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RESEARCH ARTICLE

Photoreception and phototransduction in human skin

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ABSTRACT

Light allows us to see. Seeing begins with photoreceptors in the retina where light is absorbed, converted into an electrical response and transmitted to the brain. Photoreception is highly conserved, and in animals, almost exclusively based on a single class of proteins, the opsins. Image-forming information goes to the lateral geniculate nucleus and eventual processing into visual images, sight. What may not be immediately apparent is the transmission of non-image information. However, cells in the skin contain the full set of opsins and their phototransduction cascades which are active, cover the whole solar spectrum and appear to participate in the skin's protective mechanisms. This is obviously related to collection of non-image information. Why is this system of photoreception and transmission duplicated in the skin and what is its function?

Introduction

Solar irradiation is the main factor that stimulates pigmentation in human skin. Although both UVA and UVB have been shown to induce melanogenesis, UVB-induced pigmentation has been the most studied. UVB-induced DNA damage in keratinocytes activates p53. P53 then binds to the pro-opiomelanocortin (POMC) promoter inducing production of POMC, a precursor polypeptide which can be cleaved into a range of biologically active peptides involved in diverse cellular functions, one of which is alpha-melanocyte-stimulating hormone (αMSH), the main pro-pigmentation hormone[1]. The process is mediated by keratinocytes through secretion of hormones and cytokines that stimulate melanogenesis, dendrite genesis, melanosome transfer and melanocyte proliferation[2], to act as a protective response in the skin to the potential damage to DNA by the shorter wavelengths of light. Interestingly, POMC is also synthesised in the anterior pituitary having roles in pain and energy homeostasis and immune modulation as well as melanocyte stimulation, acting through the hypothalamic-pituitary-adrenal axis. POMC can be synthesised by both keratinocytes and melanocytes, cleavage also producing adrenocorticotrophic hormone (ACTH) and β-endorphin, an opioid peptide.

This mechanism of the keratinocyte acting as the sensor and the melanocyte as the effector seems straight forward but the photosensory system in the skin is more complex than this UVB response would suggest. All skin cells have a range of photosensitive proteins and chromophores that are responsive to the whole solar spectrum, not just the UV component. Even the response to UVR, alone is more complex with immediate pigment darkening (IPD) and a more prolonged response, delayed tanning (DT), mediated by UVA and UVB, respectively.

Although, most of the effects of solar radiation exposure on the skin have been linked to UVR, UVR accounts for only 2-5% of the photons incident on the skin, visible light (VL) makes up nearly 50%. While not active enough to cause direct breakage of covalent bonds like UVR, it penetrates more deeply and is responsible for oxidative effects that can result in the same mutational events, acting on the germinative layer at the base of the epidermis. Liebel et al showed that VL has an even deeper adverse effect, activating metalloproteinases and decreasing collagen production in the dermis, resulting in photoaging[3]. In melanocompetent individuals, skin type > type II, VL can produce deeper and more persistent pigmentation than UV[4].

Traditionally, all photoreception in mammalian species is through the eyes with image and non-image photoreceptors in the retina transmitting photic information to the brain for sight and circadian entrainment and coordination. Is the photosensory system in the skin just vestigial baggage inherited from more primitive organisms through evolution or does this system provide extra sophistication to layers of adaptive response, the ultimate result being further protection of the human genome?

Vertebrate photoreception and transduction

Most animals have photoreceptors for detecting food, mate, predator/prey and orientation to the sun's light/dark cycle. In primates, it is generally accepted that all photoreception is through the retina in the eyes, as enucleation

abolishes all response to light[5,6]. Although, photoreceptors can be ocular or extra-ocular.

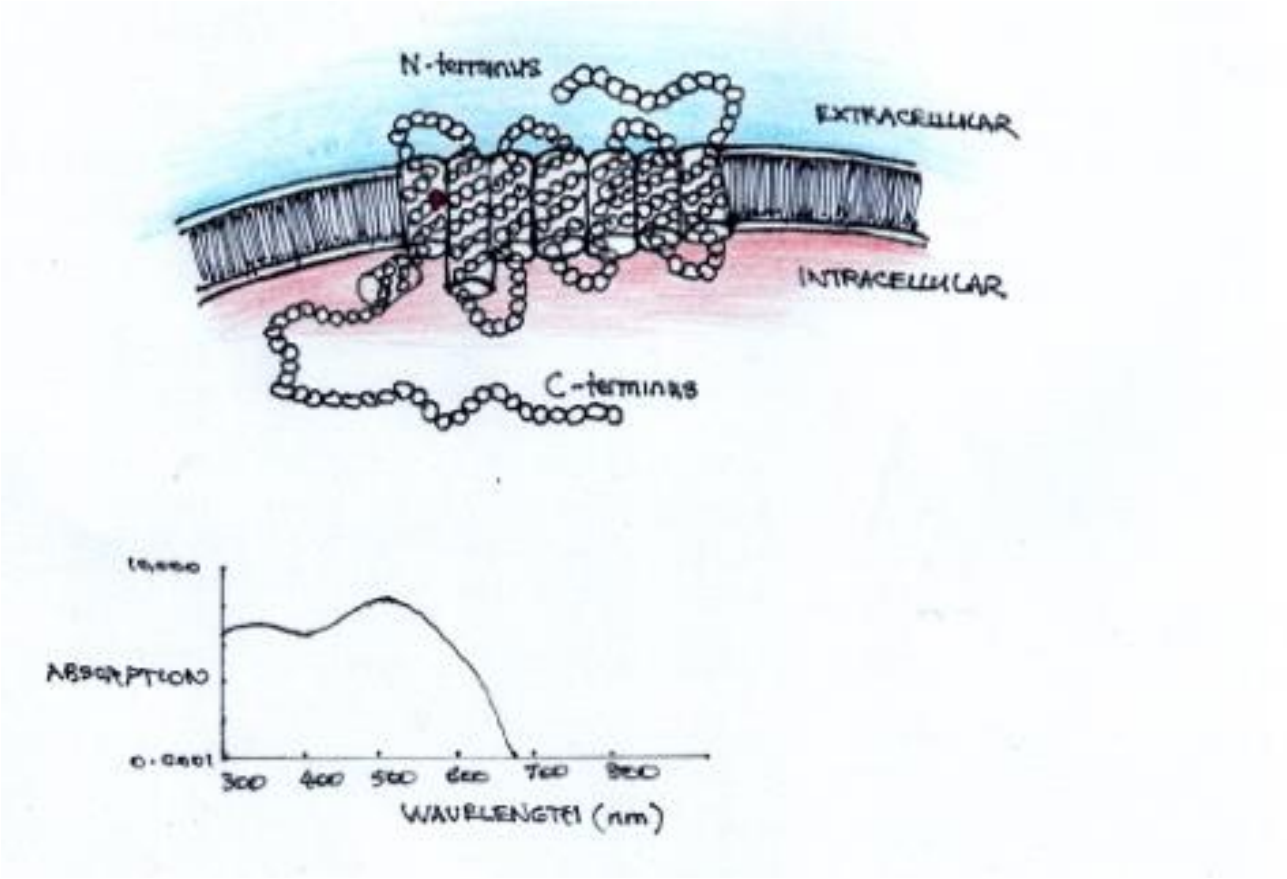
All vertebrate photoreceptors use a photopigment consisting of an opsin protein bound to a vitamin A chromophore, 11-*cis*-retinaldehyde. The first stage of light detection involved the absorption of a photon by the retinal and the photoisomerization of this molecule to the all-*trans* state. This conformational change of the chromophore allows the opsin to interact with a G-protein triggering a phototransduction cascade, ultimately giving rise to a change in receptor membrane potential. All vitamin A based photopigments have a characteristic absorption spectrum. Figure 1. This means that the maximum sensitivity (λ_{max}) may vary widely across the visible spectrum (UV at 360nm to red at 600nm) but all these pigments have the same characteristic bell-shaped curve[7]. Opsins are members of a family of G-protein coupled receptors (GPCRs) which function through activation of a guanine nucleotide binding protein and an effector enzyme. They consist of a polypeptide chain that forms seven α-helical transmembrane regions connected by cytoplasmic and extracellular loops. These helices form a bundle within the membrane, creating a hollow cavity on the extracellular surface that acts as a binding site for the retinal chromophore. Figure 1.

These photoreceptors have evolved across animal phylogeny and can be divided into three groups: ciliary (c-opsins), rhabdomeric (r-opsin) and a collection of minor groups called tetraopsins: G_o-opsin, which mediate phototransduction in certain ciliary photoreceptors, peropsin, neuropsin, encephalopsin/teleost, multiple tissue (tmt) opsin and photoisomerase which serve to regenerate the chromophore. The function of some of these groups remain unclear.

Ciliary photoreceptors are characteristic of vertebrates, whereas rhabdomeric are predominately found in invertebrates. However, in most phyla ciliary and rhabdomeric photoreceptors coexist in the same organism, implying that they arose before the protostome/deuterostome split ~250 million years ago and have evolved independently since[8]. More than a thousand opsins have been identified in the animal kingdom, all believed to have originated from a common ancestor. Opsins are classified according to molecular phylogeny but also matched to the corresponding cell types with which the pigments are associated.

The ciliary vertebrate rods and cones hyperpolarise to light, whereas rhabdomeric photoreceptors depolarise to light. However, light response polarity is not an absolute distinguishing feature between ciliary and rhabdomeric photoreceptors or between vertebrates and invertebrates. One principle is consistent, ciliary photoreceptors use a cyclic nucleotide motif for phototransduction, whereas rhabdomeric use phospholipase C (PLC) motif[9]. Figure 2. More recently another group of photoreceptors have been identified in vertebrate retinas, the intrinsically photosensitive retinal ganglion cells (ipRGC).

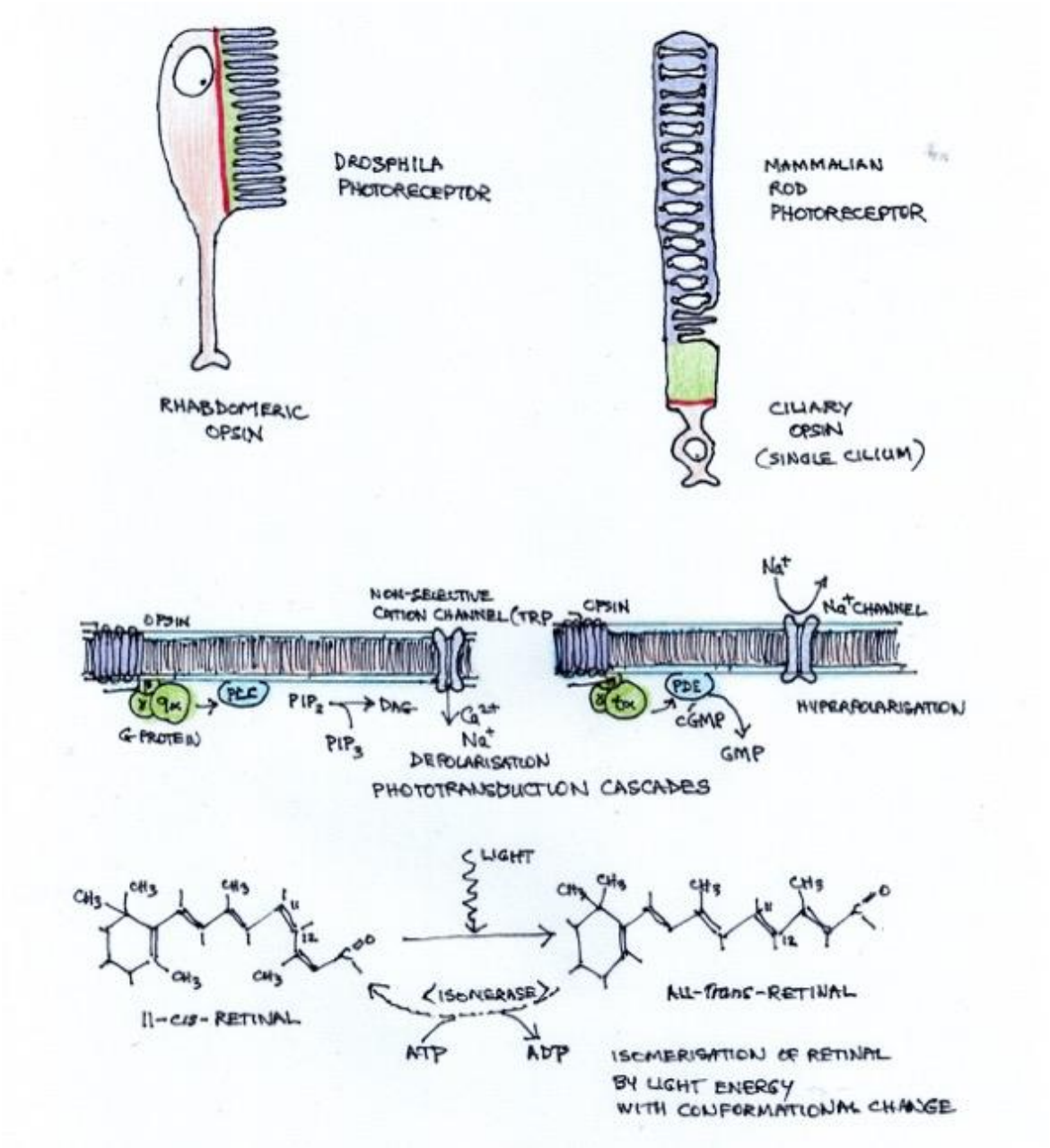
Figure 1. The structure of opsin.



Opsins consist of a single polypeptide chain forming seven α-helical transmembrane regions connected by cytoplasmic and extracellular loops. The intracellular loops mediate G-protein interactions. The retinal binding site (red) is indicated in the 7th transmembrane domain. Characteristic absorption spectrum of all vitamin A/opsin-based photopigments.

Visual imaging commences with photons detected by rods and cones and their graded potentials assembled into an image by inner retinal neurons followed by advanced visual processing in the brain. Image detection differs from the demands of non-visual irradiance detection. Rods and cones are highly sensitive radiance detectors which rapidly adapt and can only integrate signals of short duration. On the other hand, non-visual, irradiance detection, required for the circadian system is relatively insensitive to light, requiring high intensity and long duration of stimulation to bring about photoentrainment.

Figure 2. Photoreceptors, signalling cascades, and isomerisation of retinal.



There are two major types of photoreceptor cells which use different means of increasing the cell's surface area to better capture light. Rhabdomeric photoreceptors have an array of microvilli on the cell membrane, while ciliary photoreceptors have an expansion of the ciliary membrane. Each photoreceptor type is associated with specific families of photo-pigment molecules such as opsins and proteins of their respective phototransduction cascades, which converts light energy into electrical charge.

Rhabdomeric photoreception - Activation of Gq protein which activates PLC, hydrolysing PIP_2 into DAG and IP_3. Decreasing levels of PIP_2 activates TRP ion channels. Ca^{2+} and Na^+ enter the cell, depolarising it. Meanwhile, IP_3 binds to a receptor on the ER releasing Ca^{2+} from internal stores.

Ciliary photoreception - Activation of Gi protein, transduction, activates PDE which converts cGMP to GMP. Decreasing cGMP closes a Na^+ channel. Decreased Na^+ entry hyperpolarising the cell.

Isomerisation - In an inactive form, the opsin apoprotein forms a covalent bond with an endogenously produced vitamin A-derived chromophore, most often 11-*cis* retinal in mammals. Absorption of a photon by the bound retinal induces isomerisation from 11-*cis* to an all-*trans* conformation. This conformational change in the opsin moiety renders it active, able to bind to a G-protein and potentiate a signalling cascade. cGMP, cyclic guanine monophosphate; DAG, diacylglycerol; ER, endoplasmic reticulum; IP_3, inositol triphosphate; PDE, phosphodiesterase; PIP_2, phosphatidylinositol 4,5-biphopshate; PLC, phospholipase C; TRP, transient receptor potential.

Rods

Rods mediate vision in dim light (scotopic). Phototransduction takes place in the cell's ciliary outer segment. Photo isomerised OPN2 activates a G protein, transductin (G_t), which stimulates phosphodiesterase (PDE) to hydrolyse cyclic guanine monophosphate (cGMP). G_t and PDE are peripheral membrane proteins.

In darkness, the free cGMP is at high concentrations, and by direct binding, maintains cGMP-gated nonselective cation channels on the plasma membrane in an open state. These channels with the unusual property of showing no desensitisation to ligand maintains a steady inward current in darkness, depolarising the cell sufficiently (~30mV) to sustain synaptic transmitter glutamate release.

Light-induced, graded decrease in free cGMP closes the cGMP gated channels, hyperpolarising the cell, reducing or stopping glutamate release.

Cones

Cones mediate vision in bright light (photopic). They also mediate colour vision through cone cells with a variety of spectral types in the retina. Cone single photon response is 10^2 X smaller but several times faster. Cones also adapt to light more efficiently.

Cone pigment needs to be regenerated rapidly and continuously because they operate in bright light conditions. This rapid recycling requires a rapid dissociation of all-trans-retinal from the cone opsin for rapid re-isomerisation to follow, thus requiring a looser chromophore binding pocket. This more open pocket is also partially responsible for a higher thermal isomerisation rate, and thus higher noise compared to rod pigment. The molecular design for achieving rapid regeneration of bleached pigment comes with the cost of greater noise in darkness.

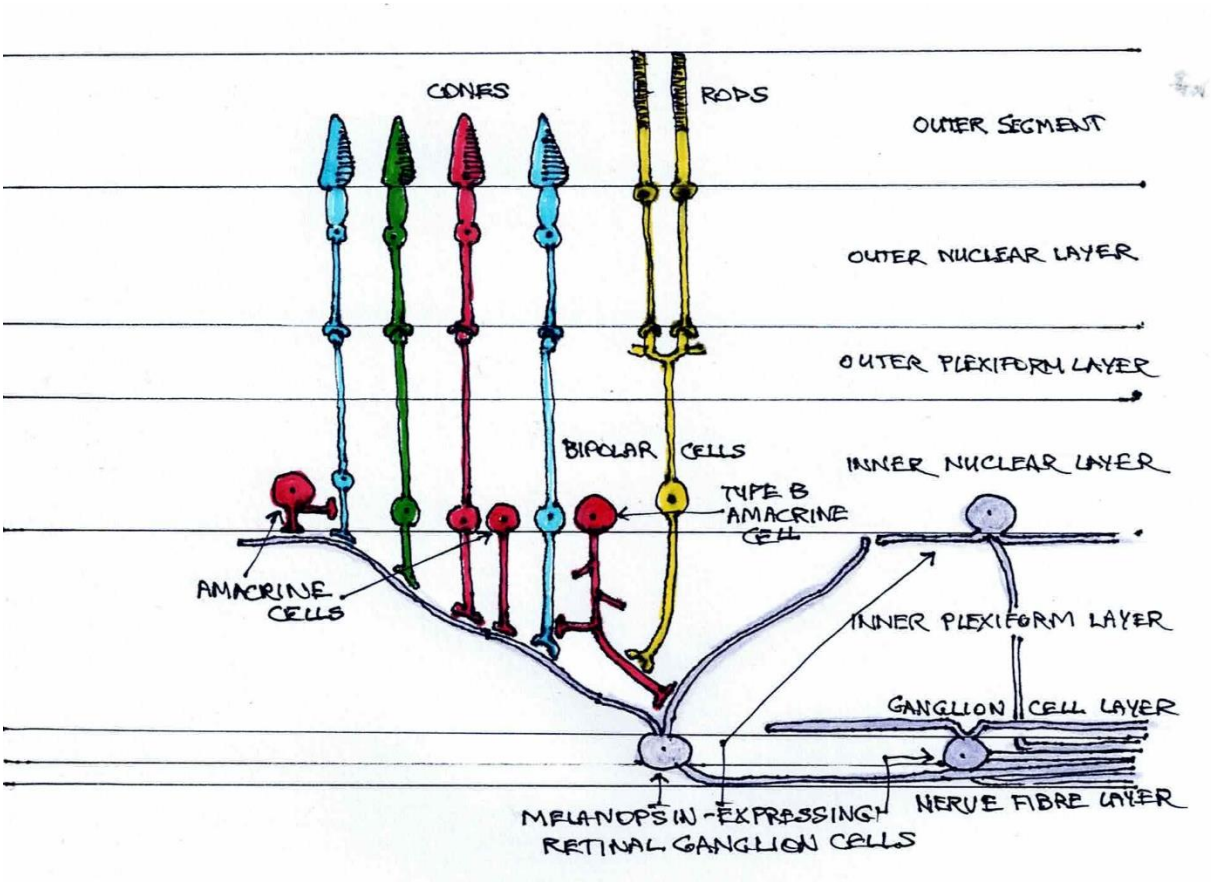
Intrinsically photosensitive ganglion cells

It was not recognised till the 1980s that the retina has a third type of photoreceptor, intrinsically photosensitive ganglion cells (ipRGCs) which use a distinct visual pigment, melanopsin, for light detection. These are 1% of all ganglion cells. They project to the hypothalamic suprachiasmatic nucleus (SCN), olivary pretectal nucleus (pupillary reflex control) and, several other brain nuclei for non-image, subconscious visual functions[12]. Non-image vision informs the organism of the presence or absence of ambient light, intensity and spectral composition for tracking time of day or seasonal changes. The SCN is innervated almost exclusively by ipRGCs. Other nuclei receive more mixed inputs from ipRGCs and conventional RGCs. Even the dorsolateral geniculate nucleus (1st station for visual imaging) receives weak input from the ipRGCs. They also signal within the retina, influencing rod and cone pathways. Table 1.

Table 1. The intrinsically photosensitive retinal ganglion cells and their neural targets.

ipRGC target	Target function
High density of fibres	
Suprachiasmatic nucleus.	Master regulator of circadian rhythm
Intergeniculate leaflet	Integration of photic and non-photic circadian clues
Olivary pretectal nucleus.	Pupillary constriction
Lower Density of fibres	
Dorsolateral geniculate nucleus.	Image forming vision.
Lateral hypothalamus	energy homeostasis
posterolateral thalamic nucleus	higher-order processing of thalamic, cortical and visual signals
posterior limitans thalamic nucleus	detection of rapid illumination changes for non-imaging vision
superior colliculus	integration of multiple modalities for gaze control
ventrolateral geniculate nucleus	visuomotor function
ventral supra-paraventricular zone	circadian and direct regulation of locomotion and sleep
ventral preoptic nucleus	promotion of sleep

Figure 3. Synaptic circuitry of melanopsin-expressing retinal ganglion cells (ipRGCs) in the retina.



IpRGCs are mainly located in the ganglion cell layer, the rest are displaced to the inner nuclear layer. They have sparse dendrites but extremely large dendritic fields. These dendrites arborise in the inner plexiform layer (IPL), forming a major plexus in the outer most boundary of the IPL and a minor plexus in the inner most boundary of the IPL. Green and red cones provide excitatory inputs through bipolar cells to ipRGC proximal dendrites. Rod cells also provide excitatory inputs through rod bipolar cells, type II amacrine cells and cone bipolar cells successively. Blue cones provide inhibitory inputs through cone bipolar cells and inhibitory (GABAergic) amacrine cells.

The circadian system

The 24-hour cycle of day and night caused by rotation of the earth on its axis and seasonal changes caused by the rotation of the earth around the sun produces a predicable change in the light environment. Organisms have evolved a representation of this cycle, the endogenous circadian clock. Thus, changes in the environmental conditions can be anticipated and physiology optimised. This selective advantage can only be provided as long as biological time remains synchronised to environmental time, entrainment. This is achieved by using time cues, *zeitgebers*, the change of light irradiance at dawn and dusk. Based on ipRGCs, utilising melanopsin, having a phototransduction cascade more common to invertebrates that innervates the suprachiasmatic nucleus for entrainment of environmental circadian time. What also needs to be appreciated is that this complete system of photoreceptors and phototransductive cascades is represented and active in the skin.

Circadian photoentrainment

Circadian photoentrainment affects a whole host of functions such as melatonin release, body temperature regulation and feeding behaviour. Circadian photoentrainment disappears after removal of the eyes, suggesting that ocular photoreceptors are exclusively responsible for photoentrainment separate to rods and cones for long-term temporal integration[13-15]. The ipRGCs exhibit high threshold for stimulation and unresponsiveness to light levels below 10^{10} photons/cm^2/s. In addition, the non-image pathway is relatively insensitive to stimulation duration of 30 secs or less. These unique physiological properties suggest that this visual pathway is suited to carry light information necessary for synchronisation of mammalian circadian oscillation to the environmental cycle of light and dark.

Twilight detection-spectral discrimination. Evolutionary considerations.

Given the multiplicity of photoreceptive tissues in non-mammalian vertebrates, why have they been lost in mammals? The 'nocturnal bottleneck' in early evolutionary history of mammals may provide the answer. Modern mammals are derived from nocturnal insectivores 100 million years ago[16]. Pineal or deep-brain photoreceptors may have been adequate for monitoring changes in diurnal light prior to this but may not have been sufficiently sensitive for mammals living in burrows or concealed through the day to avoid predation by the dominant reptiles. Changes occur not only in the amount but also the spectral composition of environmental irradiance throughout the diurnal cycle, the Chappuis effect[17]. As the sun's rays must pass through a thicker layer of atmosphere when the sun is lower in the sky, absorption of light by ozone (500-650nm) results in a relative enrichment of

shorter wavelengths (<500nm) at twilight. Detectors tuned to blue light could allow increased photon capture but change in spectral quality can also be discriminated. This chromatic response has been demonstrated in the pineal of fish[18] and parietal eye of lizards[19]. The response can be achieved by melanopsin which is a bistable photopigment, able to regenerate its chromophore using all-trans-retinal and long-wavelength light[20]. This spectral discrimination can be achieved through the two stable states of melanopsin interacting, with different downstream signalling transduction pathways. Thus, melanopsin provides an alternative means of attaining spectral discrimination. The process of evolution allows for trade-offs between structure and function influencing spectral tuning. Scotopic vision is limited by dark noise produced by thermal isomerisation of the retinal chromophore[24]. Long wavelength sensitive photopigments have been suggested to be more prone to dark noise owing to their lower excitation energy[21]. Thus, the spectral tuning of the non-visual opsins, like the visual opsins, will always be a compromise between functional constraints and the photon flux of the light environment[22,23,24].

Opsins in the skin

The concept of dermal photoreception gained attention in the 50's when Steven et al demonstrated that sea lampreys could respond to tail illumination in the absence of eyes.

Further behavioural studies demonstrated localised illumination on the skin in a range of non-human animals elicited colour change, light avoidance, shadow reflex and circadian photoentrainment. Opsins and opsin-like structures were detected in the skin and thought to mediate these behavioural changes that were critical to survival.

In humans, opsins are present in various skin cell types, keratinocytes, melanocytes, dermal fibroblasts and hair follicle cells mediating melanogenesis, wound healing, hair growth and photoaging. Opsins, the main photo transducing molecules in the retina, have been shown to be expressed in human skin and may be acting as photosensors. Currant evidence, however, suggests that opsins also have biological significance beyond light reception. Table 2 and Figure 2.

Keratinocytes

Expression of OPN1,2,3 and 5 has been identified in skin tissue and cultured human keratinocytes[25]. Kim et confirmed the expression of OPN2 in cultured keratinocytes and suggested that it could be involved in the regulation of keratinocyte differentiation. They showed that violet light (410nm) irradiation decreased keratinocyte differentiation markers with a corresponding increase in OPN2 expression[26]. OPN2 has maximum absorption spectra (ג max) 480-530nm leading one to question whether this effect is due to OPN2. However, Toh et al has since also identified peropsin, a tetraopsin, in skin tissue and cultured keratinocytes, previous thought to exclusively expressed in the retinal pigment epithelium cells of the eye. The spectral sensitivity of peropsin is unknown but the other two tetraopsins, OPN5 and RGR, have λ_{max} 380 and 470 respectively[27,28]. Irradiation with violet light (380nm) elicited the highest amplitude Ca^{2+} transits only in the presence of all-trans retinal ligand, suggesting that peropsin may contribute to the phototransduction of violet light in keratinocytes.

Table 2. Classification of opsins expressed in human skin.

Name	G protein	Absorption wavelength (nm)	Colour
C-opsin (ciliary)			
OPN1-SW	G_t	~425	Violet-blue
OPN1-MW	G_t/G_s	~530	Green
OPN_LW	G_t	~560	Yellow-orange
OPN2 Rhodopsin	G_t	~500	Green
OPN3 Endcephalopsin	G_i/G_o	~420-527	Violet-green
R-opsin (Rhobdomeric)			
OPN4 Melanopsin	G_q	~480	Blue-green
Tetraopsin (Group 4)			
Retinal GPCR opsin (RGR)		~470	Blue-green
Peropsin (RRH)			
OPN5 Neuropsin	G_i	~380	Ultraviolet

Melanocytes

Melanogenesis is a tightly regulated process influenced by a range of hormones, UVR and visible light. In response to UVR, pigmentation proceeds in several distinct steps. Initially, a transient immediate pigment darkening (IPD) takes place in response to UVA, but not UVB radiation. The wavelength that promotes the strongest response is 340nm with dose range 10-20 kJ/m^2.>100kJ/m^2 produces a more intense and persistent pigment darkening (PPD). IPD and PPD are thought to result from oxidation and redistribution of pre-existing melanin and precursors that can last up to 24 hours and blend with other pigmentary processes. Delayed tanning (DT) is dependent on *de novo* synthesis of tyrosinase and melanin. Both UVA and B can lead to DT, but UVA-induced DT is preceded by IPD and/or PPD, whereas UVB-induced DT is preceded by erythema[29,30]. It has been found, however, that IPD-induced pigmentation does not absorb in the UVR spectrum and so does not protect against the deleterious effects of UVR. Moan et al demonstrated the IPD-induced pigmentation absorbs in the white light spectrum and thus, protects against photo-degradation of folate and other chromophores in the skin such as porphyrins, flavins, and pterins, which are known to absorb in the VL spectrum[31]. Photo-degradation of folate and its metabolite methyl tetrahydrofolate, in respond to UVA and VL radiation reduces folate levels, which significantly impairs cellular division. Folate as well as DNA protection are the key roles of the pigmentary response in the skin[39].

Human melanocytes detect ultraviolet light.

Melanocytes express a variety of GPCRs and their related G proteins, including the

melanocortin 1 receptor (MC1R) coupled to $G\alpha_s$ and $G\alpha_{q/11}$-coupled endothelin-1(ET-1) receptor, known for their melanogenic response to UVB. Wicks et al discovered that human melanocytes detect UVR, initially by increasing intracellular calcium and later by increasing melanin[32]. They found that the response is retinal dependent and involves both the release of calcium from intracellular stores and an influx of calcium through transient receptor potential A1 (TPRA1) cation channels[33]. Both components of the response require heterotrimeric G protein and phospholipase Cβ (PLCβ) activation[32,33]. They found that both $G\alpha_q$ and $G\alpha_{11}$ could be activated by UVR which in turn activated PLCβ.

It had already been demonstrated in *Drosophila* that light stimulation of rhodopsin (OPN2) activated these same components which hydrolysed phosphatidylinositol 4,5 biphosphate (PIP_2) to generate diacylglycerol (DAG) and inositol 1,4,5 triphosphate (IP_3) to regulate TRP ion channels[34].

Further investigation found that decreasing PIP_2 levels caused TPRA1 activation. TRPA1 mediated influx is slow to decay, phototransduction depolarising the plasma membrane in melanocytes, permitting intracellular calcium levels to remain elevated after UVR exposure, allowing for melanin production. In the other component of the calcium response, soluble IP_3 binds to a receptor on the endoplasmic reticulum contributing to a rapid initial increase in intracellular calcium from internal stores. This biphasic reaction resulting in both a rapid initial response but also maintaining a sustained raised intracellular calcium level.

This model for UVR signal transduction resembles visual phototransduction in Drosophila photoreceptors and non-visual phototransduction in the mammalian retina[35]. Rhodopsin expression contributes to UVR-induced calcium responses, however, the differences in spectral sensitivity and G protein coupling of rhodopsin and of the UVR pathway suggest that rhodopsin is acting in conjunction with a different UVR sensitive receptor to mediate UVR phototransduction in melanocytes.

De Assis' group showed that UVA (94.4 kJ/m^2) leads to immediate pigment darkening (IPD) in murine and malignant melanocytes. They suggested OPN2 and 4 as the UVA sensors. They supported the role of calcium signalling. However, the classic OPN4 transduction pathway of phospholipase C / protein kinase C pathway is not involved, but rather the involvement of a CaMKII pathway. Knockdown of either opsin 2 or 4 resulted in complete loss of UVA-driven IPD, suggesting that both are required and cooperatively signal in both cell lines. OPN2 has been shown to be organised as dimers in rod photoreceptors and this may be the physical mechanism of cooperation between OPN2 and 4[36]. The presence of OPN4 in human skin had not been detected in two previous studies[25,39]. More recent RNA Seq analysis of transcriptome data showed expression of OPN1 SW, MW and LW, OPN2,3,4 and 5[37]. Interestingly, expression of OPN1LW and OPN4 is higher in sun-exposed skin, whereas OPN5 is higher in unexposed. They agreed with Wicks et al which reported non-canonical role of OPN2 as a UV sensor, but they were the first to show that OPN4 is also a UVA sensor[38].

De Assis' group has shown that both normal and malignant melanocytes have a photosensitive system in which OPN2 and

OPN4 act as UVA sensors. Both cell types share some signalling components, CAMKII/NOS/cGMP, which lead to immediate increase in melanin content in response to UVA. It had been previously shown that UVA radiation increased cGMP levels in mice skin[40] and NO in human skin[41]. Discrepancies with the finding of Wicks and Bellono in relation to transduction components were thought to be due to differences in protocols. The UV apparatus in the human studies showed a minor UVB wavelength, whereas theirs did not[42] which contributed to Wicks' melanin synthesis profile. Also, irradiances and dosages in Wicks' and Bellono's studies were much higher, with exposure times lower because of the irradiance. Wicks found melanin synthesis was UVR-dose dependant, but they found an immediate melanin increase after UV exposure, which decreased levels 6 hours later[42].

Human melanocytes detect visible light.

In melanocompetent individuals, skin types > II, VL can produce deeper and more persistent pigmentation than UVA. Skin types I and II showed no hyperpigmentation[4]. It was also found that shorter wavelengths of VL (blue-violet light at ~415nm) induced hyperpigmentation, whereas red light (630nm) showed no effect on pigmentation[43]. The effect of VL on darker skinned individuals can result in further hyperpigmentation, such as melasma. Conventional sunscreens may not protect against this effect, but it can be blocked by iron oxide[44].

Absence of p53 activation with VL hyperpigmentation suggests a different mode of action than the response to UVR[42]. Regazzetti et al was able to show a direct effect of shorter wavelength of VL-induced pigmentation by activation of a dedicated sensor, OPN3[45]. Although the peak absorption of OPN3 is 465nm, there is strong absorption of OPN3 in all the shorter wavelengths of the visible spectrum with a rapid decline after 465nm[47].

OPN3 is a G protein coupled membrane receptor expressed in human eyes, and the effects of VL on the eyes has been well studied but OPN3 is also expressed in the brain, liver and kidneys as well as the skin, suggesting that OPN3 may confer photosensitivity in extraocular tissues[48]. Previous studies have shown that the activation of opsin receptors leads to an increase in calcium flux. They observed an increase in calcium flux in melanocytes irradiated with blue light and upregulation of phosphorylated calcium/cadmium dependent protein kinase (CAMKII), a key enzyme in the calcium pathway. The calcium flux appeared to be specific to blue light because irradiation melanocytes with red light (630nm) had no effect. This mechanism does not occur in keratinocytes and is dose dependent. This CAMKII activation lead on to activation of the transcription factor cAMP response element-binding protein (CREB), extracellular signal-regulated kinase (ERK) and p38, leading to phosphorylation of MITF with increase in melanogenic enzymes tyrosinase and dopachrome tautomerase (DCT). They also showed that blue light induced the formation of a protein complex formed from tyrosinase and DCT. This complex lead to sustained tyrosinase activity, resulting in persistent hyperpigmentation in melanocytes of darker skinned individuals. These multimeric TYR/P proteins were observed despite the denaturing conditions of the experiments suggesting that covalent linking is induced by blue light. The multimeric proteins are not seen under basal

conditions, and they did not observe any differences between skin types III-VI. They hypothesised that they have no role in maintaining skin colour type but are only involved in the response to blue light. Their results help explain why only individuals with skin type > II are responsive to blue light and why it induces a long-lasting hyperpigmentation[46].

Olinski et al also found that OPN3 acts as a negative modulator of melanin production via coupling to a $G_{\alpha i}$ pathway, which inhibits MC1R-mediated cAMP response, leading to melanin production. Thus, reinforcing the view that OPN3 plays a key role in the regulation of melanogenesis but proposing a different mode of action[48].

Wang et al observed downregulation of OPN3 reduced intracellular calcium levels and triggered the endogenous apoptosis pathway via the mitochondria, suggesting that OPN 3 is a key receptor responsible for the survival of human epidermal melanocytes[49].

Fibroblasts

Pellicena et al identified the expression of OPN1-SW, OPN2 and OPN3 in cultured dermal fibroblasts[50] and inferred from previous findings an anti-proliferative effect of blue light (450-490nm) *in vitro* and suggested that opsins might be involved in regulation of cellular proliferation[51,52]. Lan et al provided evidence that OPN3 is the key sensor responsible for upregulation of matrix metalloproteases (MMPs) in fibroblasts upon UVA irradiation, contributing to skin aging. It was already known that chronic exposure to UVA induces an increase in MMPs leading to degradation of fibrous connective tissue. They detected all 5 opsins in fibroblasts but UVA exposure particularly increased expression of OPN3, inducing phototransduction and expression of MMPs.

Hair follicle cells

Reports showing that photo biomodulation has positive effects on hair growth has drawn attention to the presence of opsins in hair follicle stem cells[53]. Bascone et al detected OPN 2 and OPN3 in anagen hair follicles and demonstrated that blue light (453nm), which corresponds to the absorption spectrum of OPN3 prolongs the anagen hair growth phase. Silencing OPN3 abrogated the stimulatory effect of blue light. Red light had no effect[54]. Unfortunately, beyond this evidence on the functional role of opsins in hair follicle cells is lacking.

Conclusion

The question remains, why is this photosensory system reproduced in the skin? The sensory task of irradiance detection is not trivial. As demonstrated in mice, where messaging to the SCN commences at birth, whereas photosensitivity of the image forming pathway is only detected from postnatal day 10, just before eye opening[55]. Extracting time-of-day information from irradiance is complex. Amount of light, spectral composition and position of the sun all change in a systematic way and can be used by the circadian system to determine time of day. However, these parameters are subject to 'sensory noise'. Integrating this information from a multiplicity of photoreceptors will act to reduce signal noise and provide a more reliable measure of irradiance.

We now appreciate that photoreceptors do more than count photons and melanocytes do more than make melanin. The skin is at the interface with the environment and skin cells, particularly the melanocyte and other cells arising from the neural crest, are given some level of autonomy, at the periphery, to take direct protective actions. I would like to theorise that photoreception in the skin is looking beyond UV to all the shorter wavelengths of light because they all present a potential threat to skin cellular function and the genome. Beyond this, the multiplicity of sensors in the skin offers a higher level of adaptability, the hallmark of the human species. Who knowns what lies ahead for our species and its survival.

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References:

1. Cui, R., Wildlund, H., Feige, E., et al. **Central role of p53 in the suntan response and pathologic hyperpigmentation**. 2007. *Cell*; 128: 853-864.

2. Passeron, T., Ortonne, J-P. **Atlas of pigmentary disorders**. 2016.Cham. Switzerland. Springer.

3. Liebel, F., Kaur, S., Ruvolo, E., et al. **Irradiation of skin with visible light induces reactive oxygen species and matrix-degrading enzymes**. 2012. *J Invest. Dermatol;* 132: 1901-1907.

4. Mahmoud, B., Ruvolo, E., Hexsel, C., et al. **Impact of long wavelength UVA and visible light on melanocytes**. 2010. *J Invest. Dermatol;* 130: 2092-2097.

5. Nelson, R., Zucker, I. **Absence of extra-ocular photoreception in diurnal and nocturnal rodents exposed to direct sunlight**. 1981. *Comp. Biochem. Physiol*; 69A: 145-148.

6. Forster, R., Provencio, I., Hudson, D., et al. **Circadian photoreception in the retinally degenerate mouse**. 1991. *J Comp Physiol;* 169A:39-50.

7. Dartnall, H. **The interpretation of spectral sensitivity curves**. 1953. *Br. Med. Bull*; 9: 24-30.

8. Arendt, D. **Evolution of eyes and photoreceptor types**. 2003. Int. *J Dev. Biol*; 47: 563-571.

9. Nasi, E., Gomez, R., Payne. **Phototransduction mechanisms in microvillar and photoreceptors in invertebrates.** In: Stavenga, D., de Grip, W., Pug, L., editors. *Handbook of biological physics*. New York. Elsevier 2000; 389-448.

10. Jones, G., Crouch, R., Wiggert, B., et al. **Retinoid requirements for recovery of sensitivity after visual pigment bleaching in isolated photoreception**. 1989. *Proc. Natl. Acad. Sci. USA*; 86: 9606-9610.

11. Kefalov, V., Fu, Y., Marsh-Armstrong, N., et al. **Role of visual pigment properties in rod and cone phototransduction**. 2003. *Nature*; 425-531.

12. Fu, Y., Liao, H-W., Do, M., et al. **Non-image-forming ocular photoreception in vertebrates**. 2005. *Curr Opin Neurobiol*; 15: 415-422.

13. Pankey, S., Sunada, H., Horikoshi,. et al. **Cyclic nucleotide-gated channels are involved in phototransduction of dermal photoreceptors in Lymnaea stagnalis.** 2010. *J Comp. Physiol (B);* 180(8):1205-1211.

14. Xiang, Y., Yuan, Q., Vogt, N., et al. **Light-avoidance-mediating photoreceptors tile the Drosophila larval body wall.** 2010. *Nature*; 4687326): 921-926.

15. Serrage, H., Heiskanen, V., Palin, W., et al. **Under the spotlight: mechanisms of photobiomodulation concentrating on blue and green light**. 2019. *Photochem. Photobiol. Sci*; 18(8): 1877-1909.

16. Young, J. in: **The life of vertebrates**. 1962. Oxford UK. The Clarendon Press.

17. Lythgoe, J. **The ecology of vision**. 1979. Oxford UK: Oxford University Press.

18. Meissl, H. **Pineal photosensitivity: A comparison with retinal photoreception**. 1997. *Biol. Cell*; 89: 549-554.

19. Su, C., Luo, D., Terakita, A., et al. **Parietal-eye phototransduction components and their potential evolutionary implications.** 2006. *Science;* 311: 1617-1621

20. Melyan, Z., Tarttelin, E., Bellingham T, et al. **Addition of melanopsin renders mammalian**

cells photoreceptive. 2005. *Nature*; 433: 741-745.

21. Barlow, H. **Purkinje shift and retinal noise.** 1957. *Nature*; 366: 64-66.

22. Lythgoe, J. **Visual pigments and environmental light**. 1984. *Vision Res*; 24: 1539-1550.

23. Goldsmith, T. **Optimisation, constraints and history in the evolution of eyes.** 1990. *Q Rev. Biol*; 65: 281-322.

24. Barlow, R., Birger, R., Kaplan, E., et al. **On the molecular origin of photoreceptor noise**. 1993. *Nature;* 366: 64-66.

25. Haltaufderhyde, K., Ozdelik, R., Wicks, N., et al. **Opsin expression in human epidermal skin.** 2015. *Photochem. Photobiol*; 91(1): 117-123.

26. Yousef, H., Alhajj, M., Sharma, S. **Skin (integument), Epidermis.** In: StatPearls. 2020. Treasure Island (FL): StatPearls Publishing.

27. Leung, N., Montell, C. **Unconventional roles of opsins**. 2017. *Annu Rev. Cell Dev. Biol;* 33(1): 241-264.

28. Kumbalasiri, T., Provencio, I. **Melanopsin and other novel mammalian opsins**. 2005. *Exp. Eye Res*; 81(4): 368-375.

29. Mahmoud, B., Hexsel, C., Hamzavi, I., et al. **Effects of visible light on the skin.** 2008. *Photochem. Photobiol*; 84: 450-462.

30. Sklar, L., Almutawa, F., Lim, H., et al. **Effects of ultraviolet radiation on erythema and pigmentation: a review.** 2013. *Photochem. Photobiol*. Sci;12: 54-64.

31. Moan, J., Nielsen, K., Juzenione, A. **Immediate pigment darkening: its evolutionary roles may include protection against folate photosensitisation**. 2012. *FASEB. J*; 26: 971-975.

32. Wicks, N., Chen, J., Najera, J., et al. **UVA phototransduction drives early melanin synthesis.** 2011. *Curr Biol*; 21(22): 1906-1911.

33. Bellono, N., Najera, J., Oancea, E. **UV light activates a $C\alpha_{q/11}$-coupled phototransduction pathway in human melanocytes**. 2014. *J Gen. Physiol;* 142(2): 203-214.

34. Hardie, R. **Phototransduction in *Drosophila melanogaster*.** 2001. *J Exp. Biol*; 204: 3403-3409.

35. Graham, D., Wong, K., Shapero, P., et al. **Melanopsin ganglion cells use a membrane -associated rhabdomeric phototransduction cascade**. 2008. *J Neurophysiol;* 99: 2522-2532.

36. Gunkel, M., Schoneberg, J., Alkhaldi, W., et al. **Higher order architecture of rhodopsin in intact photoreceptors and its implication for phototransduction kinetics**. 2015. *Structure;* 23: 628-638.

37. Consortium, G. Human genomics. **The genotype-tissue expression (GTEx) pilot analysis: multitissue gene regulation in humans.** 2015. *Science* (N.Y.); 348: 648-660.

38. De Assis, L., Morases, M., Castucci, A., et al. **Melanopsin and rhodopsin mediate UVA-induced immediate pigment darkening: Unravelling the photosensory system of the skin**. 2018. *Euro. J Cell Biol;* 97: 150-162.

39. Jablonski, N., Chaplin, H. **Human skin pigmentation as an adaption to UV radiation**. 2010.*Proc. Natl. Acad. Sci. U.S.A.;* 107: 8962-8968.

40. Allanson,M., Domanski, D., Reeve, V. **Photoimmunoprotection by UVA (320-400nm) radiation is determined by UVA dose and is associated with cutaneous cyclic guanosine monophosphate**. 2006. *J Invest. Dermaol*; 126-197.

41. Holliman, G., Low, D., Cohen, H., et al. **Ultraviolet radiation-induced production of nitrous oxide: a multi-cell and multi-dose analysis**. 2017. *Sci. Rep*; 7: 11105.

42. De Assis, M., Moraes, A., Castucci, A. **Heat shock antagonises UVA-induced response in murine melanocytes and melanoma cells: an unexpected interaction.**2017. *Photochem. Photobiol. Sci;* 16: 633-648.

43. Duteil, L., Cardot-Leccia, n., Quelle-Roussel, C., et al. **Differences in visible light-induced pigmentation according to wavelength: a clinical and histological study in comparison with UVB exposure**. 2014. *Pig Cell Melanoma Res*; 27: 822-826.

44. Boukari, F., Jourdan, E., Fontas, E., et al.**Prevention of melasma relapses with sunscreen combining protection against UV and shorter wavelengths of visible light: a prospective randomised comparative trial**. 2015. *J Am Acad. Dermatol*; 72: 189-190.

45. Regazzetti, C., Soman, L., Debayle, D., et al. **Melanocytes sense blue light and regulate pigmentation though opsin 3.** 2018. *J Invest. Dermatol*; 138: 171-178.

46. Sugihara, T., Nagata, T., Mason, B., et al. **Absorption characteristics of vertebrate non-visual opsin Opn3**. 2016. *PLoS One*; 11(8): e0161215.

47. Koyangi, M., Takada, E., Nagata, T., et al. **Homologs of vertebrate Opn3 potentially serve as a light sensor in non-photosensitive tissue**. 2013. *Proc Natl Acad Sci USA;* 110: 4998-5003.

48. Olinski, L., Lin, E., Oancea, E. **Illuminating insights into opsin 3 function in the skin**. 2020. *Adv. Biol. Reg;* 100668.doi: j.jbior. 2019. 100668.

49. Wang, Y., Lan, Y., Lu, H. **Opsin 3 downregulation induces apoptosis of human epidermal melanocytes via a mitochondrial pathway**. 2020. *Photochem.* Photobiol; 96(1): 83-93.

50. Castellano-Pellicena, I., Uzunbajakava, J., Mignon, C., et al. **Blue light restores human epidermal barrier function via activity of opsin during cutaneous wound healing?** 2018. *Laser Surg Med;* 51(4): 370-382.

51. Tofinski, L., Demuir, E., Kauczok, S., et al. **Blue light inhibits transforming growth factor-β1-induced myofibroblast differentiation of human dermal fibroblasts.** 2014. *Exp Dermatol*; 23(4): 240-246.

52. Oplander, C., Hidding, S., Werners, F., et al. **Effects of blue light irradiation on human dermal fibroblasts. 2011**. *J Photochem. Photobiol B*; 103(2): 118-125.

53. Mignow, C., Bokchkareva, N., Uzunbajakava, N., et al. **Photo biomodulation devices for hair regrowth and wound healing: a therapy full of promise but a literature full of confusion.** 2016. *Ex Dermatol*; 25(10): 745-749.

54. Buscone, S., Mardaryev, A., Raafs, B., et al. **A new path in defining light parameters for hair growth: Discovery and modulation of photoreceptors in human hair follicles**. 2017. *Laser Surg. Med*; 49(7): 705-718.

55. Sekarans, S., Lupi, D., Jones, S., et al. **Melanopsin-dependent photoreception provides earliest light detection in the mammalian retina**. 2005. *Curr. Biol;* 15: 1099-1107.