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Opsins as main regulators of skin biology

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ABSTRACT

Opsins are light-sensitive proteins that are found across the animal kingdom. In mammals, opsins are classically associated with image-forming processes, a function exerted by cone and rod opsins. In early 2000, melanopsin was identified in the human retina as an important regulator of non-image forming events such as melatonin suppression, pupillary constriction, and circadian rhythm adjustment. The presence of different opsins and the biological processes that these proteins regulate in the skin are increasingly being described. Currently, opsins are considered light as well as thermosensors in the skin. However, additional regulatory functions, in a light and thermo-independent fashion, mostly likely via protein-protein interaction have set a new field of study. The goal of this review is to critically revise the literature on the role of opsins in skin physiology as well as in melanoma cancer.

An overview of the skin biology

The skin is the largest organ and an important physical barrier between the internal and external environments [1]. A less appreciated function of the skin is its endocrine role, which is important in regulating local biological processes, but an increasing amount of evidence clearly demonstrates that the skin also exerts systemic regulatory functions [2].

The complexity of the skin is remarkable as it contains several different cell types distributed along the epidermis and dermis. In the epidermis, stem cells differentiate into keratinocytes that undergo a differentiation process, through the various layers of the epidermis, which ultimately results in the epidermal barrier formation [3]. Another important cell type is the melanocyte, which is specialized in producing melanin pigment. Melanocytes are in the *stratum basale* and are known to connect to approximately 36 keratinocytes [4]. Melanin synthesis is triggered by photonic (ultraviolet radiation and visible light) and endocrine signals (such as melanocyte-stimulating hormone – MSH). This pigment is then transferred to neighboring keratinocytes where it migrates toward the nucleus to act as a physical shield to prevent the deleterious effects of UV radiation and visible light [5–7]. The dermis is an important sub-compartment that supports and nourishes the epidermis; it consists of fibroblasts, lymph and blood vessels, nerve endings, hair follicles, and sebaceous glands [3]. Below the dermis lies the hypodermis which is considered a part of the subcutaneous tissue. It should be stressed that hypodermis affects several biological processes of the skin such as hair growth, wound healing, aging, temperature homeostasis, and immune response, among others [8].

A remarkable function of the skin is its highly complex endocrine system. The presence of equivalents to the hypothalamic–pituitary–adrenal (HPA) and hypothalamic–pituitary–thyroid (HPT) axes, catecholaminergic, cholinergic, steroidogenic, melatoninergic, and secosteroidogenic systems has been extensively described [2,9]. Based on this large amount of evidence, the skin can be viewed as a functional peripheral neuroendocrine organ. Moreover, the skin can be also appreciated as a sensory organ, which detects environmental stimuli such as UV radiation, visible light, temperature, chemical and physical agents, and pathogens, among others [1]. The perception of these stimuli demands physiological responses to prevent damage to the organism's integrity. This includes direct communication with the brain, thus characterizing the bidirectional skin-brain axis [2]. It is believed that the skin-brain axis not only regulates the local physiological processes of the skin but also has systemic effects, thus placing the skin as an important player in systemic homeostasis [2]. The skin is also equipped with several defense mechanisms that assist this organ in coping with the aggressions of the environment. Processes such as an intrinsic immune system, neuroendocrine system, shedding and apoptosis of

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epidermal squamous cells, DNA repair, and pigmentary response have been described. Interestingly, these systems are also subject to time-of-day dependent regulation, which is exerted by the central clock, located in the hypothalamus, and local clocks [10].

Although several factors are known to affect the skin [1], our focus here will be on the photonic stimulation of the skin within the range of UV radiation and visible light. UV radiation comprises only 2% of the electromagnetic solar spectrum, in which UVB and UVA represent 5 – 10 and 90 – 95%, respectively [7]. Interestingly, the research focus in the last decades was mostly on UV radiation, which represents a small portion of the solar spectrum. One must account that UV radiation, especially UVB, represents a risk factor for skin cancer [11]; however, such restricted attention left the visible and infrared radiation, which accounts for about 47% and 51% of the solar spectrum, largely unexplored for several decades. This has resulted in a markedly reduced number of studies and a sense that these stimuli are not relevant to skin biology as discussed previously [7]. Despite the increasing awareness of sunscreen usage, there is still a growing incidence of skin cancer [11]. It is important to consider the development of comprehensive and more effective methods of skin care, including photoprotection for VL.

It has been recently shown that the skin is also equipped with a light-detecting system based on opsins (photoreceptor molecules), which is similar to the photosensitive system present in the eye [7,12]. One must also account that the skin has different chromophores, which are light-sensitive, and also participate in the cutaneous light sensor system [7,13–17]. The identification and comprehension of the photosensitive system have grown in the past years. Currently, the pattern of opsin expression across the cells and layers has become more appreciated and its recent advances in knowledge and impact on skin biology will be reviewed here.

Effects of ultraviolet radiation (UVR) and visible light (VL) on the skin

The interaction of solar radiation with the skin is influenced by tissue scattering, by light-absorption, and by photochemical transformations triggered by the excited state species of the endogenous chromophores, which are molecules present in human skin that absorb UV or VL. The lesser the flux of photons is scattered or absorbed, the deeper it will penetrate the skin, which defines the skin penetration depth of the different ranges of sun radiation. Basically, penetration depth increases with the increase in the wavelength reaching a maximum at the so-called biological window (red light and NIR). The effects of UV, VL, and IR photons on skin physiology are unique and specific to each range and can be understood by analyzing the excited state properties of the respective chromophores they excite. Both UV and VL photons get transformed in redox-active excited states that can induce oxidative damage in lipids, proteins, and nucleic acids, causing oxidative distress in skin cells [7,18–20]. Whether or not the exposure will damage molecules, cells and tissues depends on many factors, including properties of the irradiation (dose and irradiance) as well as of the molecules, cells, and tissues. It is important to say that there are huge differences between the sun irradiance and that of LED devices that are increasingly used for humans. While the solar irradiance is around 1000–1500 W/m^2 [21] several man-made devices, for example those used to measure the partial pressure of oxygen use LED emission in the red or NIR with an irradiance of 10 W/m^2 [22]. While the exposure to the LED devices and light encountered in usual working environments is completely safe to humans [23], the redox challenges induced by sun exposure trigger redox signaling responses that can be harmful [24]. A physiologically relevant reaction that is induced mostly by UVB radiation is the direct formation of cyclobutene pyrimidine dimers and 6–4 photoproducts, which cause DNA mutations if not repaired. This is because UVB photons are absorbed directly by the DNA, forming excited-state species that engage in direct photoaddition reactions [7,25,26].

The biological responses to sun exposure occur both during and after exposure. The excess of sun exposure causes acute (erythema or tanning) and chronic (melasma, photoaging, and cancer) effects. The dose that causes the erythema reaction is defined as the minimal erythemal dose (MED), which is a response mediated mostly by UVB [20]. It is important to mention that small levels of sun exposure are usually beneficial to humans [27]. Indeed, it was recently reported a substantial increase in the life expectancy of females that had active sun exposure habits, compared to those that actively avoid sun exposure [28]. UVB rays are also the major responsible for the intracellular reactions that lead to the activation of vitamin D, which has a multitude of biological activities related to calcium metabolism, as well as to other homeostatic mechanisms, including inhibition of cancer cell proliferation [29,30]. Besides, controlled levels of sun exposure cause a decrease in blood pressure and induce a variety of other biological stimuli, probably due to the activation of opsins present in skin cells [31] (see further information below).

Melanin is a natural sunscreen pigment that is produced by sun exposure stimuli, and its main biological function is to avoid or reduce DNA damage. However, under certain conditions, melanin can absorb UV or VL and form excited states. It has been demonstrated that melanin itself photosensitizes the production of singlet oxygen, which can oxidize a variety of biomolecules, including lipids, proteins and nucleic acids. Melanin is also involved in the progress of the dark reactions that occur after light exposure [32,33]. VL induces stronger and longer-lasting pigmentation in darker-skinned individuals [34]. Both UV and VL induce melanogenesis, however, with different efficiencies in different skin phototypes. UV and VL stimulate melanogenesis in darker skin people, while only VL stimulates melanogenesis in white people having the fairest skin type (skin phototype I) [35]. The profile of skin pigmentation after exposure to UV and LV is one of the strongest pieces of evidence proving that not only UV but also VL, affects skin physiology [36].

Sunscreens work by scattering and absorbing UVB and part of the UVA in solar radiation, therefore, avoiding partially or completely their positive and negative consequences. The efficacy of a given sunscreen is given mainly by the sun protection factor (SPF), which is an *in vivo* test, whose results are calculated by the ratio between the MED of a piece of skin protected by 2 mg cm^{-2} of sunscreen and the MED of an unprotected equivalent piece of skin (of individuals with fair skin when exposed to a UVB standard light source) [37]. Current scientific literature keeps adding criticisms to the way SPF measures are performed, and to the conclusions, that falsely correlate with full protection of the skin and with the increase in the time people can spend under the sun [38]. The avoidance of the erythema reaction is considered to be a positive consequence of sunscreen usage, however, in practice, it allows people to stay longer periods under the sun, with consequences that are not fully understood. Therefore, using currently available sunscreen allows people to submit themselves to much higher doses of VL and IR.

VL forms excited states of endogenous photosensitizers that trigger the photosensitized oxidation reactions. VL also penetrates much deeper into the dermis, being therefore absorbed and inducing responses in all skin layers [39]. Important to mention that the skin tumors that arise in deeper skin layers, harbor many more fingerprint mutations connected to oxidative distress than UVB fingerprint mutations (mutagenetic pyrimidine bases) [40]. Although sunscreen usage has grown steadily in recent years, the percentage of skin cancer has experienced increases at similar rates [20]. In the USA, 10,000 daily new cases are diagnosed and 25 people die of skin cancer [41]. Healthier habits concerning sun exposure will likely arise from the understanding of how the photons of different sun irradiance ranges interact with skin chromophores.

Advancements in opsins' function in skin biology

Opsins are a complex family of proteins that is classically associated with its capacity to detect light and are found in archaea to metazoan. These proteins can bind to different forms of vitamin-A analogues,

which characterizes their basis for phototransduction. Type I opsins are present in *Archaea, Bacteria*, and *Eukaryota* and are mostly associated with ion channels and pumps. These proteins are of great interest for optogenetic approaches in different animal models [42,43]. Type II opsins are present in invertebrates and vertebrates and are G protein-coupled receptors (GPCR). These proteins can be divided into several classes based on the GPCR identity [42,44]. For a mechanistic view of the phototransduction of opsins, the reader is referred to an external reading [42,44–47].

In mammals, opsins are classically associated with image formation. However, in the early 2000′s the discovery of melanopsin in a subset of retinal ganglion cells reshaped the field. Melanopsin was identified as the third photoreceptor in the retina, being responsible for participating in non-image-forming processes. Among these processes, the regulation of the central biological clock, the suprachiasmatic nucleus (SCN), by environmental light was well characterized [48,49]. Since then, the role of melanopsin in regulating a myriad of biological processes has been described [50].

Comparatively, the investigation of the opsins' role in the skin was markedly slower; the first report of cutaneous opsins was in 2001 [51]. But only a decade later, scientific interest remerged and since then several exciting papers have been published. For a historical perspective of opsin discovery in the skin, the reader is invited to read our recent review [7].

Currently, the repertoire of opsins in the skin has been described. In summary, cone opsins, *Opn1* [52–56], rod opsins, *Opn2* [51,52,54–58], panopsin, *Opn3* [53,55,56,59–61], melanopsin, *Opn4* [54–56,62,63], neuropsin, *Opn5* [53,55,56,64], and *peropsin* [65] have been reported in either murine and/or human skin as well as in different skin cell types. Moreover, opsins are known to mediate the following processes: UVR- and VL-induced pigmentation [55,58,62,66,67], UVR-dependent calcium mobilization [63,65,66,68], keratinocyte differentiation [69,70], UVR-induced photoaging [56], apoptosis [62], modulation of circadian clock genes [62,71], and hair follicle growth [72,73].

In recent years, novel evidence has been published, thus making the opsin field even more exciting. A major contributor to these recent advances is Prof. Lu's lab whose advancements are summarized next. In 2021, Lan and coworkers demonstrated that OPN5 is a UVR sensor that regulates pigmentation in human melanocytes. In this process, the UVR-induced signaling pathway requires calcium and protein kinase C (PKC), and melanocyte-inducing transcription factor (MITF) activation [74]. Still in 2021, Wang and colleagues using a keratinocyte-melanocyte co-culturing method showed that silencing *OPN3* resulted in cell cycle arrest, decreased calcium levels, and reduced tyrosinase protein and activity levels. However, melanin content was not measured [61]. Apparently, these results contradict previous observations from Oancea's lab that showed melanin increase upon *OPN3* silencing [75]. Interestingly, *OPN3* silencing in human melanocytes resulted in apoptosis [60] but in co-culture such effect was lost and a cell cycle arrest was observed [61]. In 2022, a study from the same lab showed that the negative regulator role of OPN3 in melanogenesis is associated with physical interaction with B-Raf Proto-Oncogene, Serine/Threonine Kinase ($BRAF^{V600E}$) in a BRAF/ERK-dependent pathway [76]. Recently, photoisomerase protein (retinal G protein-coupled receptor – RGR) was identified in epidermal basal, spinous layers, and skin appendages. These results indicate a possible pathway for retinal regeneration in the skin itself. Interestingly, increased RGR expression was identified in psoriatic lesions, seborrheic keratosis, and squamous cell carcinoma, as well as in keratinocytes, melanocytes, and fibroblasts. In keratinocytes, RGR knockdown resulted in reduced proliferation and migration as well as increased apoptosis [77].

The interaction of OPN3 and natural products has been published. In this study, pre-treatment of human dermal fibroblasts and murine malignant melanocytes with aqueous extract of *Polypodium leucotomos* (Fernblock®) prevented blue light-induced pigmentation, cell death, and p38 phosphorylation, and *Opn3*-induced increase of gene expression [78]. Additional evidence for the light- and thermo-independent role of melanopsin was reported by de Assis and colleagues. Using murine melanocytes, the authors showed that knocking out melanopsin (*Opn4*) increased cellular proliferation and cell cycle progression. These changes were followed by alteration in clock proteins and increased MITF, thus corroborating the higher proliferative capacity of murine melanocytes [59]. Remarkably, an opposite scenario was identified in murine malignant melanocytes [79], which will be described below. Interestingly, these findings further show that opsins' function can also be dependent on cellular background, *i.e.*, healthy *versus* cancerous tissue/cell.

Taken altogether, in recent years the knowledge of opsins' function in regulating skin biology has advanced and it has become more complex. Most of the studies focused on OPN3, OPN4, and OPN5. However, there is an important gap in knowledge regarding cone (OPN1SW, OPN1MW) and rod opsins (OPN2) function in skin biology. The presence of RGR is also of interest to skin biologists. Nonetheless, it is now clear that efforts ought to be made not only to address opsins as light sensors but as critical regulators of other biological processes, mostly due to the opsins' ability to bind and interact with proteins such as the melanotropin receptor, MC1R, and BRAF.

Opsin's role in skin cancer

Skin cancer is a global public health issue with increasing incidence worldwide. Most of these cancers arise from non-melanocyte cells (non-melanoma skin cancer) and account for a small fraction of the mortality. Although melanocyte-derived cancers (cutaneous melanoma - CM) account for approximately 2% of global skin cancer incidence, this cancer type is responsible for about 80% of all skin cancer-related deaths [80].

Melanoma etiology is multifactorial. Risk factors are UV radiation, genetic susceptibility, high nevus presence, reduced skin pigmentation, and immune suppression [81,82]. Current genetic screening has classified human CM into four main subtypes based on mutation status: *BRAF, RAS, NF1*, or triple wild type [83]. In recent years, the usage of immune checkpoint inhibitors associated with targeted therapies against BRAF and/or RAS has shown promising effects on overall survival. However, only a subset of patients benefits from immune therapy-associated regimes, thus justifying the need for additional biomarkers for therapy success [84].

An interesting gene family that could be considered as a potential therapeutic in melanoma is the clock gene. This gene family comprises a complex molecular time-keeping mechanism that allows the counting and its interpretation of external time. In fact, the importance of the circadian clock is appreciated in different diseases, including metabolic disorders and cancer [85,86]. The first study that showed a possible role of clock genes/proteins in melanoma was initially reported in 2013 [87]. In recent years, Castrucci's lab has extensively investigated the role of clock genes as important players in the molecular biology of melanoma [62,79,88–92]. Among these discoveries, the *BMAL1* gene was identified in humans as a prognostic and gene candidate for immune therapy success [91]. For a deeper view of clock genes in melanoma, the reader is referred to an external reading [10].

The first report of opsins influencing cancer development and progression was in 2012 in a human hepatocarcinoma cell model. In this study, increased OPN3 protein levels were positively associated with higher susceptibility to 5-fluorouracil [93]. A subsequent study showed that blue light-induced cellular death was reversed upon *Opn3* knockdown in mice [94]. Blue light stimulation of human colon cancer cells resulted in reduced tumor growth *in vivo* and *OPN3* expression. However, no functional experiment on OPN3 was performed [95].

Still in the search for additional biomarkers and important players in melanoma cancer, Castrucci's lab focused on OPN4. This interest arose as we identified that *Opn4* knockout cells ($Opn4^{KO}$) cells, upon repeated UVA radiation, did not undergo apoptosis compared to the wild-type counterparts ($Opn4^{WT}$) in mice. We hypothesized that this resistance

to apoptosis could be an important step in carcinogenesis as this could allow DNA damage accumulation to the daughter cells, thus favoring mutations [62]. We also observed a marked decrease in *OPN4* expression in human CM compared to healthy skin [79]. In 2022, we characterized OPN4 as an oncogene in melanoma cancer due to the following findings in the absence of *Opn4*: (1) reduced *in vivo* tumor growth and marked immune system infiltration in the tumor microenvironment (TME); (2) decreased *in vitro* proliferation and cell cycle proliferation which was associated with reduced MITF and higher BMAL1 expression (as well as *in vivo*); (3) using global proteome profiling, a less inflammatory TME, reduced GTPase and MITF activity that is associated with reduced cell proliferation. Considering the recent studies that point to the ability of opsins to physically interact with other proteins such as MC1R and BRAF [75,76], we also suggested that OPN4 may physically interact with MITF. Collectively, *in vivo* findings strongly suggest a light- and thermo-independent role of OPN4 in melanoma that favors its growth. However, considering the *in vitro* data, upon UV radiation, the absence or reduced levels of OPN4 could be an advantage as tumor growth could be higher compared to $Opn4^{WT}$ tumors.

However, one should consider the effects of OPN4 in CM as multifactorial. Our data suggest that the absence of OPN4 results in a higher immune response. We have also reported reduced DNA-related protein expression in $Opn4^{KO}$ tumors, which could lead to increased mutational errors, and consequently, immune system recognition. We have previously reported that high-expressing *BMAL1*-tumors (which also express low *OPN4*) in humans show reduced base-exciting repair scores, which is linked with increased immune system activation [62,91]. Our recent study corroborates this hypothesis as $Opn4^{KO}$ tumors in mice express high BMAL1 and lower MITF levels [79]. In parallel, the absence of OPN4 directly affects cell cycle progression and proliferation. The reduced proliferation and MITF signaling associated with increased immune system activation seem to be critical for tumor progression, thus placing OPN4 as an oncogene [79].

A valid criticism of our findings is that oncogenes often show increased expression and/or activity in cancer while *OPN4* has marked reduced gene expression in mouse and human models. In this sense, *OPN4* may not be fully classified as an oncogene, but rather as a driver of melanoma progression. Such a question is still open as the molecular mechanism of how OPN4 contributes to cancer progression is yet elusive. Our comparisons are also limited due to the comparison between human and mouse melanomas. However, one could speculate that considering OPN4 as a protector against UV-induced death, decreased *OPN4* levels in human melanoma may represent an advantage to tumor growth. However, such a hypothesis was dismissed as patients harboring tumors expressing low levels of *OPN4* (and higher levels of *BMAL1*) showed higher overall survival [62,91]. To complicate matters further, OPN4 effects are also dependent on the cellular context as in melanocytes OPN4 deletion resulted in faster cell cycle progression and growth, while in melanoma cells the opposite scenario was found [59,79].

In non-small cell lung cancer (NSCLC) in humans, *OPN4* has been reported to negatively associate with overall survival. Knocking down *OPN4* suppressed cell growth and led to apoptosis. Interestingly, AE51310, one of the small-molecule inhibitors (opsinamides) of OPN4 reduced cellular proliferation and tumor growth *in vivo* [96]. Curiously, opsinamides were designed to specifically compete with retinal binding only to OPN4, without affecting rods and cones. As only two opsinamides (AA92593 and AA41612) were extensively validated [97], one may question the specificity of AE51310 used in the previous study. Considering that the opsinamides should prevent melanopsin activation either by light or thermal energy, the results by Wang and colleagues [96] are intriguing as they suggest that basal photoactivation of melanopsin – or even its thermal activation, a known capacity of OPN4 [89,98] – may play a regulatory role in cancer development and progression.

The role of OPN3 in human CM has also been reported. A total of 20 single nucleotide variants (SNVs) were identified in human melanocytic nevi and malignant melanoma. Using predicting tools, 5 SNVs were classified as deleterious. Nine SNVs were detected in the 3′ untranslated regions (UTR) while 2 were in the 5′UTR [99]. Interestingly, *OPN3* expression in human acral lentiginous melanoma, a rare subtype of melanoma cancer, was higher in metastatic samples compared to primary tumors and melanocytic nevi. High OPN3 expression was also associated with negative survival prognostics [100]. Another interesting study from Lu's lab has in-depth evaluated the SNVs landscape of several opsins (*RGR, OPN1SW, OPN2, OPN4*, and *OPN5*) in human CM and melanocytic nevi using next-generation sequencing. A total of 107 SNVs were identified. Fourteen non-synonymous SNVs were identified in *RGR, OPN1SW, OPN2*, and *OPN4*, some of which were shown to affect protein functionality. One important finding from this study lies in the fact that mutations on opsins are a rare event, which likely overcasts a possible clinical application of opsins in melanoma treatment [101]. A follow-up functional experiment focused on OPN3 mutations revealed that some of the mutations can indeed impair OPN3 activity and result in loss of protein function [102].

The influence of opsins has also been evaluated in other cancer types. Using a bioinformatic pipeline to evaluate all cancers from The Cancer Genome Atlas (TCGA) differential expression of *OPN3* was found in several cancers compared to healthy tissue. Moreover, high *OPN3* expression, which was also confirmed by immunohistochemistry of the protein by independent investigators, has been linked to poor overall survival [103]. Taken altogether, recent studies have shed light on the complex interactions of opsins. Among its members, OPN3 and OPN4 roles in tumorigenesis have been reported. Several questions remain to be answered: (1) Do the effects shown by these opsins in cancer depend on their light and/or thermal detecting ability? (2) How protein-protein interaction contributes to the role of opsins, especially in tissues that are not directly exposed to light? (3) What is the importance of thermal energy for the role of opsins in melanoma? (4) What is the role of OPN1, OPN2, and OPN5 in cancer progression? These are some of the many questions that arise upon carefully studying the literature, which should be experimentally addressed in the upcoming years.

Opsins more than light and thermosensors–future perspectives

In this final part of the review, we hope that the reader can assimilate the following statement: "The role of opsins is complex, multifactorial, and tissue-context dependent". In fact, this is our understanding of the role of opsins in the skin. Opsins are proteins that can detect light as well as thermal energy. Still the thermal capacity of opsins requires further investigation in mammals as only a handful of papers have addressed this interesting ability. Knowing the extra-retinal presence of opsins in different peripheral tissues, which light does not reach, one may question which stimulus opsins detect. In our view, the temperature seems to be an excellent candidate. Furthermore, considering that opsins also exert light- and thermo-independent roles, opsins could be regulating different biological processes via protein-protein interaction, thus acting as light- and thermo-independent sensors. Examples of this interaction with MC1R and BRAF have been provided, and therefore, suggest that other proteins may also be regulated by opsins. Further studies on protein-protein interaction will further expand the increasing repertoires of mammalian opsins' actions not only restricted to the skin, but also in other peripheral tissues such as liver and adipose tissues, among others.

Considering the new technological advances, we foresee that the role of opsins will be further comprehended, and new functions will be revealed, which will contribute to the growing complexity and – at the same time – the beauty of this protein family.

Declaration of Competing Interest

The authors apologize for not being able to cite several important studies due to space restrictions. All authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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