Melanogenesis and Melasma Treatment

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Melanin is a complex pigment that provides colour and photoprotection to the skin, hair, and eyes of mammals. Melanogenesis, the process through which melanocytes synthesise melanin, can be altered, producing pigmentary skin disorders such as melasma which result in hyperpigmentation. Melanocytes are highly specialised dendritic cells that transfer melanin to keratinocytes in subcellular lysosome-like organelles called melanosomes, where melanin is synthesised and stored.

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1. Introduction

Melanin is a complex pigment that provides colour and photoprotection to the skin, hair, and eyes of mammals. Melanogenesis, the process through which melanocytes synthesise melanin, can be altered, producing pigmentary skin disorders such as melasma which result in hyperpigmentation. Melanocytes are highly specialised dendritic cells that transfer melanin to keratinocytes in subcellular lysosome-like organelles called melanosomes, where melanin is synthesised and stored. Fitzpatrick and Breathnach proposed in 1963 the “epidermal melanin unit”. This concept consisted of the interaction of 1 melanocyte and approximately 36 keratinocytes to produce pigmentation. More recently, the keratinocyte–Langerhans–melanocyte (KLM) unit has been proposed, which does not exclude the possibility of including other epidermal cells [1].

Several studies have suggested different mechanisms for the melanosome transfer such as cytophagocytosis, membrane fusion, shedding–phagocytosis, and exocytosis–endocytosis [2]. Melanogenesis can be regulated by genetic, environmental (ultraviolet (UV) radiation) and endocrine factors (pregnancy and ageing) [3]. Knowledge of the pigmentation process is important for designing bleaching products to treat skin hyperpigmentation.

2. Main Signalling Pathways in Melanogenesis

The SCF-c-KIT receptor tyrosine kinase pathway is also involved in pigmentation. Stem cell factor (SCF), a paracrine factor located in fibroblasts, binds to its tyrosine kinase receptor c-KIT, which is produced by melanocytes, leads to the activation of the Ras-MAP kinase signalling pathway and the regulation of MITF by phosphorylation [4][5].

Protein kinase C (PKC)-dependent signalling regulates melanogenesis by activating the PKCβ isoform via calcium and diacylglycerol (DAG), its endogenous activator. UV radiation (UVR) induces DAG formation in melanocyte

membranes, causing its translocation from the cytoplasm to the membrane, where it upregulates PKCβ, which then phosphorylates and activates tyrosinase. The receptor for activated C-kinase (RACK) controls the translocation of PKC isoforms to specific cellular compartments. The translocation of the PKA/RACK complex to the melanosome membrane leads to tyrosinase activation in human melanocytes [6]. Furthermore, the MITF-M isoform has been proposed as a key transcription factor for PKCβ, linking PKC- and cAMP-dependent signalling in the regulation of melanogenesis [7].

Hyperpigmentation is common after inflammation, although the mechanisms involved are not clear. Keratinocyte-derived paracrine factors such as interleukin (IL)-18, IL-33, granulocyte-macrophage colony-stimulating factor (GM-CSF), prostaglandin E2 and prostaglandin F2α stimulate melanogenesis, while tumour necrosis factor (TNF), IL-6 and IL-1α can inhibit melanogenesis. Fibroblasts also secrete paracrine factors that can induce melanogenesis, such as IL-33, prostaglandin E2 and prostaglandin F2α, as well as inhibitors of melanogenesis, such as TNF and IL-6 [8].

Eumelanin and pheomelanin bind to cations, anions and drugs, among other things, providing protection to melanocytes [3].

3. Key Pathways in Melasma

It is well known that the main inducer of melanogenesis is ultraviolet radiation (UVR). In keratinocytes and the photoreceptor cells located in the external layer of the epidermis, different paracrine factors such as fibroblast growth factor (bFGF), nerve growth factor (NFG), ET-1 and POMC-derived peptides, such as MSH, ACTH and beta-endorphin, are activated by UVR, starting the main signalling pathway of melanogenesis [9]. UVR can induce and activate p53 on melanocytes, a tumour suppressor protein and transcription factor that upregulates tyrosinase mRNA and protein expression [10]. Furthermore, the UVR-mediated activation of p38, a stress-response protein, activates the transcription factor upstream stimulatory factor 1 (USF-1), which induces the transcription of tyrosinase [11]. Melanogenesis can be stimulated by the binding of α-MSH to its receptor, MC1-R, promoting the synthesis of more eumelanin than pheomelanin and increasing tyrosinase activity [12]. Moreover, α-MSH induces the proliferation of melanocytes [13]. UVR has been found to decrease levels of bone morphogenetic proteins (BMPs) [6].

Melasma is caused by different exposure factors affecting genetically predisposed individuals. Thus, genetics is one of the most important causes of hyperpigmentation, as demonstrated by its occurrence within families (40–60%) [14][15]. Almost 279 genes are involved in the development of melasma [16][17].

In melanocytes and keratinocytes, the binding of oestrogen to its receptors can activate the tyrosinase and MITF pathways. Sex steroids increase the transcription of the DCT and TYR genes, thereby promoting melanogenesis in normal human melanocytes. Other studies have shown an oestrogen-induced increase in the mRNA expression of tyrosinase, TYRP1 and TYRP2, as well as increased activity of tyrosinase in normal human melanocytes [18][19].

The oestrogen-mediated upregulation of PDZ domain-containing protein (PDZK1) stimulates melanosome transfer to melanocytes and increases MITF and TYR expression in melanocytes [20].

Wnt signalling plays a critical role in melanocyte development, melanogenesis and dendritogenesis [15]. The presence of Wnt ligands prevents β-catechin degradation, which stimulates MITF. WIF-1 is an important secreted antagonist of Wnt signalling. It inhibits Wnt signalling by preventing the binding of the ligands to their cell surface receptors [4]. WIF-1 downregulation occurs in dermal fibroblasts and epidermal keratinocytes of melasma lesions, stimulating the melanogenesis and melanosome transfer. Although WIF-1 is not expressed in melanocytes [21], one study has reported the upregulation of WIF-1 in melasma skin lesions [17].

4. Treatments and Future Perspectives

Arbutin, a natural tyrosinase inhibitor and HQ derivative, has been used in the treatment of melasma in combination with lasers or ellagic acid, as well as in hydrogel masks, all without undesirable side effects, thus demonstrating less toxicity than HQ [22][23]. It competitively and reversibly binds to tyrosinase without affecting the mRNA transcription of tyrosinase [24]. Deoxyarbutin, a synthetic derivative of arbutin, is a safer and effective skin-lightening agent, with similar inhibitory effects on tyrosinase activity as those of HQ and arbutin [25][26][27][28].

Azelaic acid is a saturated dicarboxylic acid used as a treatment for skin pigmentation in several conditions such as acne and rosacea due to its anti-inflammatory property [22]. It was described that azelaic acid may directly or indirectly inhibit tyrosinase through the reduction in intracellular thioredoxin which inhibits tyrosinase by forming a bys-cysteinate inhibitors complex [29].

Chemical peelings are used for several skin disorders despite causing skin irritation and post-inflammatory hyperpigmentation. Glycolic acid is the most widely used for chemical peelings, with salicylic acid representing a safer option for sensitive and dark phenotypes [30].

Oral treatments with systemic agents have emerged as potential therapies for melasma, such as tranexamic acid and plant-based supplements (e.g., polypodium leucotomos extract, carotenoids, and melatonin). Oral tranexamic acid is successfully used in Japan and seems to be more effective than topical therapy with tranexamic acid, although its mechanism of action is unknown [31][32]. Good results have been observed with the combination of tranexamic acid and laser irradiation [33]

References

1. Nordlund, J.J. The melanocyte and the epidermal melanin unit: An expanded concept. Dermatol. Clin. 2007, 25, 271–281.

2. Wu, X.; Hammer, J.A. Melanosome transfer: It is best to give and receive. Curr. Opin. Cell. Biol. 2014, 29, 1–7.
3. Costin, G.E.; Hearing, V.J. Human skin pigmentation: Melanocytes modulate skin color in response to stress. FASEB J. 2007, 21, 976–994.
4. Kawaguchi, M.; Suzuki, T. Melanogenesis and New Signaling Regulators for the Treatment of Melasma. In Melasma and Vitiligo in Brown Skin; Handog, E., Enriquez-Macarayo, M., Eds.; Springer: New Delhi, India, 2017; pp. 92–95.
5. Li, P.; Liu, L.; Chang, C.; Gao, R.; Leung, C. Silencing Stem Cell Factor Gene in Fibroblasts to Regulate Paracrine Factor Productions and Enhance c-Kit Expression in Melanocytes on Melanogenesis. Int. J. Mol. Sci. 2018, 19, 1475.
6. Bae-Harboe, Y.C.; Park, H. Tyrosinase: A Central Regulatory Protein for Cutaneous Pigmentation. J. Investig. Dermatol. 2012, 132, 2678–2680.
7. Park, H.; Wu, C.; Yonemoto, L.; Murphy-Smith, M.; Wu, H.; Stachur, C.M.; Gilchrest, B.A. MITF mediates cAMP-induced protein kinase C- β expression in human melanocytes. Biochem. J. 2006, 578, 571–578.
8. Fu, C.; Chen, J.; Lu, J.; Yi, L.U.; Tong, X. Roles of inflammation factors in melanogenesis (Review). Mol. Med. Rep. 2020, 21, 1421–1430.
9. Lee, A.Y. An updated review of melasma pathogenesis. Dermatol. Sin. 2014, 32, 233–239.
10. Khlgatian, M.K.; Hadshiew, I.M.; Asawanonda, P.; Yaar, M.; Eller, M.S.; Fujita, M.; Norris, D.A.; Gilchrest, B.A. Tyrosinase gene expression is regulated by p53. J. Investig. Dermatol. 2002, 118, 126–132.
11. Galibert, M.D.; Carreira, S.; Goding, C.R. The Usf-1 transcription factor is a novel target for the stress-responsive p38 kinase and mediates UV-induced Tyrosinase expression. EMBO J. 2001, 20, 5022–5031.
12. Hunt, G.; Kyne, S.; Wakamatsu, K.; Ito, S.; Thody, A.J. Nle4DPhe7α-melanocyte-stimulating hormone increases the eumelanin:phaeomelanin ratio in cultured human melanocytes. J. Investig. Dermatol. 1995, 104, 83–85.
13. Im, S.; Moro, O.; Peng, F.; Medrano, E.E.; Cornelius, J.; Babcock, G.; Nordlund, J.J.; Abdel-Malek, Z.A. Activation of the cyclic AMP pathway by α-melanotropin mediates the response of human melanocytes to ultraviolet B radiation. Cancer Res. 1998, 58, 47–54.
14. Holmo, N.F.; Ramos, G.B.; Salomão, H.; Werneck, R.I.; Mira, M.T.; Miot, L.D.B.; Miot, H.A. Complex segregation analysis of facial melasma in Brazil: Evidence for a genetic susceptibility with a dominant pattern of segregation. Arch. Dermatol. Res. 2018, 310, 827–831.

15. Passeron, T.; Picardo, M. Melasma, a photoaging disorder. Pigment. Cell. Melanoma Res. 2018, 31, 461–465.
16. Lee, H.J.; Park, M.K.; Lee, E.J.; Kim, Y.L.; Kim, H.J.; Kang, J.H.; Kim, H.M.; Lee, A.Y.; Lee, C.H. Histamine receptor 2-mediated growth-differentiation factor-15 expression is involved in histamine-induced melanogenesis. Int. J. Biochem. Cell Biol. 2012, 44, 2124–2128.
17. Kang, H.Y.; Suzuki, I.; Lee, D.J.; Ha, J.; Reiniche, P.; Aubert, J.; Deret, S.; Zugaj, D.; Voegel, J.J.; Ortonne, J.P. Transcriptional profiling shows altered expression of wnt pathway- and lipid metabolism-related genes as well as melanogenesis-related genes in melasma. J. Investig. Dermatol. 2011, 131, 1692–1700.
18. Kippenberger, S.; Loitsch, S.; Solano, F.; Bernd, A.; Kaufmann, R. Quantification of tyrosinase, TRP-1, and TRP-2 transcripts in human melanocytes by reverse transcriptase-competitive multiplex PCR—Regulation by steroid hormones. J. Investig. Dermatol. 1998, 110, 364–367.
19. Cohen, P.R. Melasma treatment: A novel approach using a topical agent that contains an anti-estrogen and a vascular endothelial growth factor inhibitor. Med. Hypotheses 2017, 101, 1–5.
20. Kim, N.H.; Cheong, K.A.; Lee, T.R.; Lee, A.Y. PDZK1 upregulation in estrogen-related hyperpigmentation in Melasma. J. Investig. Dermatol. 2012, 132, 2622–2631.
21. Kim, J.Y.; Lee, T.R.; Lee, A.Y. Reduced WIF-1 expression stimulates skin hyperpigmentation in patients with melasma. J. Investig. Derm. 2013, 133, 191–200.
22. Mazurek, K.; Pierzchała, E. Comparison of efficacy of products containing azelaic acid in melasma treatment. J Cosmet. Dermatol. 2016, 15, 269–282.
23. Ertam, I.; Mutlu, B.; Unal, I.; Alper, S.; Kivçak, B.; Ozer, O. Efficiency of ellagic acid and arbutin in melasma: A randomized, prospective, open-label study. J. Dermatol. 2008, 35, 570–574.
24. Han, T.Y.; Son, I.P.; Jang, W.S.; Chang, H.S.; Kim, J.H.; Sim, Y.H.; Kim, D.H.; Kim, B.J.; Kim, M.N.; Lee, H.K.; et al. Efficacy of hydrogel mask with 2% arbutin for melasma. Korean J. Dermatol. 2011, 49, 210–216.
25. Maeda, K.; Fukuda, M. Arbutin: Mechanism of its depigmenting action in human melanocyte culture. J. Pharmacol. Exp. Ther. 1996, 276, 765–769.
26. Grimes, P.E. Melasma: Etiologic and Therapeutic Considerations. Arch. Dermatol. 1995, 131, 1453–1457.
27. Parvez, S.; Kang, M.; Chung, H.S.; Cho, C.; Hong, M.C.; Shin, M.K.; Bae, H. Survey and mechanism of skin depigmenting and lightening agents. Phytother. Res. 2006, 20, 921–934.
28. Picardo, M.; Carrera, M. New and Experimental Treatments of Cloasma and Other Hypermelanoses. Dermatol. Clin. 2007, 25, 353–362.

29. Schallreuter, K.; Wood, J. A possible mechanism of action for azelaic acid in the human epidermis. Arch. Derm. Res. 1990, 282, 168–171.
30. Sarkar, R.; Garg, V.; Bansal, S.; Sethi, S.; Gupta, C. Comparative evaluation of efficacy and tolerability of glycolic acid, salicylic Mandelic acid, and Phytic acid combination peels in Melasma. Dermatol. Surg. 2016, 42, 384–391.
31. Del Rosario, E.; Florez-Pollack, S.; Zapata, L., Jr.; Hernandez, K.; Tovar-Garza, A.; Rodrigues, M.; Hynan, L.S.; Pandya, A.G. Randomized, placebo-controlled, double-blind study of oral tranexamic acid in the treatment of moderate-to-severe melasma. J. Am. Acad. Dermatol. 2018, 78, 363–369.
32. Cho, H.H.; Choi, M.; Cho, S.; Lee, J.H. Role of oral tranexamic acid in melasma patients treated with IPL and low fluence QS Nd:YAG laser. J. Dermatol. Treat. 2013, 24, 292–296.
33. Beyzaee, A.M.; Patil, A.; Goldust, M.; Moslemi, M.; Kazeminejad, A.; Rokni, G.R. Comparative Efficacy of Fractional CO2 Laser and Q-Switched Nd:YAG Laser in Combination Therapy with Tranexamic Acid in Refractory Melasma: Results of a Prospective Clinical Trial. Cosmetics 2021, 8, 37.