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The expression of opsins in the human skin and its implications for photobiomodulation: A Systematic Review

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Abstract

Background: Skin is the organ most extensively exposed to light of a broad range of wavelengths. Several studies have reported that skin expresses photoreceptive molecules called opsins. However, the identity and functional role of opsins in the human skin remain elusive. We aim to summarize current scientific evidence on the types of opsins expressed in the skin and their biological functions.

Methods: A primary literature search was conducted using PubMed to identify articles on dermal opsins found in nonhuman animals and humans.

Results: Twenty-two articles, representing, however, a non-exhaustive selection of the scientific papers published in this specific field, met the inclusion criteria. In nonhuman animals, opsins and opsin-like structures have been detected in the skin of fruit fly, zebrafish, frog, octopus, sea urchin, hogfish, and mouse, and they mediate skin color change, light avoidance, shadow reflex, and circadian photoentrainment. In humans, opsins are present in various skin cell types, including keratinocytes, melanocytes, dermal fibroblasts, and hair follicle cells. They have been shown to mediate wound healing, melanogenesis, hair growth, and skin photoaging.

Conclusion: Dermal opsins have been identified across many nonhuman animals and humans. Current evidence suggests that opsins have biological significance beyond light reception. In nonhuman animals, opsins are involved in behaviors that are critical for survival. In humans, opsins are involved in various functions of the skin although the underlying molecular mechanisms remain unclear. Future investigation on elucidating the mechanism of dermal opsins will be crucial to expand the therapeutic benefits of photobiomodulation for various skin disorders.

Keywords

dermal photoreceptor; extraocular photoreceptor; hair follicle; keratinocytes; melanocytes; opsin; photobiomodulation; skin

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CONFLICT OF INTEREST

None.

1 | INTRODUCTION

The concept of dermal photoreception has started to gain wide-spread attention since the 1950s when Steven et al demonstrated that sea lamprey could respond to tail illumination even in the absence of the eyes.[1] Shortly thereafter, more evidence from behavioral studies supported the presence of photoreceptive elements in the skin of animals by showing that localized illumination on the skin elicits locomotion (river lamprey, *Lampetra fluviatilis*, Chordata), skin color change (octopus, *Octopus bimaculoides*, Mollusca), withdrawal behavior (pond snail, *Lymnaea stagnalis*, Mollusca), light avoidance (fruit fly, *Drosophila melanogaster*, Arthropoda), and thermoregulatory behavior (lizard, *Podarcis muralis*, Chordata).[2–9] Continuous investigations in dermal photoreception have identified mitochondrial cytochrome c oxidase (CCO), nitrosated proteins, flavoproteins generating reactive oxygen species (ROS), and light-activated calcium ion channels as endogenous photosensors.[10] More recently, opsins, which are key phototransducing molecules found in the retina, have emerged as new photosensors in the skin as several lines of scientific evidence support their expression in both nonhuman animal and human skin.[11,12]

Opsins are a large group of light-sensitive G protein–coupled receptors (GPCRs) that use retina as a ligand and trigger signaling cascades upon distinct wavelength of light. Opsins, primarily found in light-detecting cells such as the retinal photoreceptors, are widely known for their key role in visual transduction.[13–15] Opsins have evolved across animal phylogeny, and their diversity can be categorized into three large groups: ciliary opsins (c-opsins), rhabdomeric opsins (r-opsins), and tetraopsins (Table 1).[16,17] The c-opsins, which are mostly present in vertebrates, are characterized by their expression in ciliary photoreceptor cells and cyclic nucleotide signaling cascade. On the other hand, r-opsins, which are expressed in invertebrates except melanopsins, are expressed in rhabdomeric photoreceptor cells and have phosphoinositol signaling cascade. Tetraopsins, also known as group 4 opsins, include retinal G protein–coupled receptor opsins (RGR), retinochrome, peropsin (RRH), neuropsin (OPN5), and Go-opsins. In contrast to c-opsins and r-opsins, many tetraopsins are relatively poorly characterized although more recent evidence suggests their functional role in photoisomerization of *trans-form* to *cis*-form of retinal.[18–20]

Despite a crucial role in vision, a wide array of opsins has been identified in the skin of animals, including humans, suggesting their role as dermal photosensors. Studies in nonhuman animals suggest that dispersed photoreception through dermal opsins enables animals to quickly respond against potential dangers in a wild environment and increase their chance of survival.[11,14] On the other hand, very little is known about the opsin expression profiles and physiological functions in human skin.

As photobiomodulation (PBM), a form of light therapy based on nonionizing forms of light sources, is becoming a promising therapeutic approach for the treatment of various dermatological conditions, such as psoriasis, atopic dermatitis, hair regrowth, wound healing, and tissue regeneration, it is particularly important to understand the types of opsins expressed in human skin and their downstream molecular mechanisms.[10,21–24] Since each opsin has distinct absorption spectra and signaling transduction, the optimization of light

therapy tailored to the features of each opsin will maximize the benefit that PBM can offer in the clinic.

In this review, we aim to examine the types of opsins expressed in human skin cell types and their elucidated role in skin physiology. To provide a background on how dermal opsin research has evolved over time, we will begin with a brief overview of the opsin expression in nonhuman animal skin.[10,22,23,25–29]

2 | METHODS

We searched the PubMed database using the following key term combination: "(photoreceptors OR opsin OR opsin-like OR rhodopsin) AND (skin OR dermal OR melanocytes OR keratinocytes OR epidermis)." The search retrieved 484 studies published from August 1951 up to January 2020, and two independent reviewers screened all titles and abstracts in accordance with the Preferred Reporting System for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1). The following exclusion criteria were applied: (a) non–evidence-based studies including review articles, letters, and commentaries; (b) studies performed with non–human-derived immortal cell line; (c) studies written in languages other than English; (d) studies focusing on other primary photosensor molecules, such as cytochrome c oxidase (CCO), nitrosated proteins, flavoproteins, and calcium channels; and (e) studies about extraocular opsins that are not expressed in the skin.

On a further note, we acknowledge the potential bias in our literature search by using keywords, "skin" and specific skin cell types, that could result in the exclusion of literature focusing on opsins expressed in the integument of invertebrates.

3 | RESULTS

A total of 22 studies met our criteria and were included for review. Eleven studies provided the evidence of dermal photoreception and the opsin expression in nonhuman animal skin. Eleven studies describe the opsin expression and their potential function in human skin cell types including keratinocytes, melanocytes, hair follicle cells, and dermal fibroblasts. We organized our findings into two tables (Table 2 on nonhuman animals and Table 3 on humans).

3.1 | The expression and function of dermal opsins in nonhuman animals

The earliest evidence of opsin in the skin is the discovery of melanopsin (OPN4) in dermal melanophores in frogs (*Xenopus laevis*, Chordata).[18,30] In 1998, Provencio et al identified OPN4 in the frog dermal melanophores by in situ hybridization and Western blot analysis. Their goal was to identify the light-detecting molecule that is responsible for melanosome migration, which enables frogs to change their skin colors to maintain body temperature or avoid the predators.[30] Despite a discovery of OPN4 in melanophores, whether the OPN4 is the target light-sensing receptor-mediating melanosome migration remained uncertain until 2005. In 2005, Isoldi et al showed that molecular components of OPN4 signaling pathway also exist in the cultured *Xenopus* dermal melanophores and that light increases the intracellular level of inositol trisphosphate and activity of phospholipase C in dermal

melanophores during the melanosome migration, suggesting that OPN4 is the key sensor mediating melanosome dispersion in *Xenopus.*[31]

In 2010, Xiang et al identified rhodopsin-like protein called gustatory G protein–coupled receptor 28b (Gr28b) in class IV dendritic neurons on the body surface of fruit fly larvae (*Drosophila melanogaster*, Arthropoda). Although Gr28b is not exactly an opsin, it has a rhodopsin-like structure and likewise converts the light into electrical signals transmitting to the brain.[9] The group found that Gr28b enables *Drosophila* larvae to sense light over their entire bodies and move away from the light, which is critical for the survival of *Drosophila* larvae to minimize predation risk since they spend most of the time feeding by digging their heads into food.

In 2010, Mäthger et al detected the mRNA of r-opsin, also known as rhabdomeric opsin responsible for vision in mollusks, in the skin of cuttlefish (*Sepia officinalis*, Mollusca), suggesting its possible role in dermal photoreception and skin color change mediated by dermal chromatophores.[32] In 2015, other groups also detected the expression of r-opsin protein in the skin of several cephalopod species, including cuttlefish, longfin squid (*Doryteuthis pealeii*, Mollusca), and octopus (*Octopus bimaculoides*, Mollusca).[3,33] Additionally, Kingston et al identified retinochrome, a type of tetraopsin, in the skin of these species. In cephalopod eyes, the retinochrome is known to isomerize all-*trans*-retinal to 11-*cis*-retinal upon illumination and contributes to the formation of visual pigments by counterbalancing isomerization of r-opsin.[34,35] The role of retinochrome in the skin is not clear, but several lines of evidence reported that retinochrome might be involved in light-activated chromatophore expansion (LACE), which causes skin color change.[33]

In 2013, Ullrich-Lüter et al reported that purple sea urchin (*Strongylocentrotus purpuratus*, Echinodermata) expresses c-opsin in the epidermal cells of the body wall.[36] The role of c-opsins in the sea urchin remained ambiguous, but authors hypothesized that they might be involved in the so-called shadow reflex, a rapid spine movement in response to overhead shadow. Another body of studies has provided compelling evidence that dermal opsins expressed in zebrafish (*Danio rerio*) and mice (Mus *musculus*) contribute to the synchronization of the circadian rhythm.[37–39] It has been previously suggested that neuropsin (OPN5) appeared to be expressed in the hypothalamus of birds and contribute to seasonal reproduction.[40–43] However, Buhr et al demonstrated that OPN5 is also expressed in mice melanocytes and synchronize the circadian clock of the skin to the light and dark cycle.[38] Interestingly, the photic circadian entrainment by OPN5 in the skin was independent of the retina and suprachiasmatic nuclei (SCN).[38]

More recently, next-generation sequencing has emerged as a useful tool for detecting novel phototransduction genes, allowing the comparison of the differential expression of opsins in the retina and skin, and helps determine whether they share the same evolutionary history. Dissecting the evolutionary history of skin opsins can provide insights into their physiological significance in the skin. The transcriptomic analysis on the skin and retina of hogfish (*Lachnolaimus maximus*, Chordata) showed that the skin and retina have distinct phototransduction signaling cascade.[44] In contrast to two visual opsin genes and cGMP-dependent phototransduction component expression in the retina, only a single short-

wavelength opsin (SWS1) and cAMP-dependent phototransduction components were expressed in the skin. The transcriptome analysis on the skin and eye of velvet belly lanternshark (*Etmopterus spinax*, Chordata), likewise, showed distinct expression pattern in the eye and skin.[45] In the eye, rhodopsin (OPN2) and peropsin (RRH) were enriched, whereas in the skin, encephalopsin (OPN3) was most abundant. The transcriptomic data suggest that the molecular mechanism of opsins in the skin may be distinct from that of opsins found in the eye although further investigations need to be conducted.

Here, we showed several evidence of dermal opsins found in nonhuman animals to understand their biological significance. Current findings from nonhuman animal studies support that dermal opsins mediate dispersed photoreception across the body surface and allow the animals to instantly respond to changes in irradiation of local surrounding.[6,11,46] In animals that face a constant threat of unpredictable environment and predators, dermal photoreception allows them to move away from potential danger, conceal themselves by camouflage or shadow reflex, and control circadian rhythms. However, it is still unclear to what extent dermal opsins mediate such behaviors, and would require further studies to answer this question.

3.2 | The expression and function of dermal opsins in humans

Humans live in a vastly different environment in comparison with the aforementioned nonhuman animal species. For instance, humans do not need or have the ability to camouflage for survival as frogs and octopuses do. Nevertheless, a wide array of opsins is expressed throughout different skin cell types including keratinocytes, melanocytes, dermal fibroblasts, and hair follicle cells (Figure 2).[24,47] It is still unknown whether these opsins have biological functions beyond light reception in human skin cells or they are vestigial evolutionary remnants from mechanisms developed in prehistoric times. To interrogate the potential function of these opsins expressed in the human skin, it is important to first understand the physiological role of each skin cell type. Human skin consists of three basic layers–the epidermis (outermost), the dermis (middle), and the hypodermis (innermost).[48] The epidermis is comprised mainly of keratinocytes and melanocytes. Keratinocytes synthesize keratin, acting as the first line of innate immune defense against infection and external factors. Melanocytes produce a pigment called melanin, which protects the skin from UV rays.[49] The dermis contains dermal fibroblasts, which generate connective tissue allowing the skin to recover from injury, and hair follicle cells, which regulate hair growth.[49] The hypodermis is mostly made of fat and connective tissue that attaches the dermis to the body and regulates body temperature.[49] Here, we compile studies reporting the identity and the elucidated role of opsins in each cell type.

3.2.1 | Keratinocytes—In 2009, Tsutsumi et al first identified the expression of visual opsins, cone opsin (OPN1) and rhodopsin (OPN2), in both human facial skin tissue and cultured normal human epidermal keratinocytes (NHEKs) by RT-PCR and immunohistochemistry.[50] In 2013, Kim et al confirmed the expression of OPN2 in cultured human epidermal keratinocytes and suggested that OPN2 could be involved in the regulation of keratinocyte differentiation by showing that violet light (410 nm) irradiation decreases keratinocyte differentiation markers with a corresponding increase in OPN2 expression.[51]

However, the difference in the absorption spectrum of OPN2 (λ_{max}, 480-530 nm) raises a question whether the effect is mediated through OPN2. In 2015, Haltaufderhyde et al identified two other opsin types, encephalopsin (OPN3) and neuropsin (OPN5), from neonatal foreskin-derived epidermal keratinocytes in addition to OPN1 and OPN2.[47] In 2017, Toh et al identified peropsin (RRH), a type of tetraopsin which had previously been known to be exclusively expressed in the retinal pigmented epithelial (RPE) cells of the eye, in both human skin tissue and cultured NHEKs.[52] They reported that irradiation of cultured keratinocytes with violet light (380 nm) elicits the highest amplitude of Ca^{2+} transients only in the presence of the all-*trans*-retinal ligand, suggesting that RRH may contribute to the phototransduction of violet light in keratinocytes. The spectral sensitivity of RRH is unknown, but neuropsin and RGR, two other phylogenetically related tetraopsins, have maximal absorption spectra at 380 and 470 nm, respectively.[19,53] However, the pathophysiological relevance of this RRH in human skin warrants further investigation.

In 2018, Pellicena et al confirmed the expression of OPN1-SW, OPN3, and OPN5 in cultured epidermal keratinocytes of human facial and abdominal skin by immunofluorescence analysis and also showed that irradiation with blue light (447 nm) accelerates wound closure in the regenerating epithelial tongue of an ex vivo human skin wound-healing model with a corresponding increase in OPN3 expression.[54] To further explore how OPN3 mediates wound healing, they evaluated the migration, proliferation, and differentiation, which are vital for wound repair, in cultured keratinocytes following blue light irradiation. They found that low levels of blue light did not affect migration or proliferation, but stimulated differentiation of keratinocytes, which was abrogated by OPN3 knockdown. Overall, the current findings on keratinocytes suggest that OPN3 is involved in cell differentiation regulation and restoration of the barrier function.[54]

3.2.2 | Melanocytes—In 2011, Wicks et al first identified the expression of OPN2 in cultured human epidermal melanocytes (HEMs) and reported that UV irradiation induces calcium influx and melanin production in HEMs.[55] The same group later proposed that melanin synthesis occurs via calcium-mediated $G\alpha_{q/11}$ pathway, the same mechanism of visual phototransduction in the retina.[56] In 2015, Haltaufderhyde et al detected three other opsins expressed in cultured normal human melanocytes (NHMs), OPN1-SW, OPN3, and OPN5, although OPN2 and OPN3 were expressed most abundantly.[47] In 2018, Regazzetti et al proposed that OPN3 might be a key receptor responsible for visible light-induced hyperpigmentation by demonstrating that violet light (415 nm) irradiation on cultured NHMs activates calcium-dependent microphthalmia-associated transcription factor (MITF) pathway and upregulates melanogenesis-associated enzymes, whereas the violet light-induced effect was abrogated by silencing OPN3.[57] In 2019, Ozdeslik et al also suggested that OPN3 might play a key role in the regulation of melanogenesis, but proposed a different mechanism of action.[58] Ozdeslik et al found that OPN3 acts as a negative modulator of melanin production via coupling to Gαi pathway, which inhibits melanocortin 1 receptor (MC1R)-mediated cAMP response leading to melanin production.

In 2020, Wang et al reported that OPN3 is a key receptor responsible for survival of human epidermal melanocytes.[59] They observed that downregulation of OPN3 markedly reduces

the intracellular calcium level and triggers the conventional apoptosis pathway via mitochondria.

Taken all together, the existing evidence supports the expression of several opsin types in human melanocytes with OPN3 being most abundantly expressed. The mechanism of action of OPN3 in melanogenesis is debated and will require further investigations.

3.2.3 | Hair follicle cells—The presence of opsins in the hair follicle stem cells has recently gained attention as many reports have shown that PBM has positive effects on hair growth.[23] In 2017, Buscone et al detected OPN2 and OPN3 in anagen hair follicles and demonstrated that blue light (453 nm), which corresponds to the absorption spectra of OPN3, prolongs anagen hair growth phase. In contrast, red light did not affect hair growth and silencing OPN3 abrogated stimulatory effects of blue light.[60] Unfortunately, there is scarce evidence on the functional role of opsin in hair follicle cells. Elucidating the molecular target and mechanism will open new door for utilization of light therapy in alopecia patients.

3.2.4 | Dermal fibroblasts—In 2018, Pellicena et al reported for the first time that cultured dermal fibroblasts from human facial and abdominal skin tissue express OPN1-SW, OPN2, and OPN3.[54] Although the function of these opsins in dermal fibroblasts was not elucidated in their study, they inferred from the previous finding showing the anti-proliferative effect of blue light (450-490 nm) on fibroblasts in vitro that opsins might be involved in the regulation of cell proliferation.[61–63] The modulation of dermal fibroblasts by blue light has the potential for the treatment of hypertrophic scarring, such as keloids and other fibrotic skin diseases, and the role of opsins in fibroblasts is worthy of further investigations.[64]

In 2019, Lan et al provided the first evidence that OPN3 is the key sensor responsible for upregulating matrix metalloproteases (MMPs) in dermal fibroblasts upon ultraviolet A (UVA) exposure and contributes to the skin photoaging. It has been well known that chronic exposure to UVA radiation induces an increase in MMPs, which leads to the degradation of fibrous connective tissue and skin photoaging. The group detected all five opsins, OPN1-OPN5, in normal human dermal fibroblasts (NHDFs) by qPCR and Western blot analysis, but UVA exposure particularly increased the expression level of OPN3 and triggered the phototransduction and the expression of MMPs.

4 | DISCUSSION

Many studies have supported the existence of skin photosensors across different species with the evidence of behavioral, electrophysiological, and genetic studies. At the beginning, most studies supported the existence of dermal photosensitivity through animal behavior and electrophysiology analysis. Advances in molecular biology techniques eventually led to a discovery of opsins as potential photosensors in the skin and inspired great scientific interest concerning the role of opsins in the skin. A number of studies demonstrated that opsins modulate various physiological processes of the skin, including wound healing, melanogenesis, photoaging, and hair growth.[54,58]

Despite compelling evidence, further investigations are needed to validate the current findings in the literature. Many studies have been performed on cultured skin cells, which might not display the exact morphological and physiological properties of native tissue in vivo. Cultured cells may alter the native expression profiles and lose their specific phenotypes after multiple passages. Such changes can potentially provide misleading information on the gene expression in native tissue.

The research in dermal opsins has great potentials for advancing the clinical applications of PBM. There has been a growing interest in the application of light therapy to clinical cases owing to the advantages of a cost-effective and noninvasive approach. In order to maximize the benefit of light therapy, it is critical to understand the underlying mechanisms of opsins in modulating physiological processes in the skin and define light parameters that elicit such responses. Several studies have already demonstrated the great potentials of PBM for treating dermatological conditions by targeting these opsins.[21] Recent studies, which demonstrated the stimulatory effect on hair follicle stem cells and melanocytes with specific wavelengths of light irradiation, suggest that PBM could be a new promising treatment for hair loss and skin pigmentation disorders in near future.[58,60]

To enhance understanding of the mechanistic role of opsins in the skin, future investigations using Cre-based knockout mice will be a valuable tool to confirm the therapeutic efficacy and safety of PBM. Moreover, optimization of light exposure time, wavelength, intensity, and treatment interval will accelerate the clinical application of PBM. Although unlocking the therapeutic value of PBM still requires a deeper understanding of biochemical processes, the current literature strongly supports the notion that PMB is a promising therapeutic modality in clinical dermatology.

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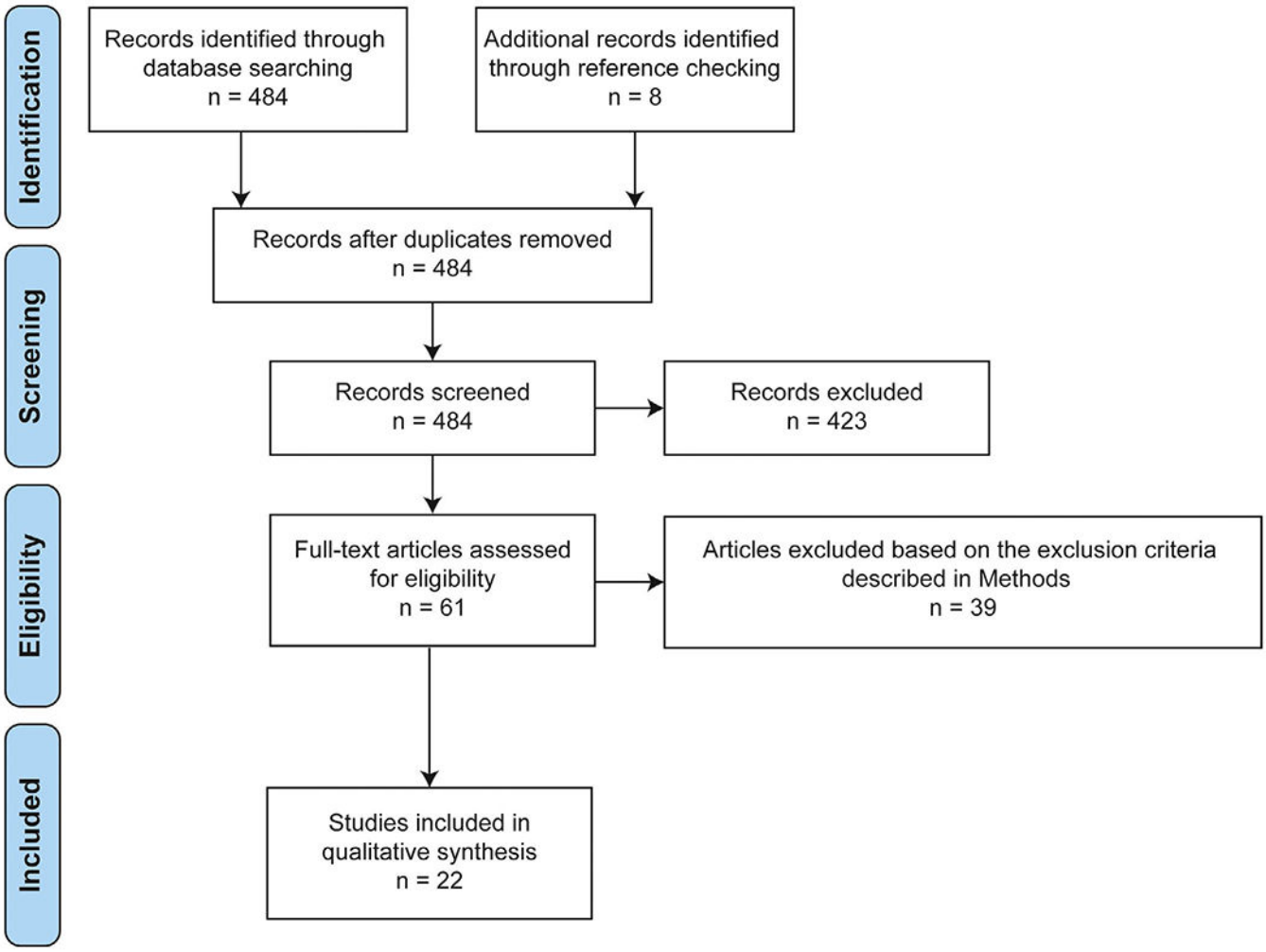


FIGURE 1.
Literature search according to the PRISMA guideline [Colour figure can be viewed at wileyonlinelibrary.com]

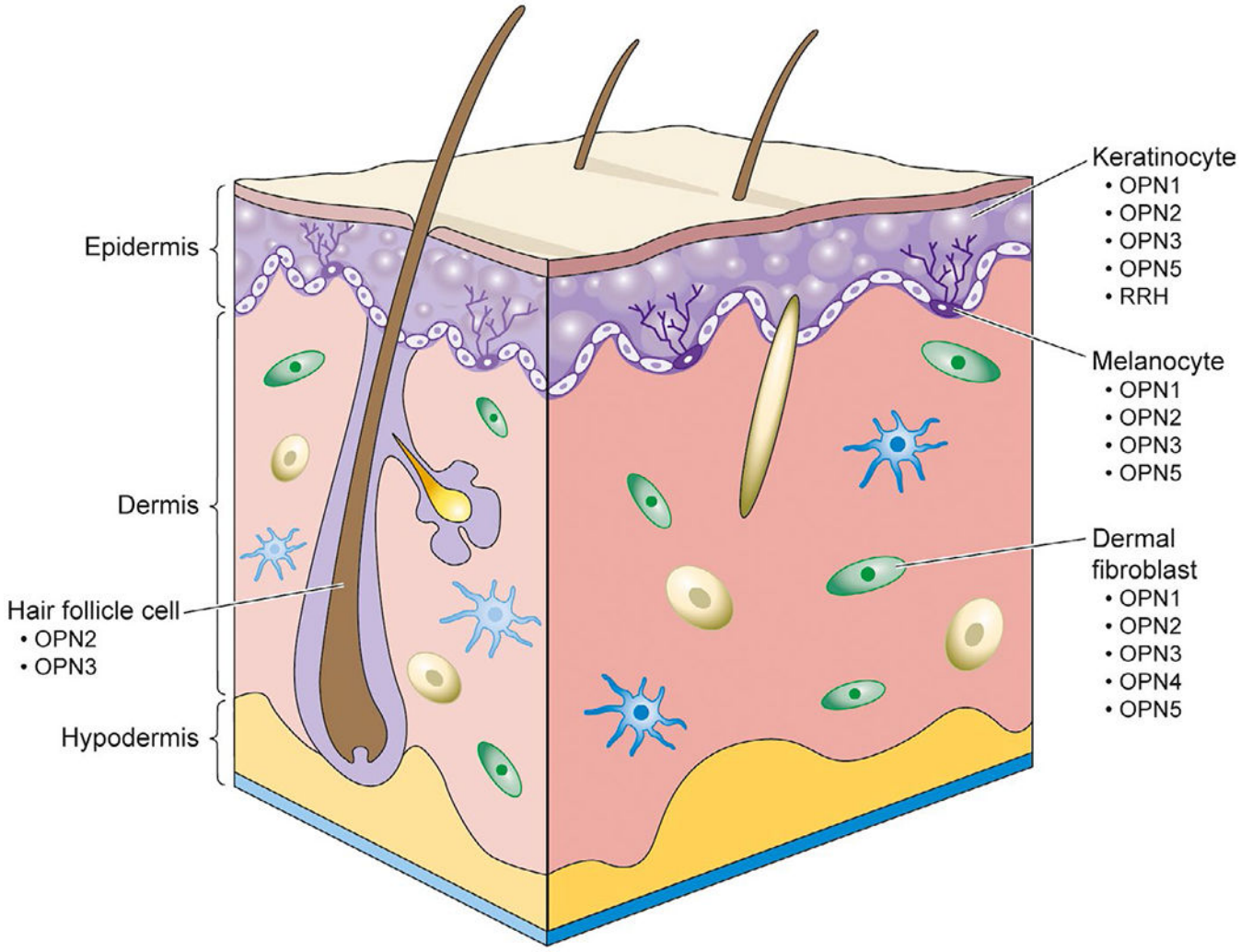
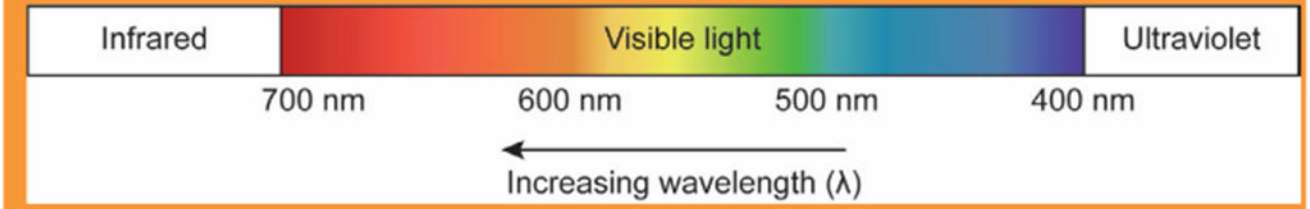


FIGURE 2.

The expression of opsins in human skin cell types [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1

Classification of selected opsins expressed in the skin



Name	G-protein	Absorption wavelength	Color
C-opsin (ciliary)			
Blue opsin (OPN1-SW)	G_t	~425 nm	Violet-blue
Green opsin (OPN1-MW)	G_t/G_s	~530 nm	Green
Red opsin (OPN1-LW)	G_t	~560 nm	Yellow-orange
Rhodopsin (OPN2)	G_t	~500 nm	Green
Encephalopsin/panopsin (OPN3)	G_i/G_o	~420-527 nm	Violet-green
R-opsin (rhabdomeric)			
Melanopsin (OPN4)	G_q	~480 nm	Blue-green
Mollusk visual opsins	G_q		
Arthropod visual opsins	G_q		
Tetraopsin (group 4 opsins)			
Retinochrome			
Retinal GPCR opsin (RGR)		~470 nm	Blue-green
Peropsin (RRH)			
Neuropsin (OPN5)	G_i	~380 nm	Ultraviolet

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TABLE 2

List of studies providing evidence of opsin expression in nonhuman animal skin

Year	Author	Species	Photosensitive protein	Detection method	Potential role	Major finding
1998	Provencio et al	Frog (*Xenopus laevis*)	OPN4	In situ hybridization, Western blot	Mediates melanosome migration for color change	OPN4 is detected in dermal melanophores
2005	Isoldi et al	Frog (*Xenopus laevis*)	OPN4	RT-qPCR	Mediates melanosome migration for color change	Light activates melanopsin phosphoinositide cascade, resulting in melanosome granule dispersion within melanophores
2010	Xiang et al	Fruit fly (*Drosophila melanogaster*)	Gr28b (rhodopsin-like protein)	Electrophysiology, light-activated signaling assay (GCaMP3 imaging)	Mediates light-avoidance behavior	Ablation of class IV dendritic arborization neurons decreases light-avoidance behavior
2010	Mäthger et al	Cuttlefish (*Sepia officinalis*)	r-opsin	RT-PCR	Mediates distributed light sensing	r-opsin mRNA is found in the skin
2013	Ullrich-Lüter et al	Sea urchin (*Strongylocentrotus purpuratus*)	c-opsin	Immunohistology, in situ hybridization	Mediates shadow reflex	c-opsin mRNA and protein are found in the epidermal cells
2015	Ramirez et al	Octopus (*Octopus bimaculoides*)	r-opsin	Immunofluorescence, gene expression analysis	Mediates the skin color change	Isolated skin tissue shows color alteration upon light illumination
2015	Kingston et al	Octopus, cuttlefish, longfin squid (*Doryteuthis pealeii*)	r-opsin, RGR	Immunofluorescence, Western blot, RT-qPCR	Mediates skin color change	Phototransduction components of the retina are found in the skin
2015	Davies et al	Zebrafish (*Danio rerio*)	OPN5	RT-PCR	Not shown	OPN5 is detected in the skin
2018	Schweikert et al	Hogfish (*Lachnolaimus maximus*)	SWS1	De novo transcriptome	Mediates color change	Skin expresses distinct phototransduction signaling cascade from that found in the retina
2019	Delroisse et al	Velvet belly lanternshark (*Etmopterus spinax*)	OPN3	De novo transcriptome	Mediates color change	Opsins are differentially expressed in the retina and skin
2019	Buhr et al	Mouse (*mus musculus*)	OPN5	Immunofluorescence, RT-PCR	Synchronizes the circadian rhythm	OPN5 regulates the amplitude of clock gene expression

Abbreviations: $G_{q\alpha}$, G_q α-subunit; Gr28b, gustatory G protein–coupled receptor 28b; OPN3, encephalopsin; OPN4, melanopsin; OPN5, neuropsinRGR, retinochrome; r-opsin, rhabdomeric opsin; RT-PCR, reverse transcriptase PCR; RT-qPCR, reverse transcription-quantitative PCR; SWS1, short-wavelength sensitive opsin.

TABLE 3

List of studies providing evidence of opsin expression in human skin

Year	Author	Cell type	Photosensitive protein	Detection method	Potential role	Major finding
2009	Tsutsumi et al	Keratinocytes	OPN2, OPN1-LW, OPN1-MW	Immunofluorescence, RT-qPCR	Not shown	First study to identify the expression of rhodopsin-like and opsin-like genes in human keratinocytes
2011	Wicks et al	Melanocytes	OPN2	Western blot, immunofluorescence, RT-qPCR	Mediates melanin production	UV radiation induces calcium influx and melanin synthesis in melanocytes; OPN2 knockdown abrogates the effect
2013	Kim et al	Keratinocytes	OPN2	Western blot, immunofluorescence	Regulates cell differentiation	Violet light (410 nm) increases the expression of OPN2 mRNA, while decreasing the expression levels of keratinocyte differentiation markers
2015	Haltaufderhyde et al	Keratinocytes, melanocytes	OPN1-SW, OPN2, OPN3, OPN5	RT-qPCR, Western blot	Not shown	Various opsin molecules are expressed in epidermal keratinocytes and melanocytes
2017	Toh et al	Keratinocytes	RRH	Immunofluorescence, RT-qPCR, Western blot	Mediates light-induced phototransduction	Irradiation with 380 nm light elicits intracellular calcium influx in cell culture; RRH knockdown downregulates the genes involved in phototransduction
2017	Buscone et al	Hair follicle stem cells	OPN2 and OPN3	Immunofluorescence, RT-qPCR	Mediates hair growth regulation	Blue light (453 nm) activation of hair follicles prolongs anagen hair growth phase. OPN3 knockdown abrogates the effect
2018	Regazzetti et al	Melanocytes	OPN3	RT-qPCR	Induces melanin production	Violet light (415 nm) irradiation induces calcium signaling and upregulation of melanogenesis-associated proteins. OPN3 knockdown abrogates the effect
2018	Pellicena et al	Keratinocytes, dermal fibroblasts	OPN3	Immunocytochemistry, RT-qPCR	Mediates cutaneous wound healing	Blue light (447 nm) induces early differentiation in keratinocytes culture and activation of OPN3 in keratinocytes OPN3 mRNA increased in irradiated keratinocyte culture in vitro migration assay
2019	Ozdeslik et al	Melanocytes	OPN3	RT-qPCR, Western blot	Negatively modulates melanin production	OPN3 inhibits MC1R-mediated cAMP response that leads to melanin production. This regulation is not mediated by calcium-dependent pathway
2019	Lan et al	Dermal fibroblasts	OPN1–5; focus on OPN3	RT-qPCR, Western blot	Mediates UVA-induced MMP	UVA induces OPN3 and phototransduction as well

Year	Author	Cell type	Photosensitive protein	Detection method	Potential role	Major finding
					production and skin photoaging	as an increase in the level of MMP
2020	Wang et al	Melanocytes	OPN3	RT-qPCR, Western blot, immunofluorescence	Regulates the survival of melanocytes	Knockdown of OPN3 triggers the apoptosis through a calcium-dependent G protein-coupled signaling and mitochondrial pathway

Abbreviations: $G_{q\alpha}$, G_q α-subunit; MC1R, melanocortin 1 receptor; MMP, matrix metalloprotease; OPN1-LW, long-wavelength sensitive cone opsin; OPN1-MW, medium-wavelength sensitive cone opsin; OPN1-SW, short-wavelength sensitive cone opsin; OPN2, rhodopsin; OPN3, encephalopsin; RGR, retinochrome; RRH, peropsin; RT-qPCR, reverse transcription-quantitative PCR; UVA, ultraviolet A.