Pigmentation and Hyperpigmentation

Pigmentation is the natural colour of a person's skin. Hyperpigmentation is characterized by the increased production and accumulation of melanin, which causes a darkened appearance to the skin in small or large areas. Three common types of hyperpigmentation are photodamage, melasma and post-inflammatory hyperpigmentation (PIH).

Melanocytes, Melanosomes and Keratinocytes

Skin colour production originates in melanocytes at the basal layer of the epidermis. The process of pigment production is known as melanogenesis. Melanocytes are branched cells with a central cell body and a number of dendrites. Melanosomes are specialized melanin-containing organelles or vesicles that are produced inside melanocytes [1]. Melanosomes mature there as they pass to the outer tips of the dendrites where they are transferred into keratinocytes. Melanocytes form epidermal melanin units as a result of the relationship between one melanocyte and 30 to 40 associated keratinocytes [2]. The ratio of melanocytes to keratinocytes is 1: 10 in the basal layer of the epidermis.

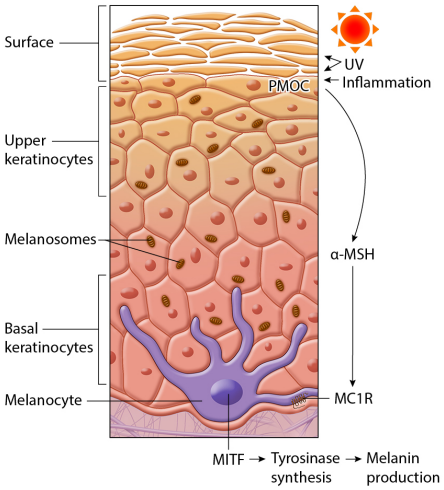
Function of Melanin

Two types of melanin are synthesized within melanosomes: eumelanin and pheomelanin. Eumelanin is a dark brown-black insoluble polymer and is the most common form of melanin. Pheomelanin is a light red-yellow sulphur-containing soluble polymer that is associated with freckles and red hair [3].

Irrespective of skin colour, every human has the same number of melanocytes. Differences in skin pigmentation result from differences in melanogenic activity, the type of melanin produced in melanosomes and the size, number and packaging of melanosomes. The melanin content of melanosomes ranges from 17.9% to 72.3% [4,5]. Skin pigmentation reflects a genetically determined level of melanin and can be modified by factors such as ultraviolet radiation (UVR), medications and endocrine influences [6,1].

Exposure to UVR increases melanogenesis. The purpose of melanin is to protect underlying tissues from harmful UVR by absorbing nearly all of the UV energy and transforming it into harmless amounts of heat energy in order to prevent DNA damage [7,8]. Eumelanin also has the ability to scavenge and quench free radicals [9,10]. Pheomelanin does not have the same properties and can even be a source for free radical production when exposed to UVR.

Overview of pigmentation of the skin



a-MSH – Alpha Melanocyte Stimulating Hormone
MC1R – Melanocortin 1 Receptor
MITF - Microphthalmia-Associated Transcription Factor
PMOC - Propiomelanocortin

Melanogenesis Regulatory Proteins

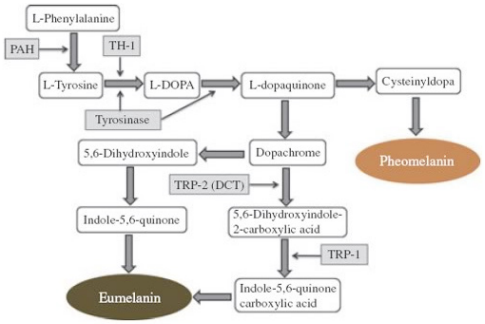
MITF (Microphthalmia-associated transcription factor) is the key regulatory transcription factor that controls melanocyte development and melanogenesis via its transcriptional regulatory effect on tyrosinase,

Melanogenesis Pathway

Tyrosinase catalyses the first two steps of melanin production: the hydroxylation of L-tyrosine to L-DOPA and its subsequent oxidation to L-dopaquinone [11,12,13]. Tyrosinase is a copper-dependent enzyme.

Following the formation of L-dopaquinone, the melanin pathway is divided into synthesis of eumelanin and pheomelanin [14]. In the eumelanin pathway, L-dopaquinone is first spontaneously converted to dopachrome. Then dopachrome is either spontaneously converted to 5,6-dihydroxyindole, indole-5,6-quinone and then eumelanin; or dopachrome is enzymatically converted to 5,6- dihydroxyindole-2-carboxylic acid, indole-5,6-quinone carboxylic acid and then eumelanin by the enzymes known as tyrosinase-related protein-1 and -2 (TRP-1 and TRP-2). TRP-1 and TRP-2 are two proteins that are structurally related to tyrosinase and reside within melanosomes. In the pheomelanin pathway L-dopaquinone combines with the amino acid cysteine to produce pheomelanins [15].

The concentration of L-tyrosine for melanogenesis depends on the conversion of the essential amino acid L-phenylalanine by intracellular phenylalanine hydroxylase (PAH) activity [16].



Gillbro J, Olsson MJ. The melanogenesis and mechanisms of skin-lightening agents - Existing and new approaches. Int. J. Cosmet. Sci. 2011, 33, 210-221.

TRP-1 and TRP-2 [17]. MITF has also been shown to be a key transcription factor for Rab27A [18], a protein important for melanosome transport to the dendritic tips of melanocytes. MITF production is controlled by the MITF gene.

Paracrine Melanogenesis Stimulators

Paracrine refers to hormones that have effect only in the vicinity of the gland secreting it. There are number of paracrine stimulators of melanogenesis such as propiomelanocortin (POMC)-derived peptides: α-MSH, β-MSH, ACTH [19]. POMC expression in keratinocytes is induced by UVR [20]. The important effect of these hormones on melanogenesis has been demonstrated in vivo where systemic administration of α-MSH, β-MSH, or ACTH increases skin pigmentation predominantly in sun-exposed areas [21,22] via multiple steps ultimately activating MITF.

Skin Lightening Agents

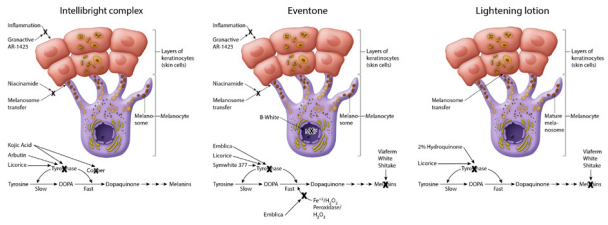
Skin lightening products are available to treat hyperpigmentation. All of these products target and reduce natural melanin production. Many of the commonly used actives have a tyrosinase-inhibiting effect such as hydroquinone, arbutin, kojic acid and some plant extracts. Other ingredients, like niacinamide, exert their lightening effect by reducing the transfer of melanin from melanocytes to keratinocytes. Substances, which increase cell turnover such as alpha hydroxy acids and retinoids, are also commonly used to remove excess melanin content from within the skin. Ingredients with novel mechanisms of action include MSH antagonists, inhibitors of MITF and other enzymes (eg. TRP-1 and TRP-2), and anti-inflammatory agents since irritation is known to stimulate hyperpigmentation.

Sunscreen

The most important product to prevent hyperpigmentation is sunscreen. A broad-spectrum mineral sunscreen with an SPF of at least 30 should be worn daily all year round to minimize future sun damage.

AlumierMD's Approach to Hyperpigmentation

AlumierMD products target hyperpigmentation using five different methods for increased effectiveness:



1) Decrease the production of pigment by complementary mechanisms in EvenTone Brightening Serum, Intellibright or Lightening Lotion
2) Block pigment transfer from melanocytes to keratinocytes with vitamin B3 (niacinamide) in EvenTone and Intellibright
3) Degrade existing hyperpigmentation with shitake mushroom extract in EvenTone and Intellibright
4) Increase cell turnover and desquamate existing hyperpigmentation with products containing retinoids (eg. retinol) or alpha hydroxy acids
5) Protect against future sun damage with a broad-spectrum mineral sunscreen

References:

1 Yamaguchi Y, Hearing VJ. Physiological factors that regulate skin pigmentation. Biofactors 2009;35:193–9.
2 Fitzpatrick TB, Breathnach AS. The epidermal melanin unit system. Dermatol Wochenschr 1963;147:481–9.
3 Ito S and Wakamatsu K. Quantitative analysis of eumelanin and pheomelanin in humans, mice, and other animals: a comparative review. Pigment Cell Res 2003;16(5): 523–31.
4 Duchon J. Chemical composition of melanosomes. Dermatol Monatsschr 1970;156:371.
5 Pathak MA, Jimbow K, Fitzpatrick T. Photobiology of pigment cells. In: Seiji M, editor. Phenotypic expression in pigment cells. University of Tokyo Press 1980;655–70.
6 Rouzaud F, Kadekaro AL et al. MC1R and the response of melanocytes to ultraviolet radiation. Mutat Res 2005;571:133–52.
7 University of Bristol. http://palaeo.gly.bris.ac.uk/melanosomes/melanin.html
8 Agar N, Young AR. "Melanogenesis: a photoprotective response to DNA damage?". Mutation Research 2005;571(1–2):121–32.
9 Dunford R, Land EJ et al. Interaction of melanin with carbon- and oxygen-centered radicals from methanol and ethanol. Free Radic. Biol Med 1995;19(6):735–740.
10 Rozanowska M, Sarna T at al. Free radical scavenging properties of melanin interaction of eu- and pheo-melanin models with reducing and oxidising radicals. Free Radic. Biol Med 1999;26(5–6):518–525.
11 Prota G. The role of peroxidase in melanogenesis revisited. Pigment Cell Res 1992. Suppl. 2, 25–31.
12 Hearing VJ. Unraveling the melanocyte. Am. J. Hum. Genet 1993:52(1);1–7.
13 Ito S, Fujita K et al. Characterization of melanogenesis in mouse and guinea pig hair by chemical analysis of melanins and of free and bound dopa and 5-S-cysteinyldopa. J. Invest. Dermatol 1984;83(1):12–14.
14 Jimbow K, Alena F et al. Regulatory factors of pheo- and eumelanogenesis in melanogenic compartments. Pigment Cell Res 1992. Suppl. 2, 36–42.
15 Gillbro JM, Olsson MJ. The melanogenesis and mechanisms of skin-lightening agents – existing and new approaches. International Journal of Cosmetic Science 2011 June;33(3):210-21.
16 Matthews DE. An Overview of Phenylalanine and Tyrosine Kinetics in Humans. J Nutr 2007 June;137(6 Suppl 1):1549S-1575S.
17 Goding CR. MITF from neural crest to melanoma: signal transduction and transcription in the melanocyte lineage. Genes Dev 2000;14(14):1712–28.
18 Chiaverini C, Beuret L et al. Microphthalmia-associated transcription factor regulates RAB27A gene expression and controls melanosome transport. J Biol Chem 2008;283(18):12635–42.
19 Thody A.J and Graham A. Does alpha-MSH have a role in regulating skin pigmentation in humans? Pigment Cell Res 1998;11(5):265–74.
20 Schauer E, Trautinger F et al. Proopiomelanocortin-derived peptides are synthesized and released by human keratinocytes. J Clin Invest 1994;93(5):2258–62.
21 Jabbour SA. Cutaneous manifestations of endocrine disorders: a guide for dermatologists. Am J Clin Dermatol 2003;4(5):315–31.
22 Levine N, Sheftel et al. Induction of skin tanning by subcutaneous administration of a potent synthetic melanotropin. JAMA 1991;266(19):2730–36.