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Cellular and Molecular Life Sciences

Review

Cellular mechanisms regulating human melanogenesis

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Abstract. The major differentiated function of melanocytes is the synthesis of melanin, a pigmented heteropolymer that is synthesized in specialized cellular organelles termed melanosomes. Mature melanosomes are transferred to neighboring keratinocytes and are arranged in a supranuclear cap, protecting the DNA against incident ultraviolet light (UV) irradiation. The synthesis and distribution of melanin in the epidermis involves several steps: transcription of melanogenic proteins, melanosome biogenesis, sorting of melanogenic proteins into the melanosomes, transport of melanosomes to the tips of melanocyte dendrites and finally transfer into keratinocytes. These events are tightly regulated by a variety of paracrine and autocrine factors in response to endogenous and exogenous stimuli, principally UV irradiation.

Keywords. Melanogenesis, melanosomes, UV, DNA damages, and melanocytes.

Melanin biosynthesis

Overview. Two types of melanins are synthesized within melanosomes: eumelanin and pheomelanin [1]. Eumelanin is a dark brown-black insoluble polymer, whereas pheomelanin is a light red-yellow sulfur-containing soluble polymer [1]. Both are indole derivatives of 3,4 di-hydroxy-phenylalanine (DOPA) and both are formed in melanosomes from tyrosine through a series of oxidative steps (reviewed in [2]). The synthesis of both types of melanin requires the enzyme tyrosinase (also called tyrosine oxidase, DOPA oxidase, monophenol, L-dopa: oxygen oxidoreductase) that catalyzes the oxidation of tyrosine to L-DOPA, the first step in a series of reactions known as the Raper-Mason pathway [3]. Conversion of tyrosine to L-DOPA is thought to be the critical and rate-limiting step in melanin biosynthesis, as inhibition of this reaction abrogates melanin synthesis [4].

Melanin biological properties. The major known function of melanin is to provide protection against UV-induced DNA damage by absorbing and scattering UV radiation. UV irradiation (wavelengths 100–400 nm) is arbitrarily divided into UVA (320–400 nm), UVB (280–320 nm) and UVC (100–280 nm). The UVC portion of the spectrum is not present in terrestrial sunlight as it is absorbed by the atmospheric ozone layer. Energy absorption by melanin is maximal at the UV portion of the electromagnetic spectrum, and decreases gradually across the visible light spectrum. UV absorbed by melanin is converted into heat, a less toxic form of energy (reviewed in [5]). Still, some *in vitro* studies suggest that melanin capacity to act as a sunscreen is limited and that melanin, when incorporated into a cream and spread over the skin, absorbs only 50 – 75% of incident sunlight [5]. Naturally, it is possible that *in vivo*, by virtue of

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localizing as a "cap" or parasol above the nucleus [6], melanin in melanosomes affords a higher level of protection. Alternatively, the high level of UV protection observed in dark tanned skin may result not only from the presence of melanin, but also from other induced responses including enhanced DNA repair capacity and anti-oxidant defenses (reviewed in [7, 8]).

Melanin intermediates as well as melanin itself, especially the red/yellow pheomelanin [9, 10], can also be harmful to the cell because, depending on their molecular weight and polymerization state, these polymers can enhance UV-induced DNA damage, most likely through the generation of reactive oxygen species [9]. It has been suggested that the increased incidence of UV-induced melanomas in light-skinned, red-hair individuals is not only due to decreased ability of pheomelanin vs. eumelanin to protect against UV-induced DNA damage, but may also be due to the mutagenic properties of pheomelanin and possibly other melanin intermediates as a result of their pro-oxidant capacity [11].

UV irradiation and melanogenesis. A major effect of UV-irradiation on the skin is tanning, also called facultative skin color, denoting increased pigmentation above baseline. In addition, UV irradiation affects melanocyte proliferation and survival both directly and indirectly through its effect on keratinocytes, inducing the synthesis and secretion of paracrine keratinocyte factors (reviewed in [6]).

DNA damage and melanogenesis. UVB irradiation is directly absorbed by cellular DNA, leading to the formation of DNA photoproducts, mainly thymine dimers and pyrimidine (6–4) pyrimidone [12]. Interestingly, the action spectrum for tanning is virtually the same as that for the formation of thymine dimers [13, 14], and UV-induced melanogenesis can be augmented in pigment cells by treatment with T4 endonuclease V, an enzyme that acts exclusively to enhance the repair of UV-induced DNA damage [15]. Moreover, treatment of melanocytes with agents that act exclusively by damaging DNA also stimulates melanogenesis [16].

Additional evidence that UV-induced DNA damage, in contrast to UV-induced cell membrane or cytoplasmic damage, is the principal stimulus for tanning derives from the observation that thymidine dinucleotides (pTT), the obligate substrate for UV-induced thyimine dimers, caused tanning. When provided to cultured pigment cells or topically applied to rodent skin, pTT was noted to increase tyrosinase level and activity, leading to increased pigmentation, clinically and histologically identical to UV-induced tanning, while the complementary adenine dinucleotide did not [17]. Subsequent work revealed that this pTT-induced tan was highly photoprotective to both rodent and human skin (reviewed in [8]). Moreover, pTT was found to activate p53 [18], mimicking UV irradiation also in this regard (see next section for the now well established role of p53 in stimulating melanogenesis). Because pTT does not detectably damage genomic DNA in treated cells or skin, and because many other oligonucleotides not containing pTT sequences, such as GAGTATGAG, also stimulated melanogenesis [19], further mechanistic studies were undertaken. Ultimately, partial or complete homology to the TTAGGG telomere repeat sequence was found to be a required feature of oligonucleotides that activated p53 [20, 21] and increased melanogenesis [8]. This is intriguing in light of the recent recognition that telomere disruption or "uncapping" leads to DNA damage signaling [22–24], including increased melanogenesis [25]. Indeed, treatment of cultured human cells with telomere homolog oligonucleotides (T-oligos) leads to the formation of DNA damage foci at telomeres [26], presumably at sites of single stranded DNA [26], leading to p53 activation and its multiple downstream events. These observations have led us to speculate [27] that the telomere sequence, TTAGGG in all mammalian species, has evolved to contain thymidine dinucleotides precisely because this is a preferred UV target (with GGG constituting the preferred target for oxidative DNA damage and chemical carcinogens). Because UV irradiation is known to introduce photoproducts and other forms of damage disproportionately into telomeric DNA, compared to the genome overall [27], disruption of the normal telomere structure with exposure of TTAGGG sequences is one attractive candidate for the physiologic melanogenic stimulus mimicked by pTT and other T-oligos.

p53 in UV-induced melanogenesis. A central role for DNA damage and/or its repair in stimulating melanogenesis is further supported by the fact that the tumor suppressor protein p53, when activated, upregulates the level of tyrosinase mRNA and protein, enhancing melanogenesis [28–31]. These findings were expanded by Cui et al. [32], who found a p53 consensus sequence in the proopiomelanocortin (POMC) gene promoter, thus establishing a continuous signaling pathway from UV-induced DNA injury to the final tanning response. It was shown that, following UV irradiation in mice, p53 activation stimulates transcription from the POMC promoter in keratinocytes, thereby increasing the release of POMC-derived α-melanocyte stimulating hormone (α-MSH), a key physiologic inducer of melanogenesis. Keratinocyte-

Table 1. UV-induced keratinocytes-derived paracrine factors (modified from Fitzpatrick's Dermatology in General Medicine [6]).

	Effects on melanocytes				
	Proliferation	**Dendricity**	**Melanogenesis**	**Melanosomal Transfer**	**Survival**
bFGF	↑				
ET-1	↑	↑	↑		
IL-1α/1β	↓	↑	↓		
ACTH	↑		↑		↑
α-MSH	↑	↑	↑		↑
PGE2/PGF2a		↑	↑	↑	
GM-CSF	↑		↑		
NO			↑		
TNF-α			↓		
NGF		↑			↑
BMP-4			↓		

GM-CSF: Granulocyte-macrophage colony stimulating factor

derived α-MSH then stimulates the melanocortin-1 receptor (MC1R) on melanocytes, resulting in increased production of eumelanin [32]. In contrast, p53 knockout control mice did not show POMC upregulation, increased α-MSH, and subsequent UV-induced tanning [32]. However, the suggested dominant role of p53-induced keratinocyte-derived α-MSH in human tanning, as opposed to tanning in a genetically manipulated mouse model, has been challenged [33] and is inconsistent with the strong p53-mediated melanogenic response of UV-irradiated human melanocytes and melanoma cells *in vitro*, in the absence of keratinocytes [28, 29, 34].

It has also been shown that p53 transcriptionally regulates the hepatocyte nuclear factor-1α (HNF-1α) that is a transcription factor for tyrosinase (reviewed in [35]). Thus it is possible that even in the absence of keratinocytes, UV directly activates p53 and HNF-1α in melanocytes to increase tyrosinase transcription. Furthermore, since UV is known to increase H_2O_2 level and H_2O_2 is a known p53 activator [36], this signaling pathway may play a role in UV-induced melanogenesis in melanocytes. Regardless of the p53 target genes in melanocytes and keratinocytes, however, it is now clear that tanning may be viewed as part of a p53-mediated DNA damage adaptive response that protects the skin during subsequent exposure to UV irradiation [29, 30, 33].

Other effects. Most UVA effects are assumed to be the result of oxidative damage mediated through UVA absorption by cellular chromophores such as melanin precursors that act as photosensitizers leading to the generation of reactive oxygen species and free radicals that can induce DNA damage [37]. In addition, it has been shown that plasma membrane lipids are also affected by UV irradiation to release membrane-associated diacylglycerol (DAG) [38], which in turn can activate protein kinase C-β (PKC-β), resulting in stimulation of melanogenesis [39, 40].

Paracrine factors induced in keratinocytes by UV irradiation and their effects on melanocytes are summarized in Table 1. These factors can act alone or synergistically with each other to modulate melanocyte function. Interestingly, UV irradiation also induces the level of TNF-α and IL-1 [41, 42], cytokines that inhibit melanogenesis [43], suggesting a fine-tuned epidermal equilibrium between melanogenic stimulation and inhibition after UV irradiation, with the final net outcome of increased melanogenesis.

Melanogenic enzymes

Tyrosinase. Tyrosinase is a glycoprotein located in the melanosomal membrane. It has an inner melanosomal domain that contains the catalytic region (approximately 90% of the protein), followed by a short transmembrane domain and a cytoplasmic domain composed of approximately 30 amino acids [44, 45]. Histidine residues present in the inner (catalytic) portion of tyrosinase bind copper ions that are required for tyrosinase activity [4].

The tyrosinase cytoplasmic domain, specifically the motif EXXQPLL (glutamic acid-X-X-glutamine-proline-leucine-leucine, where 'X' stands for any amino acid), directs tyrosinase trafficking into the melanosomes [46]. In addition, PKC-β (see below) phosphorylates two serine resides on this domain, a modification required for tyrosinase activation [44]. Tyrosinase can also be indirectly activated by tyrosine hydroxylase isoenzyme I (THI) that was shown to be present

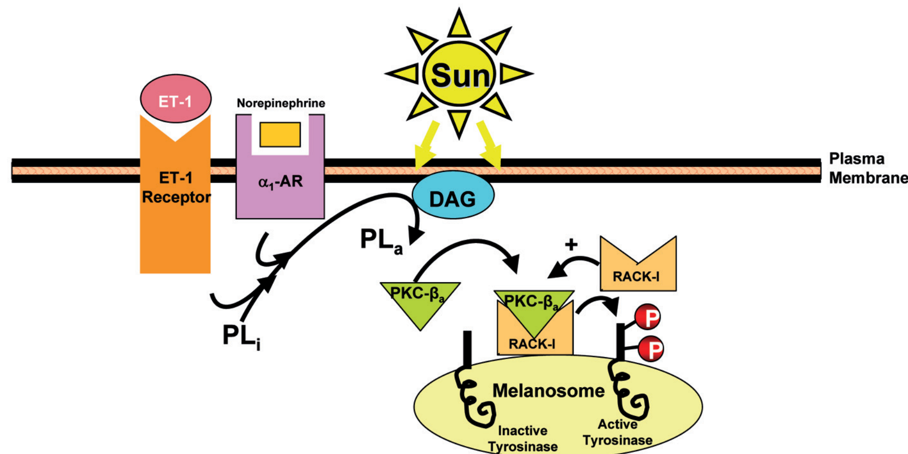

Figure 1. Activation of tyrosinase by PKC-β. UV irradiation, as well as activated cell surface receptors after binding with their specific ligands (ET-1/ET-1 Receptor and Norepinephrine/α_1-AR), releases DAG from the cell membrane. Inactive PKC-β is activated by DAG and activated PKC-β (PKC-β_a) binds to RACK-I. The PKC-β_a/RACK-I complex translocates to melanosome and then phosphorylates serine residues on tyrosinase. This phosphorylation activates the enzyme. (Modified from Fitzpatrick's Dermatology in General Medicine [6])

in melanosomes and to catalyze L-dopa synthesis, thus activating tyrosinase [47]. In addition, the enzyme phenylalanine hydroxlyase can contribute to tyrosinase activation because it catalyzes the conversion of L-phenylalanine to L-tyrosine, providing a substrate for tyrosinase [35].

Tyrosinase mutations including missense, nonsense, frameshift and deletion mutations that lead to inactivation of the enzyme are the cause of oculocutaneous albinism, a group of hereditary disorders characterized by melanin deficiency or absence (Albinism database: http://albinism-db.med.unm.edu/). Tyrosinase mutations may affect glycosylation of the protein, interfering with enzyme maturation; the copper (Cu) binding sites disrupting enzymatic activity; or the cytoplasmic domain, preventing enzyme activation (reviewed in [48]).

Tyrosinase-related proteins. Two tyrosinase-related proteins, TRP-1 and TRP-2, are structurally related to tyrosinase and share ~ 40% amino acid homology, suggesting that they originated from a common ancestral gene [49–53]. TRP-1 and TRP-2 reside within the melanosomes and, like tyrosinase, span the melanosomal membrane [54], although their precise function is not well elucidated.

Mutations of TRP-1, such as those present in a certain type of oculocutaneous albinism, result in pale skin and hair color, demonstrating a TRP-1 requirement for optimal melanin synthesis [55]. Indeed, it was suggested that TRP-1 increases the ratio of eumelanin to pheomelanin [56, 57]. As TRP-1 forms a complex with tyrosinase, it is possible that TRP-1 plays a role in tyrosinase activation and/or stabilization [58, 59]. TRP-1 also plays a role in melanosomal biogenesis, as suppression of TRP-1 expression is associated with structurally abnormal melanosomes [60].

TRP-2 complexes with tyrosinase and also with TRP-1 [61]. TRP-2 converts DOPAchrome to the carboxylated derivative dehydroxyindole-2-carboxylic acid (DHICA) during one of the later stages of melanin biosynthesis [62]. Like tyrosinase, TRP-2 enzymatic activity also requires metal ions, but it is zinc rather than copper [63].

PKC-β. PKC constitutes a family of at least 12 isoforms (reviewed in [64]) of which PKC-β is involved in regulating tyrosinase activity by phosphorylating serine residues on the cytoplasmic domain of tyrosinase [39, 40].

Activated PKC-β was shown to be associated with the melanosomal membrane [39]. Inactive PKC-β normally resides within the cytoplasm of melanocytes. Upon activation by DAG, activated PKC-β binds the Receptor for Activated C-Kinase-I (RACK-I) [65], the receptor specific for the activated PKC-β. The activated PKC-β/RACK-I complex then translocates to the melanosome membrane phosphorylates tyrosinase (Fig. 1) [66]. Tyrosinase phosphorylation appears to lead to complex formation between tyrosinase and TRP-1 [61], an event known to stabilize tyrosinase and increase its enzymatic activity [58]. While DAG also activates PKC-α isoform, RACK-I within melanocytes directs only activated PKC-β to melanosomes, thus determining the unique role of PKC-β in melanogenesis. Interestingly, PKC-β is found only within melanocytes, not epidermal keratinocytes or fibroblasts [67].

Melanogenic regulatory proteins

Microphthalmia-associated transcription factor (MITF). MITF is a basic-helix-loop-helix (bHLH) and leucine zipper transcription factor that binds to

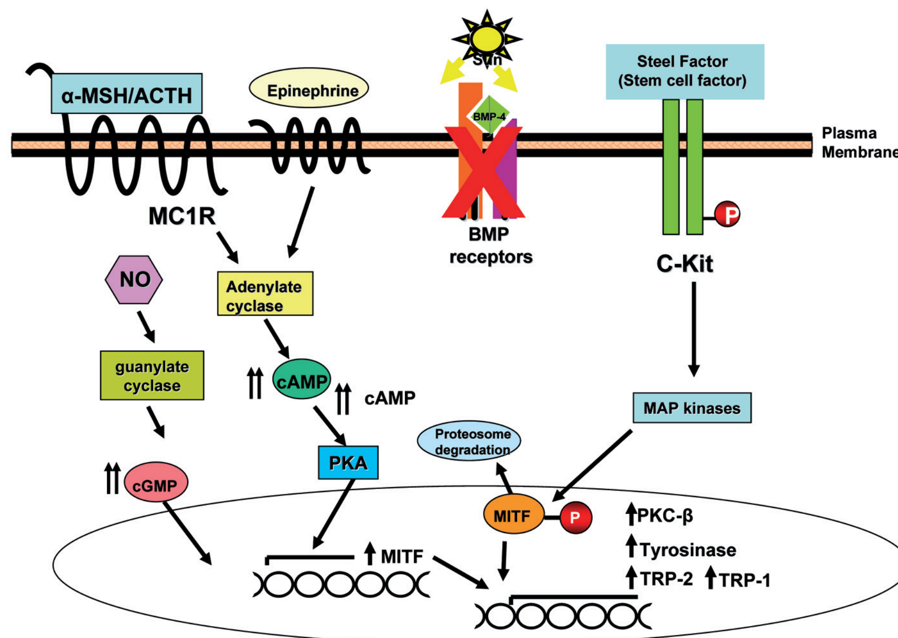

Figure 2. Selected signaling pathways regulating melanogenesis. UV irradiation upregulates the levels of α-MSH, ACTH and their cognate receptor MC1R to stimulate cAMP production. Intracellular level of cAMP can also be increased after keratinocyte-released epinephrine binds to its cell surface receptor β_2-AR on melanocytes. Steel factor (stem cell factor) by binding to c-Kit leads to receptor autophosphorylation and activation of MAP kinases. MAP kinases phosphorylate (activate) MITF, leading to transcription of the melanogenic enzymes tyrosinase, TRP-1, TRP-2 and PKC-β. NO activates the enzyme guanylate cyclase that increases the intracellular level of cGMP. UV irradiation, by decreasing the level of BMP receptors, prevents BMP-4 mediated inhibition on melanogenesis. (Modified from Fitzpatrick's Dermatology in General Medicine [6]).

conserved consensus elements in gene promoters, specifically the M-(AGTCATGTGCT) and E-(CATGTG) boxes [68], and regulates the transcription of tyrosinase, TRP-1, TRP-2 [69] and PKC-β [70]. MITF can bind as a homodimer or a heterodimer with another related family member (reviewed in [71]). MITF comprises a family of at least nine isoforms [72, 73] of which the MITF-M isoform controls tyrosinase and PKC-β transcription in melanocytes [70, 74, 75]. MITF activity and stability are regulated by its phosphorylation state. Upon phosphorylation, MITF binds to either M-box or E-box consensus sequences to activate transcription, [76, 77], but phosphorylation then decreases MITF stability and enhances its degradation in proteosomes [78, 79] (Fig. 2). More recently, MITF was shown to be a key transcription factor for Rab27a [80], a protein important for melanosome transport (see Melanosome Transport) and Pmel17 [74], a protein required for melanosome matrix formation. Therefore, MITF plays a central role in melanin synthesis, as well as melanosome biogenesis and transport.

Melanocortin 1 receptor. Melanocortin receptors (MCRs) comprise a family of five related proteins, each with seven transmembrane domains, that belong to the G-protein-coupled receptor superfamily (Fig. 2) [81]. MC1R, the receptor expressed in melanocytes [82], is activated by α-MSH and ACTH peptides derived from 39 amino acid POMC gene product (reviewed in [83–85]). Receptor-ligand interaction leads to G-protein dependent activation of the enzyme adenylate cyclase followed by increased intracellular cAMP levels activating the enzyme cAMP-dependent protein kinase (PKA) (reviewed in [83]). PKA induces MITF transcription and MITF in turn upregulates the level of several melanogenic enzymes including tyrosinase [43], promoting the synthesis of brown/black eumelanin (reviewed in [83]) (Fig. 2).

Polymorphisms within the *MC1R* gene are largely responsible for the wide range of skin and hair color among different ethnic groups [86]. At least 30 MC1R variants have been identified. Nine of them display loss of function [87, 88] and failure to elevate intracellular cAMP levels in response to α-MSH despite adequate receptor/ligand binding, while other MC1R variants have reduced affinity for α-MSH [87, 88]. The three MC1R "red hair color" variants, each with only a single amino acid substitution, are strongly associated with red or yellow hair and fair skin [89] in Northern Europeans and Australians [90–95] and with increased melanoma incidence [96]. Other MC1R

variants not associated with red hair also confer an increased risk of melanoma [97].
Agouti signaling protein (ASP) is expressed in both humans and mice [98–100]. ASP antagonizes α-MSH by competitive binding to MC1R, thus inhibiting adenylate cylcase and increases synthesis of pheomelanin relative to eumelanin. In mice, over-expresssion of ASP leads to yellow coat color. However, ther role of ASP in human pigmentation is poorly understood. At least in dogs, another gene has been identified to play a role in pigmentation [101]. A dominant black allele of cBD103 (K^B), identified in several breeds with black coat color, encodes β-defensin (K^B), a secreted protein previously studied for its role in immunity [102]. Surprisingly, this β-defensin binds MC1R in melanocytes and increases production of eumelanin, thus causing dark pigmentation [101]. It will be interesting to determine if β-defensin plays any role in human pigmentation.

β_2 and α_1–adrenoreceptors. Although MC1R/POMC/cAMP pathway has been considered the key pathway regulating melanogenesis, recent studies suggest additional receptor/ligand pathways regulating melanogenesis through cAMP. POMC-deficient mice ($POMC^{-/-}$) that lack the melanocortin ligands still display normal black coat color [103]. Histological and electron paramagnetic resonance spectrometry of the hair follicles showed a normal structure and eumelanin pigmentation [103]. This study suggests that either MC1R has adequate basal activity to induce pigmentation or that non-melanocortin pathways induce melanogenesis in this mouse. Subsequent studies demonstrated that melanocytes express both β_2 and α_1 adrenoreceptors (β_2-AR and α_1-AR, respectively) ([104, 105]). *α_1-AR* interacts with melanocyte-derived norepinephrine and increases the level of diaglycerol [105, 106]; therefore, inducing melanogenesis in PKC-β dependent pathway (Fig. 1). Also, keratinocytes produce epinephrine which then binds to β_2-AR expressed on melanocytes and increases the level of cAMP, leading to melanin synthesis [105]. Therefore, numerous pathways may act in tandem to regulate melanogenesis.

Melanosomes

The melanosome is a unique membrane bound organelle in which melanin biosynthesis takes place. Because melanosomes contain enzymes and other proteins that are also present in lysosomes, they are thought to represent a modified version of the latter. Proteins common to both organelles include the lyposomal-associated membrane proteins (LAMPS) that participate in autophagy and regulation of intravesicular pH (reviewed in [107]), as well as acid phophatase, a marker enzyme for lysosomes [107]. However, since certain LAMPS are present exclusively in melnosomes, some investigators believe that melanosomes form from a separate lineage [108].

Melanosome biogenesis. Melanosomes display four maturation stages. Stage I melanosomes or premelanosomes likely develop from the endoplasmic reticulum [43]. However, this remains controversial since Raposo and colleagues suggested that Stage 1 melanosomes are a type of multivesicular endosome [108]. They have an amorphous matrix and display internal vesicles that form as a result of membrane invagination. Premelanosomes already contain the glycoprotein Pmel17 (gp100), but it requires further processing to become a component of the final fibrillar matrix [109]. Stage II eumelanosomes have organized, structured fibrillar matrix, but no active melanin synthesis, whereas melanin synthesis can occur in stage II pheomelanosomes. Although no active melanogenesis takes place in stage II eumelanosomes, they already contain the enzyme tyrosinase. Deposition of melanin on the fibrillar matrix is found in stage III eumelanosomes, while stage IV eumelanosomes are fully melanized and their internal matrix is masked by melanin deposits (reviewed in [60, 110]).

Melanosome transport. Melanosomes are transferred from their site of origin in melanocyte perikaryon to the tips of melanocyte dendrites. Melanosome transport takes place on microtubules that are arranged parallel to the long axis of the dendrite and is controlled by two classes of microtubule-associated motor proteins: kinesins [111–113] and cytoplasmic dyneins [114–118]. Both motor proteins act as short cross-bridge structures connecting the organelle to the microtubules. Centrifugal, anterograde organelle movement is mediated primarily by kinesin, whereas centripetal movement is controlled by cytoplasmic dynein. Studies examining melanosomal transport suggest that their microtubule-dependent movement is bidirectional [119], consistent with a cooperative forward and backward pull of kinesin [111] and dynein [115], respectively. For melanosomes with net centrifugal movement, the bidirectional movement appears to terminate with myosin-Va (encoded by dilute locus)-dependent melanosomal capture in the actin-rich periphery of the dendrite [119] (Fig. 3).
Additional proteins that participate in melanosome transport include Rab27a (encoded by *ashen* locus), that mediates myosin-Va binding to melanosomes through another linker protein-melanophilin (encod-

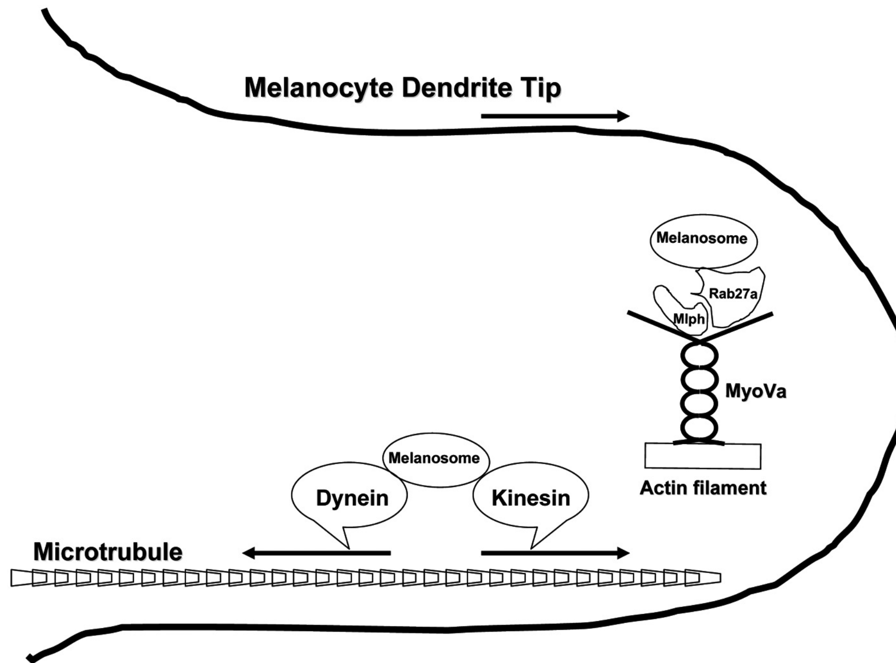

Figure 3. Schematic diagram of melanosome transport across melanocyte dendrites. Melanosomes move bi-directionally along melanocyte dendrites. They are attached to microtubules through the motor proteins kinesin (anterograde) and dynein (retrograde). At the tip of the dendrite melanosomes are captured in the actin-rich periphery. Myosin-Va mediates melanosome binding to actin through the linker proteins Rab27a and melanophilin (Mlph). (Modified from Fitzpatrick's Dermatology in General Medicine [6])

ed by *leaden* locus) [120]. In the absence of myosin-Va, melanosomes do not collect in dendrite tips.

Melanosome transfer. Mature melanosomes are transferred from melanocytes to neighboring keratinocytes and studies suggest that they are transferred in a variety of ways including exocytosis, cytophagocytosis, fusion of plasma membranes and transfer by membrane vesicles, briefly described below (reviewed in [121]).
The exocytosis pathway of melanosomal transfer involves fusion of the melanosomal membrane with the melanocyte plasma membrane followed by melanosome release into the intercellular space and phagocytosis by surrounding keratinocytes. Keratinocytes can also cytophagocytose the entire tip of a melanocyte dendrite, which then fuses with lysosomes inside the keratinocyte, is transported to a supranuclear location where the phagolysosome membranes break-up, and releases the melanosomes. Fusion of keratinocyte and melanocyte plasma membranes creates a space through which melanosomes are transferred from the melanocyte to the keratinocyte. Indeed, high resolution photography shows the presence of filopodia, slender, filliform, pointed cytoplasmic projections at the tip of melanocyte dendrites [122]. These filopodia adhere and fuse with the keratinocyte plasma membrane prior to melanosome transfer. Transfer by membrane vesicles involves shedding of melanosome-filled vesicles from melanocytes followed by phagocytosis of these vesicles by keratinocytes or their fusion with keratinocyte plasma membrane.
The molecular and cellular mechanisms involved in melanosome phagocytosis have been partially elucidated. It appears that keratinocytes express a seven transmembrane G-protein coupled receptor called protease activated receptor-2 (PAR-2). PAR-2 is activated when serine proteases cleave the extracellular portion of the receptor, exposing a new segment that acts as a tethered (attached) ligand [123, 124]. Activation of PAR-2 increases keratinocyte phagocytic activity [123, 124]. Interestingly, and consistent with its role in melanosome phagocytosis, UV induces the activity and expression of PAR-2 [125]. UV effect on PAR-2 activity and expression is more pronounced in darker skinned individuals than in those with very light skin [125]. Keratinocyte growth factor receptor has also been implicated in enhancing phagocytosis of melanosomes by keratinocytes [126].

Regulation of melanocyte function

Melanocyte behavior in skin is largely influenced by both positive and negative signals from neighboring keratinocytes and to a lesser degree dermal fibroblasts [127], as well as autocrine signals and environmental factors such as UV irradiation. UV irradiaton increases the synthesis and secretion of most keratinocyte-derived melanogenic stimulating factors and decreases that of factors inhibitory for melanogenesis, but UV

can also directly stimulate melanocyte dendricity and melanin production [34, 122].

Paracrine melanogenic stimulators

Proopiomelanocortin (POMC) and derived peptides. α-MSH and ACTH are potent stimulators of melanogenesis. Their POMC precursor is synthesized by epidermal keratinocytes, as well as by the pituitary gland, from which it was first isolated. POMC expression in keratinocytes is induced by UV irradiation and interleukins, cytokines synthesized and released during cutaneous inflammation [128, 129]. Systemic administration of α-MSH, β-MSH, or ACTH, an α-MSH analog, increases skin pigmentation predominantly in sun exposed areas [130, 131]. Also, in Addison disease [132] (decreased adrenal function) or Nelson syndrome [133] (ACTH secreting pituitary adenoma), disease conditions characterized by abnormally high levels of ACTH, generalized hyperpigmentation of the skin is observed [134].
α-MSH can also increase melanin synthesis by a mechanism independent of MC1R. By binding with 6(R)-L-erythro-5,6,7,8-tetrahydrobiopterin (6BH4), a molecule that inhibits tyrosinase activity, α-MSH removes 6BH4 inhibitory effect on this key melanogenic enzyme [135, 136]. 6BH4 also serves as a cofactor for phenylalanine and tyrosine hydroxylase. In addition, 7BH4, an isomer of 6BH4 and an inhibitor of tyrosinase, was shown to be present in melanosomes [137]. Interestingly, only β-MSH, but not α-MSH, would remove 7BH4 inhibitory activity [137].

Endothelin-1 (ET-1). ET-1, a 21 amino acid peptide first identified by its role in vascular homeostasis, also regulates melanogenesis, activating tyrosinase and increasing TRP-1 levels [138, 139]. ET-1 also stimulates melanocyte proliferation [138, 139] and dendrite formation [140]. Cultured keratinocytes synthesize and secrete ET-1 [139–141] and UV irradiation stimulates ET-1 production by keratinocytes [139, 140]. ET-1 up-regulates MC1R level and increases MC1R affinity for α-MSH [142, 143].

Steel/Stem cell factor (SCF). SCF is a keratinocyte-derived growth factor that binds the c-Kit tyrosine kinase receptor. SCF binding to c-Kit leads to receptor autophosphorylation and mitogen activated protein (MAP) kinase activation (Fig. 2). MAP kinases phoshphorylate (activate) MITF, leading to transcription of the melanogenic enzymes tyrosinase, TRP-1 and TRP-2 (Fig. 2). Besides its role as a melanocyte survival factor, SCF participates in UV-induced pigmentation and its level is induced by UV-irradiation [43]. SCF can also act synergistically with several interleukins and granulocyte-macrophage-colony stimulating factor to enhance UV-induced melanogenesis [144, 145].

Inflammatory mediators. Several inflammatory mediators can affect skin pigmentation. Prostaglandins (PGs) and leukotrienes, lipid compounds derived from arachidonic acid are mediators of inflammatory responses that affect melanocyte function. Their level is elevated in sunburned skin [146, 147] and in a variety of inflammatory dermatoses [148, 149].
Human melanocytes express PG receptors including the receptors for PGE_2 and $PGF_{2\alpha}$ [150, 151]. Indeed, $PGF_{2\alpha}$ stimulates melanocyte dendrite formation and activates tyrosinase [150, 151], and UV irradiation upregulates the level of PG receptors on melanocytes [150, 151]. Similarly, leukotrienes B_4 and C_4 increase melanin synthesis and stimulate melanocyte proliferation and motility [152]. Melanocytes also respond to histamine that is released by mast cells during cutaneous inflammation. Histamine binds H_1 and H_2 receptors to induce melanocyte dendricity and upregulate tyrosinase level [153, 154]. The disease urticaria pigmentosum is characterized by focal brown hyperpigmentation in the epidermis overlying greatly increased numbers of mast cells in the dermis [6].

Neurotrophins. Neurotrophins (NTs) are a family of molecules that enhance neuronal survival in the central and peripheral nervous systems. They include nerve growth factor (NGF) [155], NT-3 [156–158], NT-4 [159], and brain-derived neurotrophic factor [160, 161]. Melanocytes express the 75kD low affinity receptor common to all neurotrophins, $p75^{NTR}$ [162], as well as the high affinity receptors for NGF (TrkA) and NT3 (TrkC) (reviewed in [163, 164]). Keratinocyte-derived NGF, whose expression is upregulated by UV irradiation, is chemotactic for melanocytes and induces their dendricity [164]. Both NGF and NT-3, the latter expressed by dermal fibroblasts, increase melanocyte survival [164]. Specifically, after UV irradiation, NGF supplementation increases the level of the anti-apoptotic Bcl2 protein, reducing apoptotic cell death of melanocytes [165, 166]. Thus, in addition to other keratinocyte-derived cytokines, NGF appears to preserve the population of cutaneous melanocytes that would otherwise be depleted by UV damage.

Basic fibroblast growth factor. Basic fibroblast growth factor (bFGF), named for its ability to stimulate fibroblast growth, was one of the first identified melanocyte mitogens [167, 168]. It is produced by keratinocytes, but lacks a secretory signal and hence is

presumed to affect melanocytes through cell-cell contact. It binds tyrosine kinase transmembrane receptors to induce its mitogenic effect in the presence of cAMP elevating factors. Like other keratinocyte-derived cytokines, it is up-regulated in response to UV irradiation [168]. Keratinocyte growth factor, another member of the FGF family of proteins, has been shown to promote melanosome transfer from melanocytes to keratinocytes [126].

Nitric oxide. Nitric oxide (NO) is a diffusible free radical with pleiotropic bioregulatory effects in diverse cells and tissues [169, 170]. Melanocytes and keratinocytes produce NO in response to inflammatory cytokines [171 – 174], and NO production in keratinocytes is induced by UV irradiation [175]. Through the activation of secondary messengers, NO increases tyrosinase activity and melanogenesis [175] and is thus an autocrine as well as paracrine molecule that affects melanogenesis (Fig. 2).

Catecholamines. Catecholamines are a group of signaling molecules, primarily functioning as neurotransmitters and as endocrine hormones [176]. Catecholamines bind to either α_1-AR or β_2-AR and can induce melanogenesis either through PKC-β or cAMP-dependent pathways [105, 106] (see β_2 and α1-Adrenoreceptors, Figs. 1 and 2).

Melanogenic inhibitors

Numerous reports have suggested the existence of endogenous melanogenic inhibitors, [177, 178] but few specific molecules have been identified. One group of inhibitors includes sphingolipids, a class of membrane associated lipids that act as signal transducers (reviewed in [179]). Sphingolipids were shown to decrease melanogenesis, at least in part by enhancing MITF degradation via ubiquitin-meditated pathways [180, 181]. Another melanogenic inhibitor, BMP-4, down-regulates tyrosinase expression in melanocytes [182], also in part via its effects on MITF [183]. Interestingly, physiologic doses of UV irradiation, a potent melanogenic stimulator, decrease the expression of BMP by keratinocytes and of BMP receptors by melanocytes [182], presumably reducing its inhibitory effect during UV-induced tanning. Mice that transgenically over-express the physiologic BMP antagonist noggin have a darker coat color than wild-type mice and their hairs have a higher eumelanin to pheomelanin ratio [184], suggesting that this pathway also influences basal melanin levels. Reports by Wood et al. demonstrated the presence of tetrahydrobiopterines, molecules that bind tyrosinase inhibiting its activation [185 – 187].

Summary

Melanin plays a critical role in protecting against UV-induced damage and is the major determinant of skin and hair color. Melanogenesis involves complex interactions between stimulatory and inhibitory influences, both endogenous and environmental. The past two decades have brought an enormous increase in our understanding of melanogenic enzymes, melanosomes, and the intra-and inter-cellular signaling pathways that regulate human pigmentation. These insights should facilitate development of new therapeutics to address disorders of melanogenesis.

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