in the expression of melatonin production (120, 121). This can have a large impact on the expression of all circadian target genes, due to melatonin's role in the core clock mechanism.

As previously mentioned, the acetylation state of BMAL1 plays a key role in the regulation of the circadian clock. This acetylation state is determined by the histone acetyltransferase (HAT) activity of CLOCK, as well as the histone deacetylase (HDAC) activity of SIRT1 (81, 82). Melatonin has been shown to be an inhibitor of SIRT1 HDAC activity, as well as SIRT1 expression, indicating that it plays a role in the management of circadian rhythms through its effects on SIRT1 (122). Furthermore, it has been shown that the exogenous addition of melatonin to prostate cancer cells can reestablish normal circadian oscillation (103). Thus, melatonin levels are important to consider when developing potential therapies for circadian disruption.

In recent years, melatonin has been characterized as a pleiotropic bio-regulator of numerous functions and in diverse biological systems ranging from single cell to complex organisms,

including humans (123–125). It has been shown to play a role in the modulation of defense responses (126, 127), body weight and reproduction (117), tumor growth inhibitory, and anti-jet lag effects (128, 129), as well as acting as a potent antioxidant (130, 131), a chemotoxicity reducing agent (131) and a putative anti-aging substance (132–134). It is these pleiotropic characteristics that have made this endogenous factor of particular interest to researchers. The diverse effects of melatonin on cellular and organismal health have prompted investigations into mechanistic actions of melatonin against a variety of stresses including oxidative stress generated from UV exposure. When examining melatonin's protective effects, it is important to note that while melatonin was initially identified as a pineal hormone, melatonin synthesis occurs in other tissues besides the pineal gland. The evidence for this is the presence of significant levels of melatonin, higher than that which could be achieved from melatonin levels found in plasma, in bile fluid, bone marrow, cerebrospinal fluid, ovary, eye, lymphocytes, gastral mucosa, and skin (126, 135–145). The existence of these localized melatoninergic systems suggest the importance of melatonin in biological response to specific local stressors (137, 143, 146, 147). This is especially important when studying the protective effects of melatonin against UV-induced skin damage, as the melatoninergic antioxidative system (MAS) has been described as highly differentiated in the skin (137).

Intracutaneous Synthesis of Melatonin and its Protective Role in Skin

The first evidence of melatonin synthesis in the skin was found in the Syrian gold hamster. It was found that the skin of this organism displays activity for arylalkylamine-N-acetyltransferase (AANAT), which is a key enzyme involved in melatonin biosynthesis (148, 149). Further studies demonstrated that mammalian skin has an abundant concentration of the precursor molecules required for melatonin production and a fully functioning melatoninergic system (140–142, 150, 151). Further proof of melatonin production in the skin came from organ-cultured human scalp hair follicles that not only showed melatonin production but could be stimulated to further melatonin production (152). From this, it is reasonable to assume that melatonin production does happen in the skin and is likely to provide a protective role in this organ against multiple environmental and endogenous stressors.

Melatonin has been suggested to protect the skin through several mechanisms, one of which is via its antioxidant effects (147, 153). As an antioxidant, melatonin is a strong scavenger of UV-induced ROS, preventing potential DNA damage that could lead to cancer. Melatonin has been shown to be a stronger ROS scavenger than vitamin C or vitamin E, both of which have been used therapeutically against cytotoxic events (154). Melatonin is a highly lipophilic hormone that easily gains access to the intracellular structures through its ability to cross the cellular membranes. This allows melatonin to protect intracellular structures such as mitochondria and DNA from oxidative damage. It also provides a means by which melatonin can access the DNA and promote the upregulation of other genes responsible for oxidative protection such as Cu/Zn-superoxide dismutase (CuZn-SOD), Mn-superoxide dismutase (Mn-SOD), catalase and glutathione peroxidase (GPx) (155). A second major mechanism by which melatonin protects the skin is its ability to modulate UV-induced apoptosis (147, 153). Melatonin inhibits intrinsic apoptosis pathways by antioxidant protection of mitochondrial membrane potential from UV-related formation of mitochondrial ROS (156). This shows how melatonin is itself protective and also in part responsible for activating other endogenous enzymatic protective systems against oxidative stress (137, 155). Thus, the protective effects of melatonin could potentially lead to greater cell survival in response to UV stress. Several studies have shown that cells treated with melatonin do, in fact, have a higher survival rate. Fischer *et al* showed that treatment of human keratinocytes with melatonin for 30 minutes prior to UV exposure resulted in higher

cell viability than untreated cells (157). Pretreatment of the keratinocytes with melatonin before UV exposure has been shown to downregulate the genes associated with skin photodamage and mitogenic signaling following UV exposure (140, 158). These findings demonstrate the protective effects of melatonin against intraepidermal keratinocyte apoptosis induced by UV-irradiation or sunburns.

Conclusions

Light, melatonin, and circadian rhythms are all intertwined in a complex system (Figure 2). The balance required for proper maintenance of this system depends on the appropriate amount of exposure to light, and can have a significant impact on the normal cellular functioning. Disruption of our light – dark cycles, such as created by wide use of artificial lights, can dramatically alter the balance in circadian rhythms. The extension of our exposure to light can result in aberrant expression patterns of essential genes that are controlled by circadian rhythms, such as melatonin. This further exacerbates the irregularities, as melatonin itself feeds back into the circadian system through its role in the inhibition of the histone deacetylase, SIRT1. Melatonin also has a role in the skin as a protective agent against damaging UV light, and changes in its expression levels can therefore contribute to the development of skin cancer.

In addition to its damaging role in contributing to skin cancer, UV exposure also has positive and protective effects, necessitating a balance in the level of UV exposure required to maintain optimal health. Although UV exposure is detrimental to skin health and key to the carcinogenesis process, it does not explain all skin cancers, including the increase in melanoma incidences of indoor workers. There has been speculation to tie this in with vitamin D production and/or the breakdown of vitamin D stores within the skin which is more common in indoor workers. With all the lifestyle changes we have seen over the past century, there has also been an increase in the incidences of many cancers. Many variables could contribute to the causes of these increases. However, the role that changes in environmental stressors play cannot be ignored. Further understanding of circadian regulations is needed to develop novel strategies towards circadian related conditions and diseases which encompass a wide range from behavioral conditions to cancers.

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>Photo Dr Desotelle<

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>Photo Ms Wilking<

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>Photo Dr Ahmad<

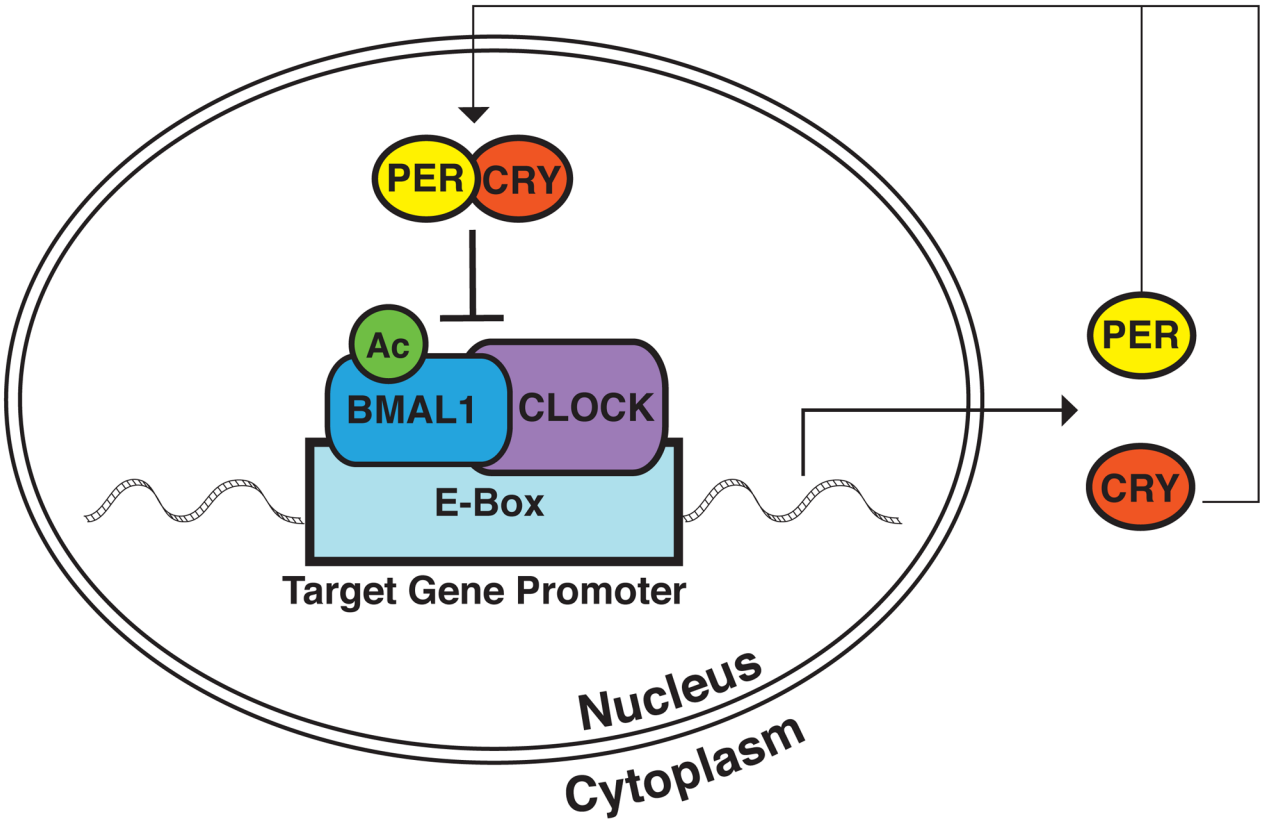

Figure 1. The Circadian Clock Network

BMAL1 and CLOCK proteins form a heterodimer in the nucleus followed by binding to the E-Box region in the promoter of their target genes, thereby initiating transcription. Two families of target genes, the Periods (PER) and Cryptochromes (CRY), then act in a negative feedback loop by forming a heterodimer, translocating to the nucleus, and interfering with BMAL1/CLOCK-induced transcription. The acetylation state of BMAL1, which is altered by CLOCK histone acetyltransferase and SIRT1 histone deacetylase activity, plays a large role in the regulation of this system.

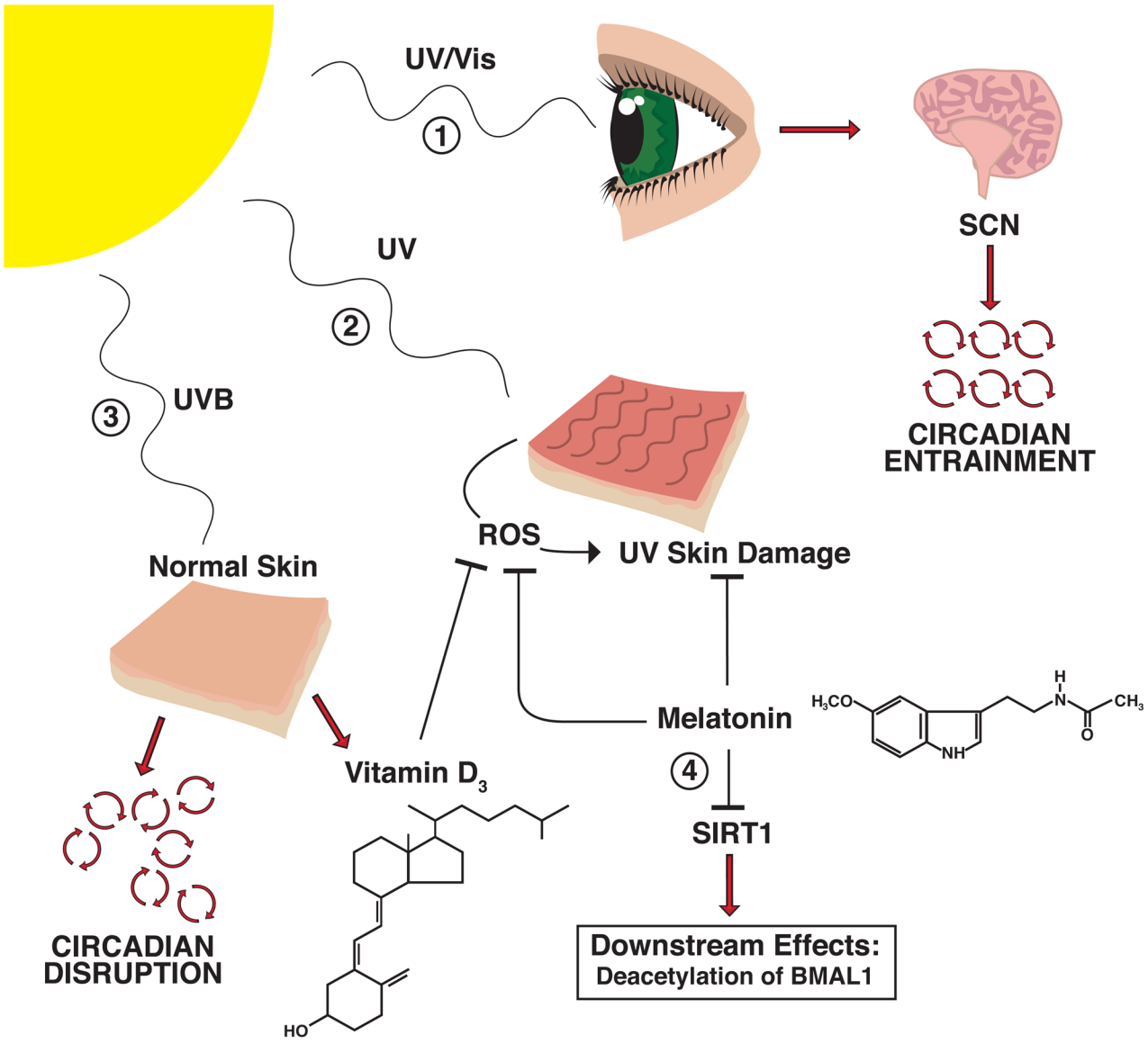

Figure 2. Light, Circadian Rhythms, and Melatonin

1) UV or visible light from the sun is sensed by the retina, which signals the suprachiasmatic nucleus (SCN) region of the brain, enabling entrainment of circadian rhythms throughout the body. 2) UV light induces skin damage. Both Melatonin and Vitamin D_3 have protective effects against this damage, through the inhibition of reactive oxygen species (ROS) formation as well as other mechanisms. 3) UVB light exposure can cause disruption of the circadian rhythms in normal skin, but also has the protective effect of producing Vitamin D_3. 4) In addition to its protective effects against UVB skin damage, melatonin also plays a role in the regulation of circadian rhythms, through its inhibition of the HDAC SIRT1.