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Revisiting the role of melatonin in human melanocyte physiology: A skin context perspective

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Abstract

The evolutionarily ancient methoxyindoleamine, melatonin, has long perplexed investigators by its versatility of functions and mechanisms of action, which include the regulation of vertebrate pigmentation. Although first discovered through its potent skin-lightening effects in amphibians, melatonin's role in human skin and hair follicle pigmentation and its impact on melanocyte physiology remain unclear. Synthesizing our limited current understanding of this role, we specifically examine its impact on melanogenesis, oxidative biology, mitochondrial function, melanocyte senescence, and pigmentation-related clock gene activity, with emphasis on human skin, yet without ignoring instructive pointers from non-human species. Given the strict dependence of melanocyte functions on the epithelial microenvironment, we underscore that melanocyte responses to melatonin are best interrogated in a physiological tissue context.

Current evidence suggests that melatonin and some of its metabolites inhibit both, melanogenesis (via reducing tyrosinase activity) and melanocyte proliferation by stimulating melatonin membrane receptors (MT1, MT2). We discuss whether putative melanogenesis-inhibitory effects of melatonin may occur via activation of Nrf2-mediated PI3K/AKT signaling, estrogen receptor-mediated and/or melanocortin-1 receptor- and cAMP-dependent signaling, and/or via melatonin-regulated changes in peripheral clock genes that regulate human melanogenesis, namely *Bmal1* and *Per1*. Melatonin and its metabolites also accumulate in melanocytes where they exert net cyto- and senescence-protective as well as anti-oxidative effects by operating as free radical scavengers,

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The paper is dedicated to Aaron B. Lerner, a discoverer of melatonin, and mentor of one of the co-authors (A. T. Slominski).

stimulating the synthesis and activity of ROS scavenging enzymes and other antioxidants, promoting DNA repair, and enhancing mitochondrial function.

We argue that it is clinically and biologically important to definitively clarify whether melanocyte cell culture-based observations translate into melatonin-induced pigmentary changes in a physiological tissue context, i.e., in human epidermis and hair follicles *ex vivo*, and are confirmed by clinical trial results. After defining major open questions in this field, we close by suggesting how to begin answering them in clinically relevant, currently available preclinical *in situ* research models.

INTRODUCTION

The ancient amphipathic indolamine, melatonin, which is believed to exist in all living organisms on Earth[1,2], not only is the key neurohormone that regulates the circadian clock[3] and antioxidant activities[4,5], but also an astonishingly versatile molecule with a plethora of other complex biological functions[6-8] (Table 1). Dermatologist Aaron B. Lerner discovered melatonin as the active molecule that exerts potent skin lightening effects on amphibian melanophores[9]. Since then, melatonin has long captured the attention of skin biologists and investigative dermatologists for its multitude of documented activities, many of which are relevant to human skin physiology and pathology, ranging from anti-aging[10-13], UV-protection[14-17], immunomodulation[18,19], and anti-melanoma activity[21-23] to potential hair growth-promoting[24,25] and pigmentation-modulatory effects[25-27].

Yet, it remains unclear how exactly intracutaneously synthesized melatonin impacts on human skin and hair follicle pigmentation *in situ* and *in vivo*, how it affects other human melanocyte functions, and whether it protects these melanocytes from damage and/or senescence *in situ*. Even less is known about the relative contribution of insufficient melatonin synthesis and/or melatonin receptor expression in human skin in the context of melanocyte and skin pathology. Moreover, it is not yet entirely clear which of melatonin's receptors or pathways mediate each of its functional effects in human skin, which receptors/pathways are involved in its modification of mitochondria and cellular metabolism, or which nuclear receptors are plausible candidates for its bioregulation. To a considerable extent, this may be owed to the fact that the bulk of published melatonin studies have utilized cell culture methodology or animal models, while human skin and hair follicle organ culture has been under-employed, even though these assays would have been most instructive from a physiological perspective. Additionally, melatonin's mechanisms of actions in human skin are very complex and have not been dissected as systematically as desired, perhaps due to few investigative dermatologists conducting such research in the past decades, limited industry and NIH funding, and challenging requirements (e.g., ethical rules and IRB approval) for conducting experiments with humans.

Therefore, the current review re-explores the role of melatonin in human melanocyte physiology. We argue that it is timely and both clinically important and biologically instructive to now clarify definitively whether the previously reported observations regarding melatonin's effects on isolated human melanocytes *in vitro* (see below) really translate to a human tissue context, i.e. where melanocyte activities are closely controlled by

their intimate interactions with epidermal or hair follicle (HF) keratinocytes within the epidermal[26,28,29] or HF pigmentary unit (EPU, HFPU)[30-32].

This tissue context-perspective on human melanocyte biology is critically important, but too often ignored. Besides several pigmentation-regulatory growth factors, cytokines, and eicosanoids, keratinocytes produce and secrete major pigmentation-stimulatory neurohormones, such as α-melanocyte stimulating hormone (MSH), adrenocorticotropin (ACTH), corticotropin-releasing hormone (CRH) and thyroid-releasing hormone (TRH)[18,19-23] and rigorously control melanocyte functions through interactions with corresponding G-protein coupled receptors[26,39,40] and by regulating E- and P-cadherin expression on their cell surface[41,42].

With recent insights into the impact of neurotransmitters (e.g. acetylcholine) released by sympathetic nerve fibers innervating the bulge, as in murine HF melanocyte stem cells[43], a tissue context-dominated perspective on examining the role of melatonin in human pigmentation and melanocyte physiology has become even more important, but also more complex. Such a tissue context perspective must include the skin mesenchyme, since additional inputs on pigmentation originate from dermal fibroblasts in the human EPU[39,40], inductive fibroblasts in the HF's dermal papilla, and perifollicular dermal white adipose tissue which secrete HFPU- and melanogenesis-stimulatory hepatocyte growth factor[46,47]. These mesenchymal inputs rhythmically switch HF pigmentation on and off in a strictly hair cycle-dependent manner, with induction of HF melanocyte apoptosis during each phase of HF regression (catagen) and reconstruction of a new HFPU during each re-entry into the phase of active hair growth (anagen) from resident progenitor cells[31,48]. This dramatic remodeling of the HFPU, the cyclic mesodermal-neuroectodermal interactions that govern it, and the rhythmic extrapineal synthesis of melatonin within human HFs[49] make the HFPU a fascinating and instructive model system for exploring the impact of melatonin on the complex controls of human hair pigmentation, which contrasts against the much less dynamic, constantly active EPU. This also illustrates why one cannot expect to recreate such a complex and dynamic cell-cell interaction system in melanocyte cell culture.

Importantly, melatonin and its precursors, serotonin and N-acetylserotonin (NAS), are synthesized within mammalian skin[17,50-52], explicitly also in human skin, HFs, and resident cell populations of human epidermis or dermis[52,53]. Furthermore, the entire biochemical machinery necessary for transforming L-tryptophan into melatonin is expressed in all main tissue compartments of human skin, by epidermal and HF keratinocytes and melanocytes, dermal fibroblasts, and even mast cells[17,53-55].

Since melatonin synthesis, metabolism, signal transduction (Figure 1), target genes, and mechanisms of action have been extensively reviewed elsewhere[8,56-60], it suffice to summarize here some salient features. Melatonin is synthesized in a multistep process from tryptophan[60] in the pineal gland and numerous "non-classical", extrapineal tissues in the human body such as skin and HFs (see below)[25,40], also in intact, wild-type rodent (including mice) skin[14]. While one key step in the classical (intrapineal) pathway of melatonin synthesis involves the conversion of serotonin to N-acetyl-serotonin (NAS, obligatory precursor to melatonin) by aralkylamine N-acetyltransferase (AANAT), there

exists an alternative pathway operating in peripheral organs , such as that found in the AANAT-mutant C57BL/6 mouse strain[61]. Serotonin within C57BL/6 mice skin can instead be acetylated to NAS by arylamine N-acetyltransferase (NAT)[61], which can then be transformed to melatonin by the enzyme common to both classical and alternative pathways, hydroxyindole-O-methyltransferase (HIOMT)[52]. Therefore, it is misleading to characterize C57BL/6 mice as a 'natural melatonin knockdown' species[14,49,61].

Due to melatonin's amphiphilic nature, it can readily penetrate any cell, tissue and cellular compartment[62-65]. Here, melatonin exerts its complex effects dependent on the expression, localization and types of melatonin receptors involved[66,67], i.e. the cell membrane-bound, G-protein coupled MT1 and MT2 receptors, and on several membrane-bound receptor-independent mechanisms[68] (Figure 1). It has been clarified that melatonin and its metabolites are not ligands for the nuclear receptor retinoid-related orphan receptor-α (ROR-α aka NR1F1), as shown by crystallography studies[69,70], modeling and receptor functional assays[71]. However, melatonin may indirectly modulate ROR-α and other ROR activities[70,72].

Moreover, facilitated by their dendritic morphology, which greatly augments their cell surface and thus contact area, melanocytes operate as multimodal sensory and stress-response cells[73-77]. Melanocytes also engage in bidirectional communication with their tissue-specific intraepithelial habitat[73], for example, by secreting catecholamines, cytokines, eicosanoids, acetylcholine, melanocortins, ACTH, CRH, endorphins, enkephalins, nitric oxide, serotonin, and reactive oxygen species produced during melanogenesis[17,36,51,78-90]. Thus, melanocytes contribute actively to shaping the signaling and metabolic milieu they reside in[74,76]. Transfer of melanosomes into keratinocytes likely promotes keratinocyte terminal differentiation and other functions[39,54,55]. Recently, aging melanocytes have even been reported to act as drivers of epidermal senescence[91].

Taken together, the crucial tissue context in which melanocytes operate renders it impossible to fully grasp how melatonin regulates human pigmentation under mere cell culture conditions, even when primary human melanocytes are co-cultured with selected isolated other cell populations, since even such co-culture system cannot recapitulate the complexity of physiological interactions between neural crest-derived, epithelial and mesenchymal cells that control pigmentation *in situ*[73-75].

This review synthesizes the currently available evidence regarding melatonin's effect on melanogenesis, oxidative biology and damage responses, senescence, and peripheral clock genes in the wider context of human melanocyte physiology within their cutaneous habitat. These include conditions of excessive oxidative stress, which underly melanocyte pathology, e.g. in vitiligo[92,93] and hair graying[30,94,95]. We define major open questions, suggest how to answer them using currently available preclinical assay systems, and discuss the clinical relevance of systematically characterizing the role of melatonin in human melanocyte function in health and disease from a tissue context perspective.

SKIN AS A TARGET AND SOURCE OF MELATONIN BIOACTIVITY

Human skin possesses all key enzymes, substrates, and cofactors necessary for melatonin synthesis[51,52], and melatonin synthesis in human scalp HFs *ex vivo* is stimulated by noradrenaline, just as in the pineal gland[49]. Given that this key psychoemotional stress-associated neurotransmitter can promote the depletion of melanocytes stem cells from their niche in murine HFs[43], one wonders whether noradrenaline-induced up-regulation of HF melatonin synthesis simultaneously activates melatonin-dependent cytoprotective mechanisms (see below). Importantly, both keratinocytes and melanocytes of the EPU can also synthesize catecholamines[96,97] and thereby could, in theory, augment their own melatonin synthesis in an autocrine and paracrine manner, possibly in response to local tissue stressors.

Human skin and HFs also are important targets of melatonin bioactivity and express melatonin receptors (MT1/2)[35,58,81]. Animal studies involving pinealectomy or melatonin administration have demonstrated changes in HF growth, cycling, and pigmentation (Table 2). The latter has raised the question how exactly melatonin affects human epidermal and HF melanocytes[17,24,48] within their natural tissue habitat, rather than in culture isolated from their key communications with epidermal and HF keratinocytes, papillary dermal fibroblasts[99], and HF dermal papilla fibroblasts[30,31]. Yet, dissecting how exactly endogenous melatonin alters human melanocyte biology *in situ* is challenged by melatonin's complex interactions and rapid metabolism[100,101], which make it exceptionally difficult to dissect precisely which phenotypic effects are regulated by melatonin itself versus its many metabolites, as well as by differential effects dependent on dose, cellular and hormonal environment, tissue, species, gender, age, race, and external (environmental) and internal stress levels[24,98,102,103]. Therefore, the results from *in vitro* and animal studies on the pigmentary impact of melatonin could be misleading as they cannot fully reflect the human *in vivo* condition. It is for this reason that we advocate the use of standardized, site- and gender-specific human skin and hair follicle organ culture models to definitively clarify the effects of melatonin on human skin pigmentation in UV-exposed versus non-exposed skin.

CLINICAL POINTERS

Clinical observations provide important pigmentary background information when interpreting *in vitro* and animal results under melatonin administration. Few studies have examined the effects of melatonin on pigmentation in humans without pigmentary disorders. In both former- and never-smoker postmenopausal women who received microdermabrasion, neither oral (2.5 mg/day) nor topical (0.5 mM) melatonin had significant effects on skin pigmentation[104]. Another pilot study saw no effects of oral melatonin on arm, leg, or back skin pigmentation of seven subjects[105]. This could have resulted from an insufficiently short observation period or the rapid metabolism of orally delivered melatonin upon liver passage.

There is an extreme scarcity of any documented potential cutaneous effects from the extensive ingestion of melatonin. This, in part, is likely best explained by ingested melatonin's extensive and rapid metabolism during its first pass through the liver, where

it is rapidly hydroxylated to 6-hydroxymelatonin with further sulfation or glucuronidation before reaching the skin. These biochemical modifications minimize the impact of orally administered melatonin on human skin function. Therefore, to see cutaneous effects of melatonin, it is best for it to be synthesized *in situ* or applied topically.

Very few studies have investigated melatonin effects on human pigmentation disorders. In one patient with adrenal hyperplasia-associated diffuse skin hyperpigmentation, a month of high-dose (1 g/day) oral melatonin decreased skin pigmentation, yet failed to alter skin pigmentation in three other patients with idiopathic hyperpigmentation and one patient with Addison's disease[106]. In a small cohort of patients with acanthosis nigricans, oral melatonin (3 mg/day) reportedly reduced hyperpigmentation[107]. In patients with melasma, topical (5% cream) and oral (3 mg/day) melatonin reportedly showed significant skin-lightening effects[108]. Other studies also reported decreased skin pigmentation and enhanced protection against photoaging after topical melatonin[15,25,109,110]. These limited clinical observations suggest that melatonin may exert (direct or indirect) melanogenesis-inhibitory activities in human epidermis *in vivo*, yet conclusive evidence remains to be provided.

Interestingly, patients with vitiligo had significantly lower immunohistochemically-assessed melatonin-associated immunoreactivity in both lesioned and non-lesioned skin when compared to skin of heathy controls, suggesting a role for melatonin deficiency in the pathogenesis of vitiligo[111]. However, serotonin, 5-hydroxyindoleacetic acid (5-HIAA) and melatonin serum levels have been reported to be increased in a relatively small cohort of vitiligo patients[112]. Yet, the pathobiological significance and therapeutic potential of melatonin in vitiligo[113] remains unexplored and requires systematic additional investigation.

Serum melatonin levels decline with age[10], which may contribute to the slow decline of organ function characteristic of aging[114]. Thus it is conceivable that a gradual loss of melatonin in aged or graying HFs along with an age-dependent accumulation of oxidative damage in the HFPU and correspondingly reduced oxidative damage protection of HF melanocytes by both systemic and intrafollicularly-produced melatonin levels contributes to hair graying[30].

DIRECT IMPACT OF MELATONIN ON MELANOGENESIS

(1) Melatonin and its metabolites tend to inhibit melanogenesis, tyrosinase activity, and/or melanocyte proliferation *in vitro*

In normal human epidermis, melatonin and its metabolites, e.g., N1-Acetyl-5-Methoxykynuramine (AMK), N(1)-acetyl-N(2)-formyl-5-methoxykynuramine (AFMK), 6-hydroxymelatonin (6-OHM), and 5-methoxytryptamine (5-MT), accumulate *in vivo*[103,115]. In human epidermal melanocytes *in vitro*, melatonin and its metabolites inhibit melanocyte proliferation[103] and some[103] but not all[115] metabolites inhibit melanogenesis by decreasing tyrosinase activity. Of all melatonin's metabolites, 6-OHM showed the greatest inhibition (50%) of tyrosinase activity in normal human epidermal melanocytes *in vitro*[103]. In contrast, melatonin and its metabolites had no effect on melanogenesis in human SKMEL-188 melanoma cells, except for 5-MT (at 10 μM) which even stimulated melanogenesis[103]. Yet,

in another human melanoma cell line, MNT-1, melatonin inhibited melanin production at high doses (1, 100, and 1000 μM)[116].

Interestingly, in rodent melanoma cells, melatonin at low concentrations (0.1-10 nM) inhibited melanocyte proliferation but had no effect on melanogenesis, while at high concentrations (≥0.1 μM) it inhibited the induction of melanogenesis and tyrosinase activity but not proliferation[23]. Similarly high doses of melatonin were required to inhibit anagen-associated tyrosinase activity in histocultured skin from C57BL-6 mouse, and two high and low affinity binding sites were detected in crude skin extracts[117]. These are consistent with high doses of melatonin required for phenotypic effects in normal human epidermal melanocytes[103].

Thus, melatonin's effects on melanogenesis and melanocyte proliferation appear be to be rather variable, dependent on dose, tissue type, species, and signaling environment[24,98]. This further underscores that understanding the physiological and pharmacological responses of human melanocytes to melatonin stimulation is best studied in a full-thickness human skin or HF organ culture (*ex vivo) or in vivo*, rather than in cultured isolated melanocytes (*in vitro*).

(2) Mechanisms of melatonin regulation of human melanogenesis

Besides targeting its specific membrane receptors on melanocytes, in human skin, several indirect or non-classical mechanisms by which melatonin may regulate melanogenesis deserve consideration. For example, melatonin can downregulate estrogen receptor expression in mouse HFs[49], which could antagonize 17-ß-estradiol's stimulatory effects on melanogenesis[118]. However, at ≤1 μM melatonin did not inhibit intrafollicular melanin synthesis in organ-cultured human anagen VI scalp HFs[49]. Of note, anti-melanogenic activity of melatonin in rodent melanomas and murine skin organ culture required higher than 1 μM concentration to observe the phenotypic effect[23,117].

Though ROR is no longer a credible direct nuclear hormone receptor for melatonin, an indirect modulation of ROR signaling activity by melatonin which could impact on melanogenesis remains theoretically conceivable[70]. Additional indirect mechanisms of action must also be considered. The observed melanogenesis inhibition by melatonin in Siberian hamster HF melanocytes appears to have antagonized the pigmentation-promoting effects of α-MSH[119], likely by reducing expression of cognate α-MSH receptors (MC-1R), as described in mouse melanoma cells[120], and/or counteracting the promotion of melanogenesis by α-MSH or L-tyrosine (based on *in vitro* data from hamster and murine melanoma cells)[23]. Since specific binding of tritiated-melatonin to purified membrane and nuclei melanocyte fractions were detected[23,117], the anti-proliferative effect of melatonin was proposed to be mediated through interaction with MT receptors, while the melanogenesis-inhibitory effect might involve interaction with a putative nuclear receptor.

In normal human epidermal melanocytes, the central regulator of oxidative damage responses, nuclear factor erythroid 2-related factor 2 (Nrf2)[121,122], is targeted by melatonin to upregulate antioxidant defenses[15], but decreases melanogenesis through a pathway involving activation of PI3K/AKT. Activated PI3K/AKT signaling leads to inactivation of

glycogen synthase kinase-3 (GSK-3) and microphthalmia-associated transcription factor (MITF), which inhibits the transcription of *TYR, TRP-1, and TRP-2* (melanogenesis-associated enzymes) and decreases melanin synthesis[123] (Figure 2). Thus, it is conceivable that melatonin may inhibit melanogenesis in normal human epidermal melanocytes also through activation of Nrf2 and subsequent activation of the PI3K/AKT pathway.

MELATONIN, OXIDATIVE STRESS, AND THE MELANOCYTE ECOSYSTEM

(1) Melatonin and its metabolites regulate antioxidant enzyme expression and direct free radical scavenging

Melatonin and its metabolites [e.g., cyclic-3-hydroxymelatonin (C-3HOM) and AMK][124] are powerful direct scavengers of reactive oxygen (ROS) and nitrogen species (RNS)[125,126] that protect human melanocytes from oxidative damage[15]. Moreover, once melatonin binds to MT1/2 receptors, the downstream signaling cascade stimulates expression of numerous antioxidant enzymes[125,127] (Figure 3). These properties of melatonin may play a key role in maintaining skin[15] and HF[128] pigmentation, given that melanogenesis itself is a cytotoxic process that generates ROS and quinone and semiquinone compounds, which are buffered by melanin itself as well as by other mechanisms[129-131].

Furthermore, melatonin can activate Nrf2, a transcription factor regarded as the master regulator of antioxidant defenses [e.g., defense against ultraviolet (UV) B radiation-induced oxidative skin damage][15], in part by upregulating its expression in human epidermal melanocytes. Nrf2 is also significantly up-regulated in response to oxidative stress in human anagen HFs, namely in the HFPU[132]. Interestingly, the melatonin-induced activation of Nrf2 in human epidermal melanocytes exposed to oxidative stress occurs independently of melatonin receptors[15], possibly by regulating the Keap/Nrf2/ARE pathway and suppressing the ubiquitin/proteasome system, thereby increasing Nrf2-ARE activation and expression and activity of antioxidant enzymes[1,114]. Furthermore, Nrf2-ARE activation is necessary for protecting human epidermal melanocytes from hydrogen peroxide- (H_2O_2) induced oxidative stress[133], either by metabolically eliminating ROS or by reducing their generation[1], thereby preventing DNA damage and premature senescence[11,15].

Melatonin's activation of NQO2, a detoxifying enzyme that directly reduces H_2O_2 and dangerous quinones, is another means of defense against oxidative stress[134,135], which has not yet been identified in human HF melanocytes. However, NQO2 gene expression occurs widely in human skin[7,98], including epidermal melanocytes[15] and microarray data point towards its expression in murine HFs[136]. Also, intracellular melatonin at concentrations higher than 1 nM interacts with the calcium/calmodulin complex, which inhibits nitric oxide synthase 1 (NOS1 or nNOS) and its generation of RNS[56,137-139]. Furthermore, melatonin and its metabolites protect human epidermal melanocytes from UV-B-induced damage/apoptosis (see (3) below) by enhancing p53-stimulated DNA repair[15]. The discussed antioxidant mechanisms of melatonin and its metabolites are described in further detail in figure 3.

(2) Decreased melatonin levels related to ageing- or oxidative stress-related hair graying

Loss of human hair pigmentation (e.g., ageing- or stress-related graying) is thought to primarily result from oxidative damage that disrupts differentiated HF melanocytes of the HFPU and melanogenesis-related enzymes, with subsequent damage to HF melanocyte stem cells, eventually determining whether or not greying is reversible[30,43,94,95].

A study using murine HFs demonstrated the protective effect that superoxide dismutase (SOD)[140], an enzyme involved in melatonin's antioxidant defense properties[125,127], has against hair graying. Also, aged, gray HFs have increased reactivity to reducing and oxidizing agents when exposed to radiation-induced oxidative stress[141], decreased antioxidant defense (e.g., decreased CAT activity and expression)[142], and increased accumulation of tryptophan[143]. This invites two melatonin-related hypotheses: (a) decreased enzymatic conversion of tryptophan to melatonin in graying HFs, and/or (b) increased production of tryptophan used to enhance melatonin synthesis for combating oxidative stress within the HFPU.

The fine regulation of redox balance between free radicals and antioxidants is critical for maintaining normal functions in human epidermal[129,131] and HF[130] melanocytes. Without the melatonin-associated antioxidant defenses, it is possible that human epidermal and HF melanocytes may be substantially more susceptible to oxidative damage that results in cellular dysfunction, such as directly impaired tyrosinase activity by blunting methionine sulfoxide repair[95], and apoptosis[94,142,145] and. However, the potential association between reduced melatonin levels/expression in aging and graying HFs and other hypopigmentary conditions still needs to be clarified.

(3) Melatonin enhances protection of melanocytes against UV radiation

Oxidative stress generated by UV radiation (UVR) and visible light (VL) has the potential to induce cosmetically unappealing hyperpigmentation[146]. For this reason, the use of topical and oral antioxidants has become increasingly prevalent as therapy in adjunct to sun protection to prevent UVR- and VL-induced hyperpigmentation[146,147]. Pronounced photoprotective effects of "natural" and synthetic antioxidants were demonstrated in animal and human studies when applied topically before exposure to UVR, but no protective effects by antioxidants (e.g., melatonin, vitamins) were found by some authors when applied after exposure to UVR[147]. In contrast, others have demonstrated the protective action of melatonin and metabolites applied directly after UVB exposure[15], such as their protection from and reversal of UVB-induced damage in cultured human epidermal melanocytes[15]. Similar effects were seen for vitamin D derivatives[148-150]. It must be noted, however, that active forms of vitamin D are more efficient in photoprotection than melatonin[150,151].

(4) Melatonin regulates senescence progression and promotes mitochondrial homeostasis

Mitochondria play a vital role in skin and there exists increasing evidence that mitochondrial dysfunction and oxidative stress are key features in senescence and aging skin with direct links to skin and hair ageing phenotypes (e.g., uneven pigmentation and hair graying)[30,152,153]. Melatonin is found in especially high concentrations in

mitochondria[154,155], where it is transported to[156], synthesized[157], or metabolised[101]. Within mitochondria, cytochrome c converts melatonin to its potent antioxidant metabolite, AFMK[158], and its secondary product, AMK in the presence of H_2O_2[101].

The abundance of damaging free radicals generated by oxidative phosphorylation make the mitochondria an optimal location for such high concentrations of melatonin[114]. Various mechanisms have been proposed regarding melatonin's ability to reduce mitochondrial oxidative stress and help maintain mitochondrial homeostasis, however, these remain to be fully studied in the context of human melanocytes

One proposed anti-aging mechanism that may be relevant in this context involves the stimulation of sirtuin3 (SIRT3) by melatonin in mitochondria, leading to the deacetylation and activation of superoxide dismutase-2 (SOD2), which enzymatically dismutates superoxide anion radicals[159]. Furthermore, melatonin can inhibit premature senescence by upregulating expression of sirtuin1 (SIRT1), which reduces oxidative stress, decreases expression and activation of p53, and inhibits NF-κB signaling[11].

Melatonin may also act on mitochondrial uncoupling proteins to dissipate the proton gradient across the inner membrane to moderately reduce inner membrane potential, thereby increasing activities of complexes I and III, accelerating ETC electron transport, and decreasing electron leakage from the ETC; effects that reduce free radical formation[160]. Melatonin's alleviation of oxidative damage in the mitochondrial matrix and intermembrane space[2] has been proposed to decrease cardiolipin oxidation, mitochondrial permeability transition pore (MPTP) opening[161], cytochrome c release, and mitochondria-related apoptosis, all of which are beneficial effects to slow aging and preserve cellular functioning[114], likely also in human epidermal and HF melanocytes. Melatonin can also increase H_2O_2 scavenging[114] and its metabolite 6-OHM can directly increase the electron flux through the respiratory chain and enhance ATP production by donating electrons[162].

Finally, melatonin maintains the optimal mitochondrial membrane potential ($\Delta\psi m$)[163] through its abilities to block the MPTP in conditions of stress and activate uncoupling proteins in normal conditions[160].

(5) Melatonin regulates melanocyte autophagic flux

Autophagy is a critical cellular process that, in part, involves the removal of misfolded or aggregated proteins and clearance of damaged organelles, such as mitochondria (mitophagy), endoplasmic reticulum and peroxisomes[164]. Autophagy is activated in conditions of oxidative stress[165], including aging[166], and plays a key role in protecting normal human epidermal melanocytes from oxidative stress-induced apoptosis, loss of mitochondrial membrane potential, and intracellular ROS generation[167,168], as well as in the regulation of melanogenesis, melanosome formation and maturation, and melanosome degradation in normal melanocytes and keratinocytes[169-172].

The key role of melatonin in the regulation of autophagy has been documented in the context of various organ systems and pathologies[173]. Melatonin can help maintain cellular homeostasis either through autophagy promotion or suppression, depending on

cellular requirements and oxidative stress levels[174]. Since autophagic flux is required for maintenance of anagen and thus pigment production in human HFs[175], it is possible that the intrafollicular synthesis of melatonin[49] contributes to adequate autophagy levels. However, it is unknown whether melatonin impacts on autophagy in human epidermal and HF melanocytes. Yet, since melatonin and autophagy are so closely related to oxidative stress in melanocytes, a relationship between them is anticipated[166].

Melatonin prevents initiation of mitophagy through maintenance of the optimal $\Delta\psi m$[176]. Also, melatonin may reduce autophagy in epidermal and HF melanocytes indirectly by either reversing mitochondrial dysfunction through reduced oxidative stress or by improving endoplasmic reticulum efficiency, resulting in less misfolded proteins, which are effects exerted by melatonin in the context of other organs systems and pathologies[173].

SIRT1 is an autophagy substrate and stimulator that works by preventing the acetylation of key autophagy proteins (via deacetylation) (e.g., ATG5, ATG7 and ATG8/LC3)[177,178]. SIRT1 levels are reduced through autophagic–lysosomal degradation in aging tissues, which could contribute to melanocyte cell cycle arrest and a pro-inflammatory senescence-associated secretory phenotype during skin aging[179]. Considering melatonin's ability to upregulate SIRT1 expression[11] (see (4) above), intracutaneously produced melatonin may thus positively regulate autophagy and exert anti-aging properties by stabilizing SIRT1 levels. The role of melatonin in skin aging has been recently extensively reviewed[274].

MELATONIN AND PERIPHERAL CIRCADIAN CLOCK GENES

The peripheral clock genes *Bmal1* and *Per1* are known to control pigmentation in human epidermal and HF melanocytes while their silencing in human HFs *ex vivo* stimulates melanogenesis, tyrosinase expression and activity, TYRP1/2 expression, melanocyte dendricity[121]. It is unknown how melatonin, the key neuroendocrine regulator of the central circadian clock [6], impacts on the pigmentary activity of human epidermal and HF melanocytes through the peripheral clock. Yet, cell culture studies (e.g., human epidermal keratinocytes[180] and mouse neuro2A cells[181]) provide instructive clues as follows: melatonin may regulate peripheral clock-associated pigmentary effects, probably through activation of Nrf2, which triggers PI3K/AKT signaling[15]. PI3K/AKT signaling leads to stimulation of both BMAL1[181] and then PER1, which inhibits melanogenesis enzymes (tyrosinase, TRP-1, and TRP-2) and melanogenesis[121,123], as hypothesized in figure 4 (for detailed discussion, see supplementary text 1).

OPEN KEY QUESTIONS AND MODELS TO ANSWER THEM

To decisively advance the field, several open questions in addition to those already posed above must be clarified.

(1) Does exogenous melatonin robustly inhibit melanogenesis in human epidermis and/or HFs, and if so, by which mechanism(s)?

The majority of melatonin effects on mammalian melanogenesis have been observed in cell culture studies, even though – for the reasons discussed above – it is most meaningful

to study melanocyte activities within their natural tissue habitat, rather than in isolation. Therefore, to best determine melatonin's therapeutic potential in pigmentary disorders, and to clarify definitively whether it indeed robustly inhibits human melanogenesis *in situ*, it is critical to study melatonin in human epidermal and HF melanocytes in skin and HF organ culture. In these *ex vivo* assays, besides pharmacological antagonist and blocking-antibody studies, gene silencing can be performed for mechanistic research to elucidate the exact mechanisms by which melatonin alters key regulatory elements of melanogenesis along the lines synthesized in Figures 1-4. It is important to do this in a strictly hair cycle-standardized manner as HF pigmentation is active only during active hair growth (anagen) and HF cycling impacts substantially on extrafollicular skin physiology (e.g., by a maximal HF production of melanotropic neuropeptides and growth factors during anagen), which may in turn also affect the response of intraepidermal melanocytes to melatonin.

(2) Does melatonin regulate human melanocyte proliferation, survival, and/or senescence under physiological circumstances and via which receptor or pathway?

Similarly, whether melatonin regulates the proliferation, survival and/or senescence of human epidermal and HF melanocytes *under physiological conditions* remains unclear. There is sufficient evidence that melatonin can affect these phenotypic traits *in vitro*. However, it remains to be established where melatonin ranks in the hierarchy of other local regulators of these melanocyte activities. Again, this is best studied in human skin and HF organ culture assays *ex vivo*. Ideally, this is complemented by studying human skin xenotransplants on SCID mice for long-term preclinical *in vivo* studies directly in the human target organ, and by knocking out or overexpressing cell type-dependent local production of melatonin, individual receptors (MT1 vs MT2), or different signaling pathways in defined human skin cell populations that are co-cultured under 3D conditions in human skin "equivalents". This will also require the development of MT1-selective agents to match the abundance of available MT2-selective agents[182].

(3) Can melatonin prevent and/or treat pigmentation disorders?

Ultimately, we need definitive answers to this question regarding which human pigmentary disorders can effectively be prevented or managed by melatonin administration, either topically or systemically. Above, we have delineated the rationale and preliminary clinical observations that encourage one to explore melatonin treatment in the pathophysiology and/or management of, for example, vitiligo, melasma, hair greying, and solar-related hyperpigmentation. However, more rigorous, well-controlled, prospective, randomized clinical trials are needed to determine utility and mode of application (systemic or topical) of melatonin, its metabolites, and its chemically synthesized derivatives, using optimally standardized and sensitive methods for recording changes in human skin/hair pigmentation. Also, skin or HF tissue samples from patients with such pigmentary disorders (perhaps beginning with vitiligo, melasma and hair greying) should be systematically screened for abnormalities in the cutaneous melatonin system, then organ-cultured, exposed to melatonin of varying concentrations, and analyzed for changes in key melanocyte biology read-outs *in situ* (e.g., melanin production, tyrosinase activity, expression of c-kit, gp100, MITF, TRP-1, TRP-2, Ki-67, senescence markers).

THERAPEUTIC PERSPECTIVES

The multiple levels at which melatonin and its metabolites could intervene with human skin pigmentation invite therapeutic applications. In addition, melatonin's safety, lack of or very low toxicity, and pleiotropic effects (e.g., UV protection, potent antioxidant activity, DNA repair, anti-aging, anti-inflammation, and melanogenesis inhibition) make melatonin an attractive therapeutic candidate for treatment of pigmentary disorders, such as melasma[108] and acanthosis nigrans-associated hyperpigmentation[107].

Its photoprotective[16,17], anti-photoaging[11,110,183-186], anti-oxidative damage-protective[5,15,56,101,125,127,134] and DNA damage-repair[15] properties also raise the possibility that melatonin may be useful to slow intrinsic and extrinsic skin aging and may exert melanocyte-protective properties in vitiligo and perhaps even aging-associated hair graying resulting from oxidative damage to the HFPU[30]. In fact, melatonin and its metabolites (e.g., AFMK) protect melanocytes *in vitro*[15] from UV-induced DNA damage and apoptosis[185,187] when applied both before[188] and immediately after UVB exposure[15]. This renders melatonin an effective therapeutic candidate for the prevention and management of solar radiation-induced pigmentation disorders[16,189-191]. Finally, melatonin's regulation of autophagy[192] (see above) might be exploited to treat pigmentary disorders with recognized autophagic defects such as vitiligo[165,197], tuberous sclerosis[193], and Cockayne syndrome[194].

Due to its ability to penetrate the stratum corneum[195] and to thus evade prominent first-pass metabolism of oral melatonin by the liver[12], topical administration of melatonin may be superior to the oral route, and permits administration of high melatonin doses directly to human skin target cells, namely epidermal and HF melanocytes and their keratinocyte environment in the EPU and HFPU. Indeed, the use of topical sunscreen fortified with melatonin offers superior sun protection and the ability to counteract UV radiation-induced oxidative stress[187]. A topical sunscreen formulation fortified with melatonin and pumpkin seed oil reportedly had enhanced photoprotective effects[196]. Also, the application of 12.5% melatonin cream protects skin from natural sunlight-induced erythema[197]. New topical formulations such as nanostructured lipid carriers[198,199] and ethosomes[200] promise optimized melatonin delivery in future clinical trials.

Given that theophylline (which is licensed for topical application as a cosmetic agent) can increase melatonin levels released by organ-cultured human skin into the medium[201] while noradrenaline stimulates melatonin synthesis within human scalp HFs *ex vivo*[49], it is also possible that the intracutaneous synthesis of melatonin can be stimulated by topically applied agents that increase intracellular cAMP levels and thus intracutaneous production of endogenous melatonin.

To our knowledge, genetic disorders associated with melatonin deficiency and its receptor deficiencies have not yet been described but may well have been missed. In addition, melatonin's nuclear receptors, as opposed to its membrane receptors (MT1 and MT2), still must be definitively identified. Of note, many of melatonin's protective effects in melanocytes described above, such as melatonin's role as a free radical scavenger[125,126] and stimulator of DNA repair[15] and antioxidant enzyme expression and activity[1] are independent

of MT1 and MT2 signaling. Therefore, MT1 and/or MT2 genetic disorders would not directly alter receptor-independent protective effects in melanocytes. While deficiencies in melatonin synthesis or receptor expression levels in the human system, namely in human skin, clearly await more systematic scrutiny, this limits what can be deduced from the study of dysfunctional MT1/2, even if patients become identified, for example, with receptor mutations. Furthermore, no genetically mutant mice are currently known that have substantial melatonin synthesis or MT receptor deficiencies in their skin.

CONCLUSIONS

1. In normal human epidermal melanocytes, melatonin and its metabolites, such as AFMK, 6-OHM, and 5-MT, inhibit melanogenesis, tyrosinase activity, and melanocyte proliferation *in vitro*. Yet, it is unclear how robustly this translates to the physiological tissue context in human epidermis and HFs. Instructive organ culture assays are readily available to clarify this.

2. Melatonin may inhibit melanogenesis not only by stimulation of MT receptors (MT1/2), but also indirectly by cell desensitization to estrogens, reducing skin sensitivity to α-MSH stimulation, and activation of Nrf2 and PI3k/AKT pathways and/or MAPK signaling. Additional indirect mechanisms/targets by which melatonin may regulate human melanocyte physiology include calcium-calmodulin complex, NOS1, p53, cytochrome c, ETC enzymes, SIRT3/SOD2, and possibly NQO2 (see Figures 1 and 2).

3. Besides accounting for dose-, application mode-, species-, gender-, age-, and ethnicity-dependent differences in the melatonin response of melanocytes in a given tissue location, much greater attention must be paid to the tissue context in which melatonin affects human melanocyte physiology, such as the specific hormonal tissue environment, internal and external stressors, and local determinants of melatonin metabolism through indolic and kynuric pathways.

4. There is good *in vitro* evidence that melatonin can unfold powerful oxidative damage-limiting effects on melanocytes, namely under skin photodamage conditions, through MT1/2 activation, direct ROS scavenging, Nrf2 activation, promotion of mitochondrial homeostasis, calcium/calmodulin complex-induced inhibition of NOS1, and possible action on NQO2. Yet, whether melatonin really does so under physiological conditions and inhibits melanocyte senescence in human epidermis and HFs *in situ*, remains to be conclusively demonstrated.

5. Dysfunctional mitochondria and inadequate autophagy may also contribute to premature senescence and accelerated aging in human epidermal and HF melanocytes. Melatonin's high concentrations in mitochondria and ability to help maintain mitochondrial homeostasis and modulate mitophagy justify the expectation that melatonin will become useful not only in limiting melanocyte senescence, a potential driver overall skin aging, but also invites clinical melatonin applications in the emerging field of "mitochondrial dermatology".

6. Since silencing of the core peripheral clock genes, *Clock, Bmal1,* and *Per1* stimulates melanogenesis in human epidermis and HFs *in situ,* melatonin may regulate peripheral clock-controlled pigmentary effects. One conceivable pathway is the activation of Nrf2 and PI3K/AKT signaling, which is expected to promote BMAL1 and PER1's downstream melanogenesis-inhibitory effects, e.g., on tyrosinase activity.

7. The field is challenged to now move from *in vitro* to *ex vivo* and preclinical *in vivo* studies, using available human skin and HF organ culture assays as well as human skin xenotransplants on immunocompromised mice, to definitively clarify the relevance of melatonin in human melanocyte physiology and to more rigorously probe how therapeutically useful melatonin really is in selected human pigmentary disorders, ranging from hair greying to melasma and vitiligo.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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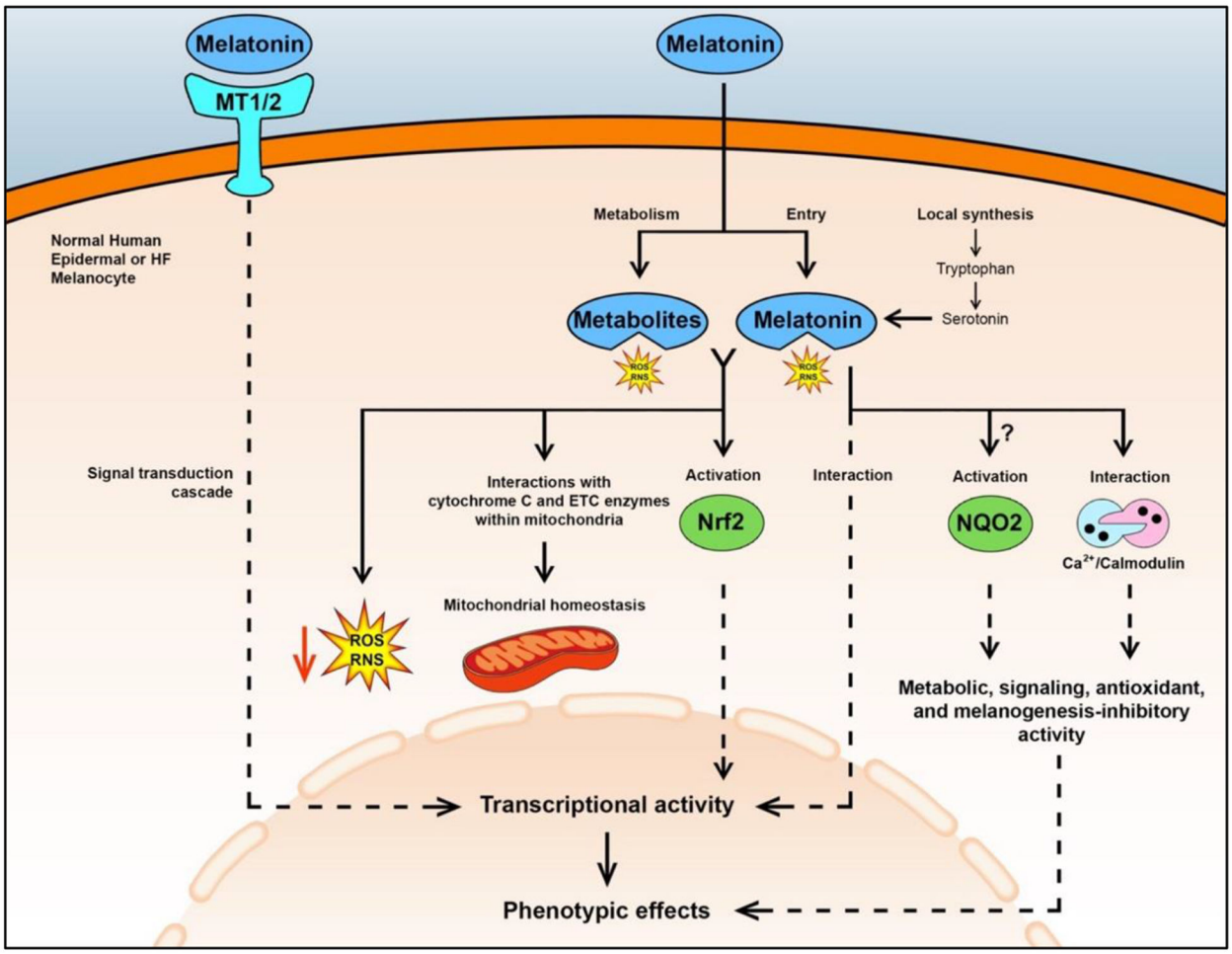

Figure 1. Schematic summary of melatonin's effects in human epidermal and HF melanocytes.

Exogenous or endogenously synthesized melatonin can regulate phenotype in these cells through interactions with membrane-bound MT1/2 receptors NQO2, and the calcium/calmodulin complex or through stimulation of Nrf2 (reviewed in[56]). However, it is not fully understood if melatonin activates NQO2, a detoxifying enzyme[7,261,262] Noteworthy phenotypic effects of melatonin include melanogenesis inhibition, and stimulation of DNA repair, and expression and activity of antioxidant enzymes (e.g., superoxide dismutase and catalase) (reviewed in[8]). Melatonin may also be transported to different subcellular compartments, but the detailed mechanism is not fully understood[25]. Furthermore, melatonin can be synthesized within these melanocytes. Melatonin and its metabolites, such as cyclic-3-hydroxymelatonin (C-3HOM) and N-acetyl-5-methoxyknuramine (AMK), directly scavenge ROS/RNS[125,126] and help maintain mitochondrial homeostasis through interactions with cytochrome C and enzymes of the electron transport chain. Specifically, cytochrome C within mitochondria is thought to be involved in the conversion of melatonin to its potent antioxidant metabolite, N(1)-acetyl-N(2)-formyl-5-methoxykynuramine (AFMK)[158], and its secondary product, AMK, when in the presence of hydrogen peroxide[101]. Also, melatonin may interact with cytochrome C and electron transport chain (ETC) enzymes within mitochondria to promote mitochondrial homeostasis and decrease

free radical formation[160]. Furthermore, melatonin may affect the transcription of peripheral clock genes *Bmal1* and *Per1* with alterations in melanogenesis and other melanocyte activities[27,123,181]. Direct effects are shown by solid lines and multiple reactions and signaling are shown by dashed lines. Melatonin receptors 1 and 2 (MT1/2); hair follicle (HF); reactive oxygen species (ROS); reactive nitrogen species (RNS); nuclear factor erythroid 2-related factor 2 (Nrf2); N-Ribosyldihydronicotinamide:Quinone Reductase 2 (NQO2).

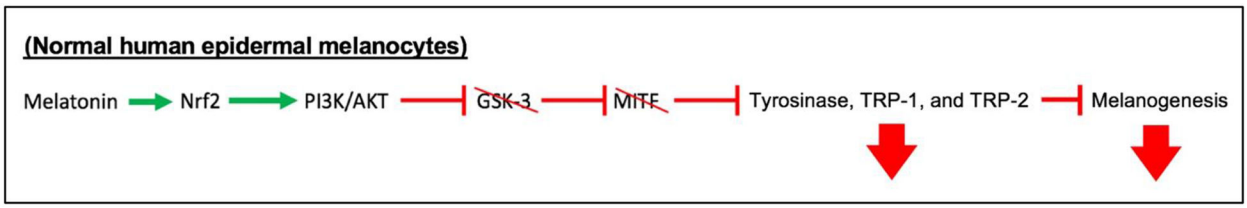

Figure 2. Schematic summary describing PI3K/AKT pathway modulation and its effects on melanogenesis.

In normal human melanocytes, melatonin stimulates Nrf2[15], which can activate the PI3K/AKT pathway to phosphorylate (i.e., inactivate) GSK-3. Without GSK-3, MITF remains unphosphorylated (i.e., inactive), leading to decreased transcription of tyrosinase, TRP-1, and TRP-2, thereby decreasing melanogenesis[123].

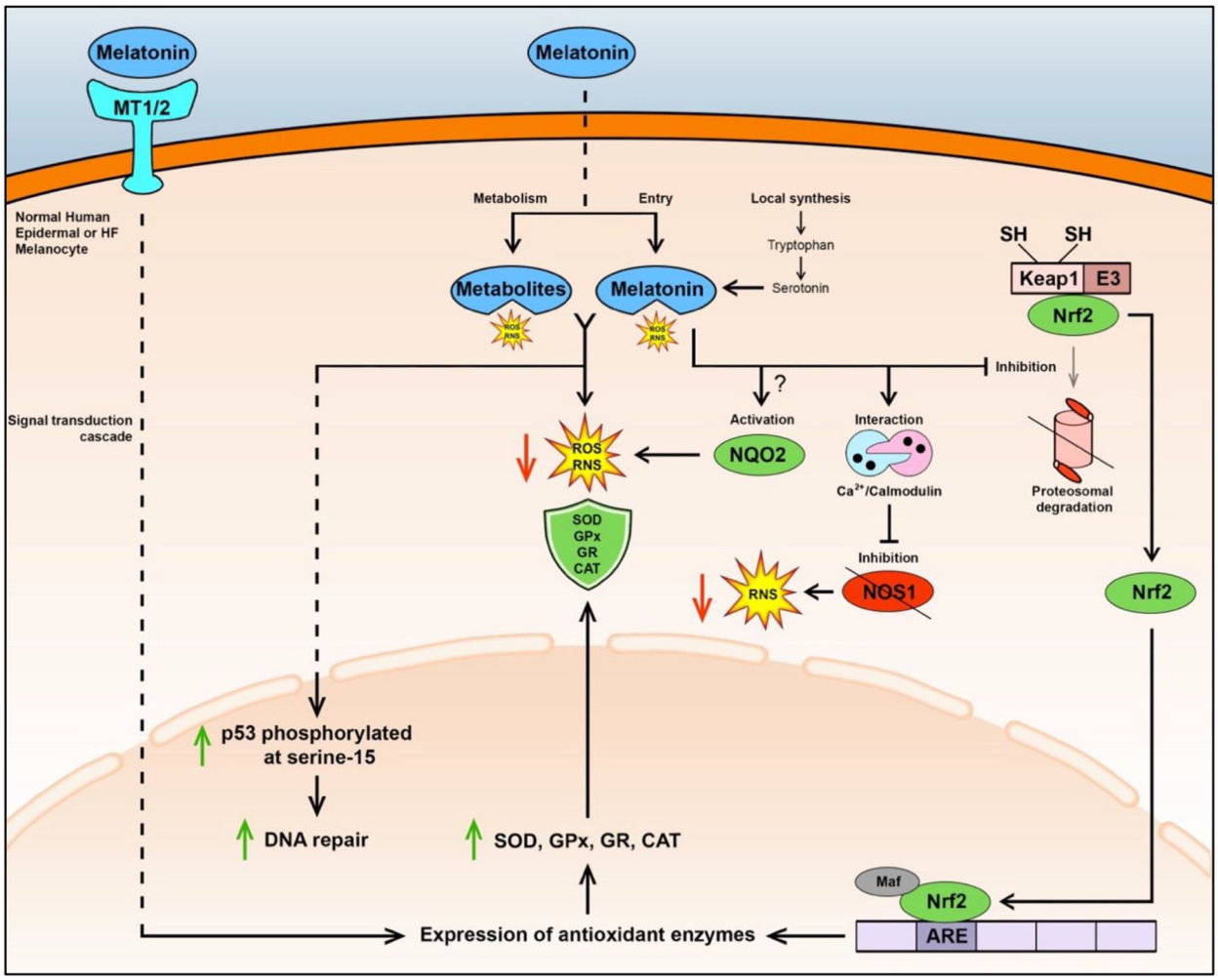

Figure 3. Schematic summary describing antioxidant defense mechanisms by melatonin and its metabolites in human melanocytes.

Melatonin can bind to MT1 and MT2 receptors on the cell membrane, triggering a signaling cascade that leads to expression of antioxidant enzymes (e.g., SOD, GPx, GR, and CAT) for defense against ROS and RNS[125,127]. Melatonin may also be transported to the cytoplasm, but the detailed mechanism is not fully understood[25]. Furthermore, melatonin can be synthesized within these melanocytes. Melatonin and its metabolites, such as C-3HOM and AMK, can directly scavenge ROS/RNS[125,126]. Furthermore, melatonin and its metabolites, including AFMK, 6-OHM, 5-MT, and NAS, protect human epidermal melanocytes from UV-B-induced damage/apoptosis by enhancing phosphorylation of p53 at Serine 15, thereby leading to activated p53 accumulation in the nucleus and stimulation of DNA repair[15]. Melatonin may activate NQO2, thereby reducing oxidative stress[134,135], however this mechanism's presence in these melanocytes is not fully understood[7]. Melatonin at concentrations higher than 1 nM within the cell can interact with the calcium/calmodulin complex leading to inhibition of NOS1-mediated generation of RNS, with potential reductions in RNS levels[25]. Melatonin may also inhibit the Keap1-E3 ligase complex and the ubiquitination and proteasomal degradation of Nrf2, thereby preserving high Nrf2 levels that translocate to the nucleus. In the nucleus, Nrf2 may couple with Maf, a transcription

factor, allowing Nrf2 to bind ARE on the promoter region of genes encoding antioxidant enzymes (e.g., SOD and GPx), resulting in their increased expression and activity, which then convert ROS and RNS to unreactive products[1]. Direct effects are shown by solid lines and multiple reactions and signaling are shown by dashed lines. Reactive oxygen species (ROS); reactive nitrogen species (RNS); superoxide dismutase (SOD); glutathione peroxidase (GPx); glutathione reductase (GR); catalase (CAT).

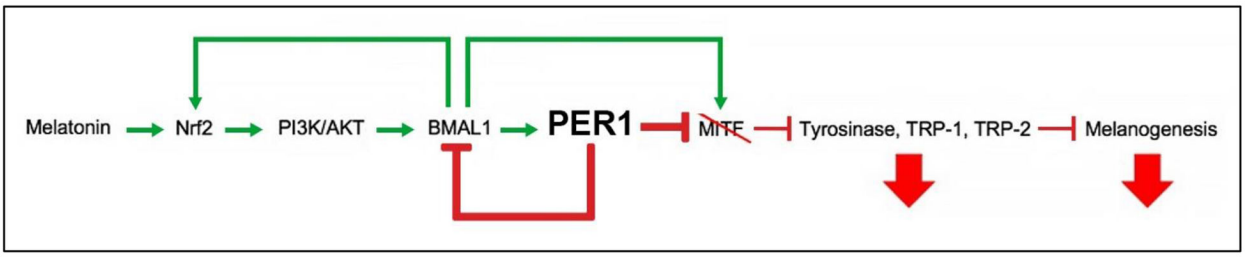

Figure 4. Schematic summary describing hypothesized mechanisms by which melatonin may regulate melanogenesis in normal human epidermal and HF melanocytes.

Melatonin may activate the PI3K/AKT pathway, via Nrf2 activation[15], to stimulate expression of *Bmal1*, thereby increasing BMAL1 levels[181]. BMAL1 may increase expression of Nrf2 to further stimulate this PI3K/AKT pathway[263] and PER1 to inhibit MITF downstream[121]. PER1 also translocates to the nucleus and inhibits transcriptional activity of BMAL1[264,265], thereby preventing BMAL1's stimulation of MITF transcription[266]. Decreased MITF levels lead to decreased expression of melanogenesis enzymes tyrosinase, TRP-1, and TRP-2 and results in decreased melanogenesis[123].

Table 1.

A selection of recognized melatonin functions

Melatonin functions: *Examples*	**References**
Aerobic glycolysis inhibition (glycolytic)	202
Anti-aging	11,114,203
Anti-inflammatory	204-206
Anti-melanoma: anti-proliferative and anti-invasive effects	21,23,207,208
Anti-neoplastic: anti-proliferative and cell cycle arrest	209
Antioxidant	190,210
Blood pressure regulation	211
Body mass regulation	212
Bone mass regulation	213,214
Cardioprotection	211,215
Circadian rhythm regulation	3,6
DNA repair	15
Dopaminergic neuron development in the substantia nigra	216
Estrogen receptor regulation	49
Gastrointestinal tract protection	214
Immune cell proliferation and cytokine release	18,19
Inner ear protection	217
Insulin secretion regulation	218
Liver disease protection	219
Mitochondrial function and biogenesis	220
Nephroprotection	221
Neuroprotection	222
Retina protection	223,224
Reproduction and sexual maturation regulation	225,226
Sensitization of cancers to radiation and chemotherapy	227-231
UV protection	98,145,185,190,232,233
Wound healing	234

Table 2.

Effects of melatonin on hair growth and pigmentation

Growth		
Species	**Effect**	**References**
Mouse	Influence on the hair cycle by the pineal gland	235
Weasel	Induction of molt	236
Mink	Induction of autumn molt	237
Soay rams	Stimulation of molting	238
Limousine ram	Increased HF activity and reduced prolactin plasma levels	239
Mink	Induction of winter fur growth (supposedly by inhibition of prolactin)	240
Cashmere goat	Increase of growth initializing activity of secondary HFs in springtime	241
Red deer	Premature molting of summer pelage and reduced serum prolactin concentrations	242
Merino sheep	No influence of pinealectomy on wool growth and hair density	243
New Zealand goat	Induction of pro-anagen phase	244
Cashmere goat (cultured HFs)	Increase of hair shaft elongation and DNA-synthesis	245
Domestic pig	Increase of pelage development and cycle frequency	246
Ferret	Earlier change of winter and consecutive spring coat	247
Raccoon dogs	More rapid shedding of mature underfur hairs and growth of new underfur hairs; suppression of prolactin levels	248
Siberian Husky dogs	No change in hair growth or anagen rate (topical administration)	249
Rex Rabbit offspring	Maternal melatonin supplementation increased HF density, reduced hairiness, and improved fur quality of offspring	250
Cashmere goat	Continuous subcutaneous implantation of melatonin promoted cashmere to enter the anagen 2 months earlier and induce secondary hair follicle development.	251
Human (cultured HFs)	Increase of hair shaft elongation (30 μM); Decrease of hair shaft elongation (1–5 mM)	252
Human (cultured HFs)	No influence on hair shaft elongation, matrix keratinocyte proliferation/apoptosis and hair cycling (10^{-12}–10^{-6} M)	49
Human (trichograms)	Slight increase of anagen hair rate in women with androgenetic and diffuse alopecia	253
Human (clinical assessment)	Topical melatonin loaded in antioxidant nanostructured lipid carriers significantly increased hair density and hair shaft diameter when compared to topical melatonin alone in men with androgenetic alopecia	198
Pigmentation		
Species	**Effect**	**References**
Weasel	Induction of hair color change	236
Mammalians	Effects on hair color	254
Djungarian hamster	Pattern of melatonin release induced by experimentally induced photoperiods modifies molt into summer pelage	255
Siberian hamster (cultured HFs)	Post-tyrosinase inhibition of melanogenesis (10^{-10}–10^{-6} M)	256
Yellow mice (C3H/He-A*vy)	Slight reduction of coat darkening	257
Mountain hares	Season-dependent effects of melatonin on fur color	258
Djungarian hamster	Induction of the winter molt and pelage color change	259

Growth		
Species	**Effect**	**References**
Djungarian hamster	Change of fur color	260
Mouse	Inhibition of melanogenesis	117
Human (cultured HFs)	No effect on pigmentation (10^{-12}–10^{-6} M)	49

Hair follicle (HF).