REVIEW ARTICLE

Decoding melanogenesis: An integrated view of enzymatic, genetic, and signaling regulation

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Abstract

Melanogenesis is a complex and tightly controlled biological process responsible for producing melanin pigment that gives skin its color and protects it from ultraviolet radiation damage. This review summarizes the main molecular pathways and mechanisms governing melanin production, integrating cellular, biochemical, and genetic aspects. Melanin is produced in melanocytes within specialized organelles called melanosomes, with enzymes such as Tyrosinase, Tyrosine-related protein 1 (TRP-1), and Tyrosine-related protein 2 (TRP-2), playing critical roles in melanogenesis and determining whether melanin is eumelanin or pheomelanin. The master regulator of melanocyte functions is the microphthalmia-associated transcription factor (MITF), which controls cell viability, cell differentiation, and the expression of melanogenic enzymes. Further, the processes are also modulated by various signaling pathways such asCyclic adenosine monophosphate (cAMP)/Protein kinase A (PKA), Mitogen-activated protein kinase (MAPK), Phosphoinositide 3-kinase (PI3K)/Protein Kinase B (AKT) and Wingless/Integrated–Beta-catenin signaling pathway (Wnt)/β-catenin in response to hormones and environmental conditions. Dysregulation of the intricate network governing melanogenesis results in pigmentation disorders (hyperpigmentation or hypopigmentation) that should be efficiently treated with targeted therapies that require a good understanding of the mechanisms.

Key words: Melanogenesis, microphthalmia-associated transcription factor, tyrosinase, signaling pathways, pigmentation disorders

INTRODUCTION

Melanogenesis is the process by which melanocytes produce the pigment called melanin.[1] Melanin, a biopolymer, is synthesized within melanocytes and packaged into specialized organelles called melanosomes. It determines the color of the skin, hair, and eyes, and provides essential photoprotection by absorbing and dissipating ultraviolet (UV) radiation.[2] Mammals produce two types of melanin: Insoluble brown-black eumelanin and soluble yellow-red pheomelanin.[3] After biosynthesis, eumelanogenic melanosomes form ellipsoidal granules with lattice-like internal structures, while pheomelanogenic melanosomes are oval with granular substructures. Eumelanin provides dark pigmentation, acts as an antioxidant, and offers strong UV protection. In contrast, pheomelanin produces reactive oxygen species when exposed to UV light, gives light or reddish pigmentation, and provides minimal UV protection. Melanocytes originate from neural crest-derived melanoblasts. Following neural tube closure, melanoblasts migrate along a dorsolateral pathway to the hair follicles and the basal layer of the epidermis, where they mature into melanocytes.[4] In the skin, melanocytes transfer melanin to surrounding keratinocytes, with one melanocyte typically interacting with approximately 36 keratinocytes.[1]

Melanogenesis is regulated by several intracellular signaling pathways that coordinate melanocyte activity in response to

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internal and external stimuli.[3] The binding of melanocyte-stimulating hormone (α-MSH) or adrenocorticotropic hormone (ACTH) to the melanocortin-1 receptor (MC1R) activates the cAMP/protein kinase A (PKA) pathway, increasing intracellular cAMP levels and further modulating melanogenesis by regulating the transcription of microphthalmia-associated transcription factor (MITF), a master transcription factor of melanocyte development and differentiation. In addition, melanocyte survival, proliferation, and differentiation are influenced by the phosphoinositide 3-kinase (PI3K)/Akt and Wnt/β-catenin signaling pathways.[5] Melanogenesis is a complex, multi-phase process, and its disruption can lead to various pigmentation disorders, including hypopigmentation (vitiligo, albinism) and hyperpigmentation (melasma, freckles, lentigines, and post-inflammatory hyperpigmentation), which may occur with or without changes in melanocyte numbers.[6,7]

This review provides a comprehensive overview of the molecular and cellular mechanisms of melanogenesis. Although anti-melanogenesis effects have been widely studied at the cellular level, focusing on enzymes, genes, and signaling networks, these aspects are often investigated independently. Amore effective approach would be to integrate and correlate these factors, which may lead to more comprehensive and improved outcomes. This review aims to provide a complete understanding about the cellular architecture of melanin formation, the biochemical pathways of melanogenesis, the genetics regulatory mechanisms controlling the process, and the intercellular signaling pathways involved in melanogenesis. Through this comprehensive approach, the review aims to present a detailed and unified understanding of melanin synthesis.

CELLULAR ARCHITECTURE OF MELANIN PRODUCTION

The cellular architecture of melanin production involves melanocytes, which contain specialized organelles called melanosomes where the melanin is synthesized, stored, and transported to skin, hair, and eyes to shield the skin from UV-induced DNA damage.

Structure and Location of Melanocytes

A melanoblast is an immature precursor cell that develops into a melanocyte. Melanocyte is a pigment producing cell, originating from the neural crest-derived melanoblast.[8,9] During embryogenesis, melanoblast migrates to basal layer of the epidermis and hair follicles to differentiate into matured melanocytes [Figure 1]. In the epidermis, melanocytes located in the basal layer these cells possess dendritic extension which facilitate interaction with surrounding keratinocytes and enable the transfer of melanin-containing organelles (melanosomes) to keratinocytes.[10] Any abnormalities in the function or proliferation of melanocytes can lead to diseases such as melanoma.[1]

Developmental Stages of Melanosomes

Melanosomes are specialized lysosome-related organelles in melanocytes in which melanin is synthesized, stored, and matured.[12] The formation of melanosome is a highly regulated stepwise maturation process (stage) comprising four distinct phases [Figure 2]. Each step involves specific biochemical and structural modifications that ultimately result in the formation of an organelle with complete pigmentation. Melanosomes are acidic in early stages and share protein with lysosomes.[13,14] During transport, melanosomes move in both directions along microtubules to the cell periphery and are coupled to the active skeleton. Myosin Va, melanophilin, and Rab27a form a tripartite complex that mediates short-range migration of melanosomes at the cell periphery. In melanocytes, melanosome delivery is regulated by a balance between actin and microtubule-dependent transport pathways.[14]

- Stage I–premelanosome formation

Stage I is the first stage in melanosome development, during which premelanosome (immature organelles) are formed. They resemble early or sorting endosomes and resemble spherical vacuolar compartments that contain membrane vesicles inside them.[5,15] At this point, there is no melanin. This organelle is also similar to lysosomes in that it is very acidic. Stage I is primarily important because it signifies the start of melanosome biogenesis, the point at which the fundamental structural framework of the organelle is constructed, although it cannot produce or hold pigment yet.[14]

- Stage II–fibrillar matrix formation

Stage II is a major structural change where the melanosomes change shape from a sphere to an elongated or elliptical

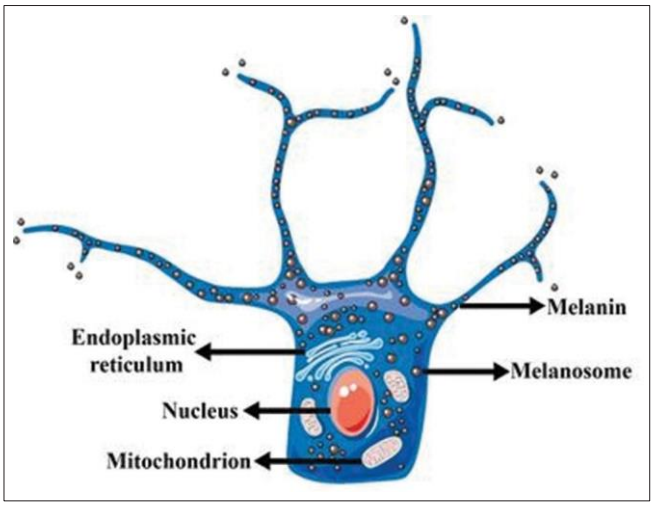

Figure 1: Schematic representation of a melanocyte showing intracellular organelles involved in melanogenesis[11]

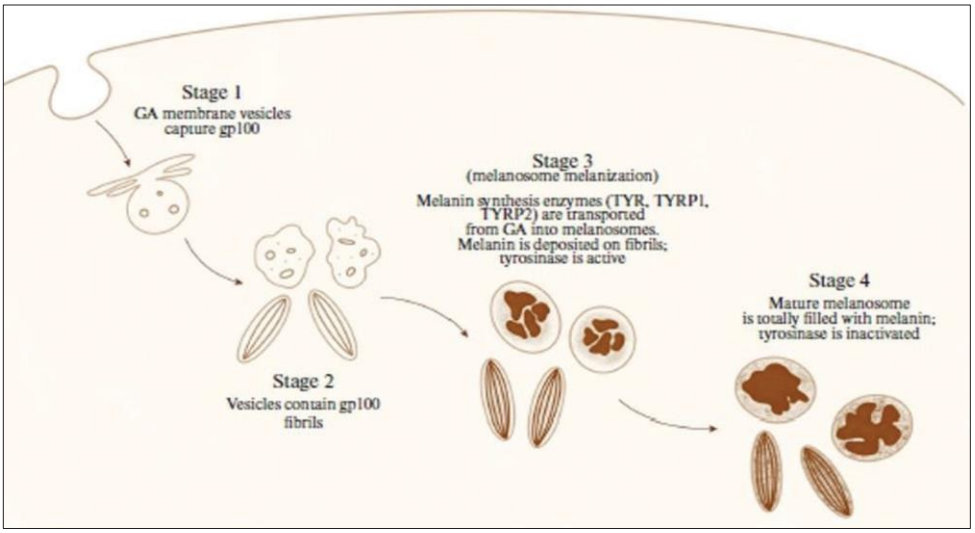

Figure 2: Stages of melanosome biogenesis and maturation in melanocytes[14]

form. In this stage, organized proteinaceous fibrils within the lumen are formed that act as a scaffold for subsequent melanin deposition.[5,14] Although melanin synthesis has not yet started, the internal architecture is highly ordered, which permits an efficient pigment accumulation in the following stages. This fibrillar matrix underlies the homogeneous deposit of melanin necessary for the proper development of melanosomes.[14]

- Stage III–melanin deposition stage

The formation of melanin occurs in the melanosomes, starting from stage III, which represents the beginning of active melanogenesis. Throughout this stage, the internal structure slowly becomes darker and thicker as melanin deposits onto the prepared fibrillar structure. Because the organelle contains a higher concentration of melanin, it now begins to be somewhat pigmented, transforming it from a structural organelle into a functional one. Increasing enzymes activity, which triggers the production of melanin, drives pigment production of the organelle.[14]

- Stage IV–fully mature melanosome

Stage IV is the final nature stage of the melanosomes. The organelle has completely developed and it is fully functional and pigmented. Melanin concentration is maximal in the organelle, and the internal fibrillar matrix is masked by the density packed melanin; at this stage, the organelle looks like a dense, dark sphere under the electron microscope and ready to be transferred to the melanocytes dendrites, where it will donate its content to keratinocytes. Melanosomes at Stage IV are important in determining the pigmentation of skin and providing protection from UV.[14]

Interaction between Melanocytes and Keratinocytes

Approximately one melanocyte can interact with 30–40 surrounding keratinocytes. This interaction is regulated by a paracrine signaling network where the keratinocytes release several factors that influence melanocytes activity. Melanocytes form a functional unit with keratinocytes known as the epidermal-melanin unit.[10,16] Keratinocytes regulate melanocyte behavior by secreting a variety of signaling molecules, including growth factors, cytokines, and inflammatory mediators.[17] These factors affect how melanocytes grow, change shape, and make melanin. Melanocytes require an internal scaffolding to generate dendrites, allowing them to interact with keratinocytes and transport melanin. Melanin transfer depends on the interaction of melanocytes with keratinocytes. Melanocytes are well organized for efficient production of melanin that is transferred to keratinocytes.[9]

Melanin Transfer Process

Once melanin is synthesized in mature melanosomes through dendritic process, it is then transported to surrounding keratinocytes and accumulates above the nucleus to protect the DNA from UV damage. Any disruption in melanosomes transfer can lead to uneven pigmentation or depigmenting disorders.

- Cytophagocytosis model

According to the cytophagocytosis model, melanin is engulfed through keratinocytes phagocytosis of dendritic processes. The cytophagocytosis model involves the uptake of melanin by phagocytosis of the dendrite tips by keratinocytes.[10] In this case, the melanocytes have projections, dendrites, which come into contact with nearly keratinocytes. The keratinocyte membrane envelops the dendritic tip containing melanosomes, which is then formed into an intracellular vesicle [Figure 3]. The melanosomes within the vesicle are bounded by both melanocyte and keratinocytes membrane. Lysosomes then fuse with the vesicle, and the membranes surrounding the melanosomes are digested. The melanin granules are thus freed into the cytoplasm of keratinocytes.

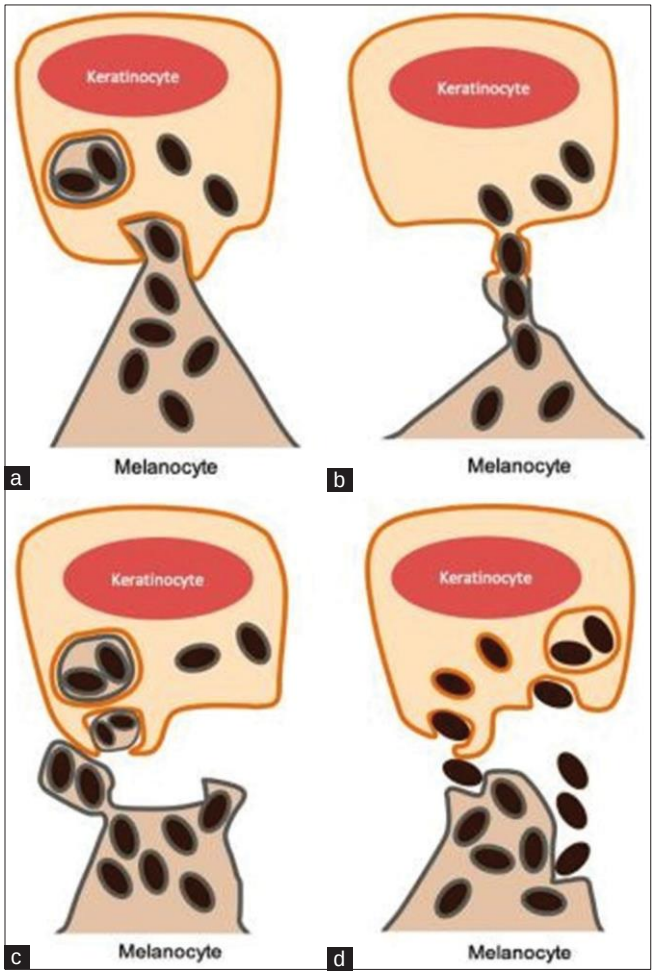

Figure 3: Schematic representation of the four proposed mechanisms of melanosome transfer from melanocytes to keratinocytes: (a) Cytophagocytosis, (b) Membrane fusion, (c) Shed vesicles, (d) Exo/phagocytosis[10]

This is a phagocytic model; however, it is rather limited, as most evidence has shown that melanosomes are surrounded by one membrane rather than two or more.[14]

- Membrane fusion model

This hypothesis suggests that the transfer of melanin proceeds by the fusion of the membranes of the melanocyte and keratinocytes. The melanocyte's dendrite attaches to the keratinocyte, and localized membrane fusion produces cytoplasmic links between the two cells [Figure 3]. For instance, filopodia and tubule-like structures, into which melanosomes are transported directly into the keratinocyte's cytoplasm from the melanocytes, avoiding entry into the extracellular space. During this transfer, melanosomes remained within a membrane sac. Although filopodia has been reported, this model does not seem widely accepted as direct transfer has not been adequately proven.[14]

- Shed vesicle model

Many melanosomes are enclosed in membrane-bound vesicles, which are secreted into the intercellular space, and which can be taken up by the keratinocytes by phagocytosis [Figure 3]. Following uptake by the keratinocyte, the membranes around the vesicles gradually degrade, allowing individual melanosomes to be released into the cytoplasm. This explains the simultaneous transfer of more than one melanosome and is supported by ultrastructural findings.

Keratinocytes receptors, for example, the protease-activated receptor-2 (PAR-2), which act to stimulate the phagocytosis of the vesicle, and hence melanin transfer, have also been identified.[14]

- Coupled exocytosis-phagocytosis model

The model of coupled exocytosis-phagocytosis is the most accepted one at the present time. At present, the coupled exocytosis-phagocytosis model is the most commonly accepted scheme of melanin transfer. Mature melanosomes are directed to the dendrites of melanocytes, fused with the melanocytes plasma membrane and the melanin core (melanocore), which is devoid of a membrane, is discharged into the intracellular space [Figure 3]. The melanocore is then recognized and engulfed by keratinocytes. Following phagocytosis, the melanocore is enclosed in a single membrane of keratinocyte origins, resulting in a structure called melanosomes. The melanin will then be transferred to the supranuclear region of the keratinocytes, where it protects against UV-light. This scheme has good experimental support, in particular from the finding of single-membrane melanin-containing organelles within keratinocytes.[14]

MAJOR ENZYMES IN MELANOGENESIS AND THEIR MODULATION

Melanogenesis is a complex multi-step process that is primarily regulated by an enzyme such as Tyrosinase, Tyrosine-related protein 1 (TRP-1), and Tyrosine-related protein 2 (TRP-2).

Tyrosinase

Tyrosinase plays a significant role, and it acts as a rate-limiting enzyme that catalyzes the conversion of tyrosine to L-DOPA and L-DOPA to dopaquinone.[5] Tyrosinase is a copper-dependent glycoprotein, and its activity is regulated by various factors like phosphorylation by protein kinase c-β and the electron donors such as Nitric oxide and Ascorbic acid. Tyrosinase activity is also regulated by transcriptional and post-transcriptional mechanisms.[15,18] In melanoma cells, tyrosinase expression is altered, which causes a change in melanogenic activity that leads to tumor progression.[1]

TRP-1

TRP-1 is an enzyme that functions as a supporting enzyme to stabilize tyrosinase enzymes and is responsible for the production of eumelanin. TRP-1 enzyme protects against oxidative stress and thereby maintains cellular integrity during melanin synthesis.[15,16]

TRP-2

TRP-2 enzyme is known as a dopachrome tautomerase (DCT). It requires zinc for its activity, and it also plays a key role in determining the type and quality of melanin produced within melanocytes.[5,13]

BIOCHEMICAL PATHWAY OF MELANOGENESIS

Melanogenesis is a multi-step enzymatic process that starts with the amino acid tyrosine, which acts as a precursor molecule for melanin synthesis.[5] These reactions occur within melanosomes. The amino acid tyrosine gets oxidized to dihydroxyphenylalanine (DOPA) and then converted to dopaquinone, which is catalyzed by the enzyme called tyrosinase.[15] In the dopaquinone pathway, it diverges into two branches, which lead to the formation of eumelanin and pheomelanin. The formation of eumelanin and pheomelanin is also influenced by the presence of amino acids called cysteine.[3,16] Eumelanin is a brown-black pigment which provides strong protection against UV radiation, while pheomelanin is a red-yellow pigment that provides less UV protection[2,17] [Figure 4].

INTRACELLULAR SIGNALING PATHWAYS GOVERNING MELANOGENESIS

Melanogenesis is a highly regulated biological process that is controlled by a network of various intracellular signaling pathways in response to environment hormonal, and cellular stimuli [Figure 5]. These pathways primarily act by regulating MITF, which serves as a master regulator of melanogenic enzyme expression.[5] External stimuli such as UV exposure, inflammatory factors, and endocrine signals activate the receptor on melanocytes and initiate intracellular signaling o modulate gene expression, enzyme activity, and melanosome formation. The integrated action of these pathways ensures precise regulation of melanin synthesis and allows the skin to respond effectively to environmental stress, thus maintaining pigmentation balance.[5]

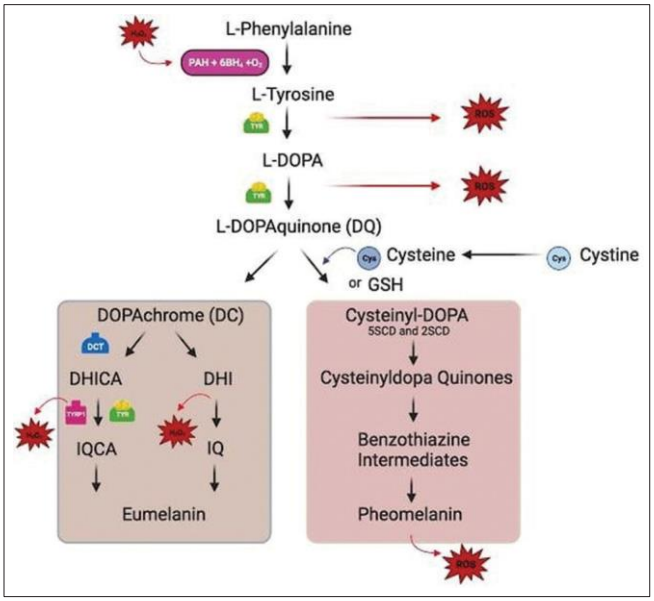

Figure 4: Biochemical pathway of melanogenesis showing the enzymatic conversion of L-phenylalanine and L-tyrosine into eumelanin and pheomelanin through a series of oxidative and cyclization reactions.[19]

cAMP/PKA Pathway

The cAMP/PKA pathway is an important and central regulatory pathway in melanogenesis. The MC1-R agonist, such as (α-MSH or ACTH), binds to MC1-R receptor, which is a G-protein-coupled receptor located on the melanocyte membrane. This process will activate the adenylate cyclase, which may lead to an increase in intracellular cAMP levels. Then it will activate a PKA and translocate into the nucleus. This phosphorylates the transcription factor, such as CREB (cAMP response element binding protein). Then the phosphorylated CREB binds to the specific DNA sequence and promotes the transcription of MITF, thus increases the MITF expression. Finally, it enhances the transcription of melanogenic enzymes such as tyrosinase, TRP-1, and TRP-2, thereby increasing melanin production.[5]

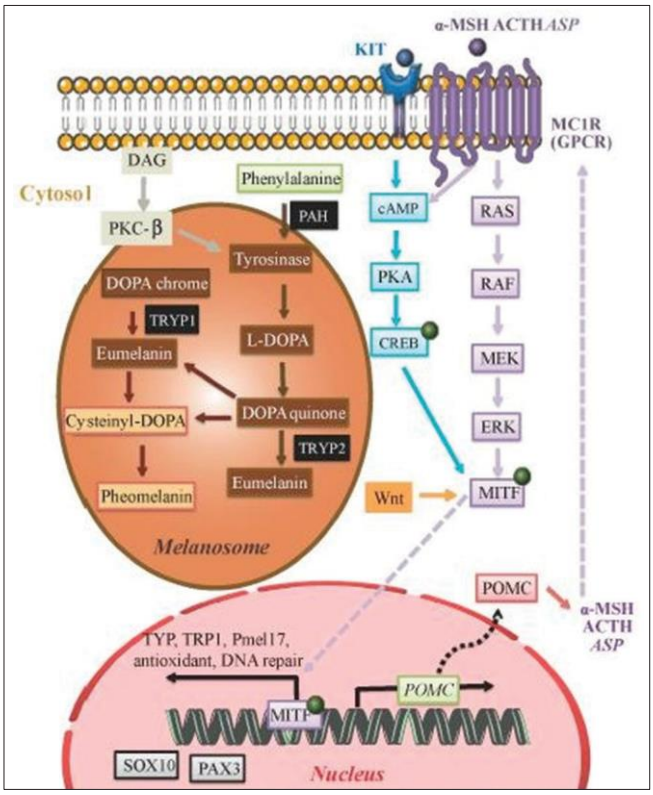

Figure 5: Molecular signaling pathways involved in the regulation of melanogenesis.[5]

MAPK Pathway

The MAPK pathway is known as mitogen-activated protein kinase, activated by various sex tracellular signals such as growth factors, cytokines, and UV radiation. Once activated, the MAPK pathway leads to phosphorylation of MITF, which either enhances its transcriptional activity or promotes degradation. This pathway has two types of activation, such as short-term activation and long-term activation. In the short-term activation, it enhances MITF

activity and increases melanogenesis. In long-term activation, it may lead to MITF degradation and decrease melanin production. This pathway also regulates melanocyte proliferation and differentiation and helps to prevent excessive pigmentation.[5]

PI3/AKT Pathway

PI3K acts as a negative regulator of melanogenesis. Activation of the PI3K/AKT pathway leads to phosphorylation and activation of AKT, that down regulators the MITF expression, thus inhibiting melanogenic enzyme activity and decreasing melanin synthesis. This pathway also plays a crucial role in cell survival, metabolism, and resistance to apoptosis. It also helps the cell to protect from DNA damage and UV-induced damage.[5]

Wnt/β-catenin Pathway

Wnt/β-catenin pathway is essential for melanocyte development, differentiation, and long-term maintenance. This pathway is activated by Wnt ligand and then the β-catenin is stabilized in the cytoplasm, moves into the nucleus, and interacting with transcription factors to promote MITF expression. This pathway plays a significant role during embryogenesis by regulating the formation and migration of melanocytes from neural crest cells.[5]

Hormonal Regulation

Hormones can either stimulate or inhibit melanogenesis depending on how they interact with specific biological pathways. In this pathway, hormones such as α-MSH or ACTH activate the MC1R receptor or the cAMP pathway, which may lead to an increase in melanogenesis. These hormones play an important role in the body's response to UV exposure, where they increase melanin production or function as a protective mechanism for the skin. Other hormones, such as estrogen and progesterone, can also cause pigmentation by indirectly interacting with various signaling pathways. EX: In pregnancy, the estrogen level is increased, which may lead to conditions such as melasma (hyperpigmentation).[6]

GENETIC CONTROL OF MELANIN FORMATION

Melanogenesis is tightly regulated by genetic mechanisms that are functionally interconnected with upstream intracellular signaling pathways. External stimuli such as UV radiation, α-MSH, and various growth factors activate signaling cascades including the cAMP/PKA, MAPK, PI3K/AKT, and Wnt/β-catenin pathways [Figure 6]. These pathways converge at the transcriptional level to regulate the expression and activity of key melanogenic genes, particularly the MITF. Among these, the CAMP/PKA pathway enhances MITF transcription through CREB phosphorylation, while the Wnt/β-catenin pathway promotes MITF expression via β-catenin interaction with LEF/TCF transcription factors. Conversely, the PI3K/AKT pathway negatively regulates melanogenesis by suppressing MITF expression. The MAPK pathway exerts dual regulation, where transient activation enhances MITF activity, whereas prolonged activation leads to its degradation. MITF serves as a central molecular link between extracellular signaling pathways and the genetic regulation of melanogenesis, integrating multiple upstream signals to coordinate melanocyte function and melanin production.

Thus, MITF functions as a master regulator of melanin production because it coordinates various aspects of melanocyte functions such as cell differentiation, proliferation, and melanin production.[8] MITF functions by binding to specific DNA sequence especially in the promoter region, thereby activating its transcription. Once the gene is transcribed, it produces protein for melanin synthesis and melanocyte survival. MITF maintains melanocyte viability by regulating the genes involved in cell cycle control and resistance to apoptosis. At the transcriptional level, the upstream signaling pathways increase the MITF expression, thereby increasing melanin synthesis. At post-transcriptional level, MITF undergoes phosphorylation alter its activity, localization, and stability.[12] MITF contains five isoforms, which include MITF-A, MITF-B, MITF-C, MITF-Hand, and MITF-M. These isoforms differ only in N-termini and expression patterns. Among these isoforms, M-promoter has particular attention because it has function on melanocyte-lineage cells and it is also essential for melanocyte differentiation. MITF promoter is upregulated by transcription factors such as PAX3 and SOX10.[16,17]. Wnt3 regulates β-catenin, which translocates into the nucleus and interacts with LEF/TCF, thereby stimulate MITF transcription. MITF can also regulate the expression of enzymes such as Tyrosinase, TRP-1 and TRP involved in melanin synthesis.[13]

ROLE OF MELANOGENESIS IN SKIN DISORDERS

Hyperpigmentation

Hyperpigmentation is a common skin disorder characterized by dark patches and uneven skin tone caused by excessive

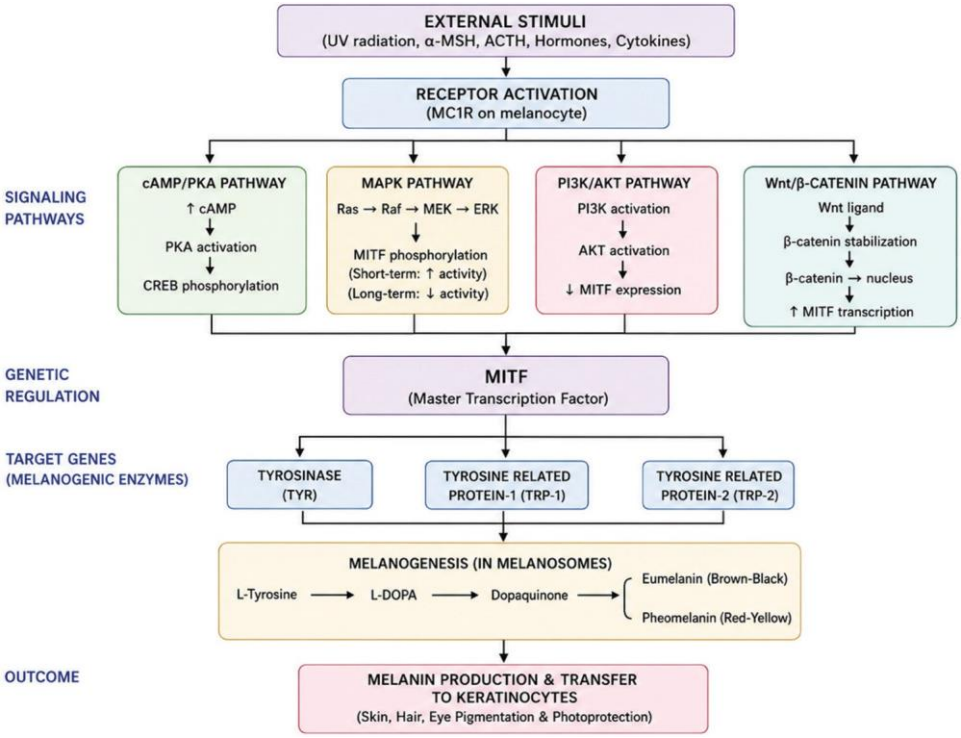

Figure 6: Molecular and genetic regulation of melanogenesis. External signals modulate microphthalmia-associated transcription activity through multiple signaling pathways, regulating the expression of TYR, tyrosine-related protein 1, and tyrosine-related protein 1 and thereby controlling melanin production

melanin production. Common examples of hyperpigmentation were melasma, post-inflammatory hyperpigmentation, freckles, and lentigines.[6,20]

Post-inflammatory hyperpigmentation

Post-inflammatory hyperpigmentation increases pigmentation acquired after a cutaneous inflammatory process. The causes of post-inflammatory hyperpigmentation include acne, atopic dermatitis, allergic contact dermatitis or secondary to irritants, trauma, psoriasis, lichen planus, drug eruptions, etc. People with higher basal amounts of epidermal melanin are more prone to this skin condition.[21]

Melasma

The word melasma originates from the Greek word melas means black. It appears as stains in the form of brown to bluish gray shades with irregular borders [Figure 7]. It is localized more in photo-exposed areas. It usually affects the face, neck, and less commonly the arms and sternal regions. Factors linked to melasma are UV exposure and genetic predisposition.[20]

Periorbital hyperpigmentation

Periorbital hyperpigmentation, also known as dark circles, which affect both the gender of all ages and races. The lesions vary in intensity according to fatigue or lack of sleep [Figure 8]. It also worsens with skin-aging.[7]

Hypopigmentation

Hypopigmentation is the loss of skin color, resulting in patches or spots that are lighter than your natural skin tone. It happens when the skin cells, melanocytes, do not produce enough melanin.[6,22]

Oculocutaneous albinism

Oculocutaneous albinism is a Biallelic mutation disorder, caused by decrease or absence of melanin synthesis in melanocyte [Figure 9]. Patients who were suffering from albinism have a normal number of melanocytes, but the melanin synthesis is partially or fully absent. Individuals who were suffering from ocular albinism cannot oxidize tyrosine into DOPA, so the melanin synthesis gets decreased.[23]

Vitiligo

Vitiligo is an acquired, chronic disease characterized by the loss of melanin pigment in skin and hair. It appeared as a white macular with potential depigmentation of skin and hair. In USA, Europe, and Japan, the prevalence of this disease ranges from 0.5% to 3.1%.[25]

Post-inflammatory hypopigmentation

Post-inflammatory hypopigmentation is an acquired pigmentation disorder that shows a greater impact on skin color. It occurs due to a decrease or absence of melanin

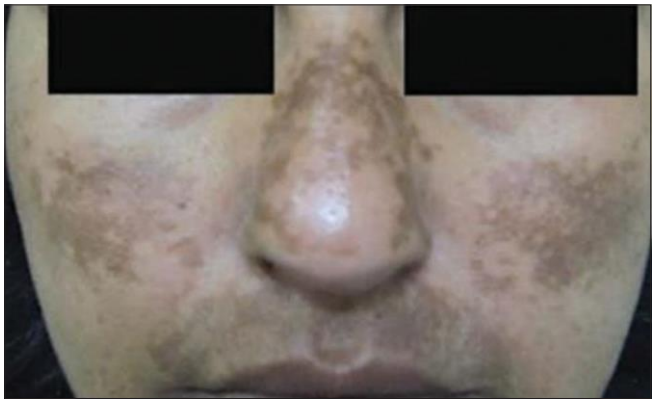

Figure 7: Melasma[20]

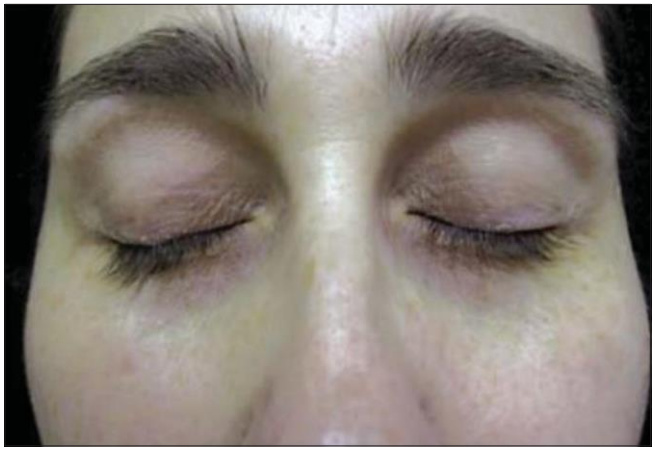

Figure 8: Periorbital hyperpigmentation[20]

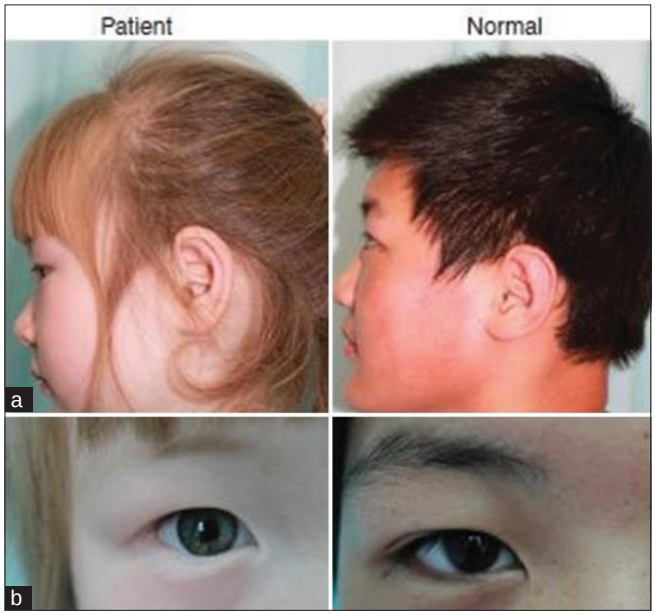

Figure 9: (a and b) Oculocutaneous albinism[24]

synthesis due to cutaneous inflammation, sequelae of inflammatory or infectious dermatoses. The mechanism of post-inflammatory hypopigmentation was decreasing melanin production, blocked transfer of melanocyte to keratinocyte, or melanocyte death. Diseases associated with post-inflammatory hypopigmentation were pityriasis alba, lichen striatus, pityriasis lichenoid chrinica, extragenital lichen sclerosis, and progressive macular hypo melanosis.[22]

DISCUSSION

Melanogenesis is a highly coordinated and multi-layered biological process that integrates cellular organization, enzymatic activity, genetic regulation, and intracellular signaling pathways. This review highlights how melanocytes function as specialized cells that synthesize and distribute melanin through well-organized structures, such as melanosomes.[4,5] The progressive maturation of melanosomes ensures efficient synthesis, storage, and transfer of melanin to keratinocytes, thereby maintaining skin pigmentation and photoprotection. At the biochemical level, melanogenesis is primarily regulated by tyrosinase, the rate-limiting enzyme, along with tyrosinase-related proteins TRP-1andTRP-2, which influence the type and quality of melanin produced.[13,15] The balance between eumelanin and pheomelanin synthesis is critical, as these pigments differ significantly in their photoprotective and oxidative properties. This highlights the importance of enzymatic control in determining pigmentation outcomes. A key aspect of melanogenesis regulation involves intracellular signaling pathways, including cAMP/PKA, MAPK, PI3K/AKT, and Wnt/β-catenin.[5,13] These pathways respond to environmental, hormonal, and cellular stimuli, and collectively regulate the expression and activity of the MITF. MITF acts as a central regulator, linking upstream signaling events to downstream melanogenic enzyme expression. The interplay between these pathways ensures a tightly controlled response to external factors such as UV radiation.[13]

Dysregulation of these pathways can lead to various pigmentation disorders. Overactivation of melanogenesis results in hyperpigmentation conditions such as melasma and post-inflammatory hyperpigmentation, whereas reduced melanogenic activity leads to hypopigmentation disorders such as vitiligo and albinism.[6] Understanding these mechanisms provides a strong foundation for developing targeted therapeutic strategies. Despite significant advances in understanding melanogenesis, most studies focus on individual components such as enzymes or signaling pathways in isolation. There is a need for more integrated approaches that consider the interaction between cellular, biochemical, and genetic mechanisms. Such comprehensive studies may provide deeper insights into pigmentation regulation and improve the development of effective treatments.

CONCLUSION

Melanogenesis is a complicated and strictly regulated biological process that plays a key role in determining

pigment color of skin, hair, and eyes and protecting against UV light.[3] A complete picture of the entire melanogenic pathway, including melanocyte structure, melanosome maturation, biochemic pathways, enzymatic regulation, genes controlling melanogenesis, and intercellular signaling pathways, has been discussed. The most significant function of MITF as a master transcription factor and co-function of different signal pathways, including cAMP/PKA, MAPK, PI3K/AKT, and Wnt/β-catenin showed a complex control system of melanogenesis, and any abnormalities will result in pigmentation abnormalities, thus demonstrating the vital role of control specificity.[5,13] The comprehensive and overall understanding of melanogenesis will be useful to develop new therapeutic strategies to treat hyperpigmentation and hypopigmentation diseases. The future study may find the interaction between gene, molecule, and environment to obtain novel, specific, and efficient therapies. Overall understanding of melanogenesis will promote the development of new treatment strategies in dermatology.[6,22]

FUTURE ASPECTS

Despite considerable advances, there are still important gaps in our knowledge of melanogenesis as a coordinated biological network. The existing research is mainly focused on individual components (enzymatic, genetic, or signaling pathways) and not on the overall system. This limits the possibility of providing a holistic understanding of the dynamic interplay. Future studies should aim to utilize integrative systems-level approaches to help in elucidating the interactions between signaling cascades and transcriptional regulators, such as MITF Melanogenesis' complex regulatory networks may be unraveled by computational modeling and multi-omics technologies. Further studies are necessary to better understand the impact of oxidative stress, environmental factors, and epigenetic modifications in their entire context. These discoveries will require the development of precise mechanism-based therapeutic techniques that will allow targeted and tailored therapies for pigmentation disorders.

REFERENCES

1. Li C, Kuai L, Cui R, Miao X. Melanogenesis and the targeted therapy of melanoma. Biomolecules 2022;12:1874.
2. Hida T, Kamiya T, Kawakami A, Ogino J, Sohma H, Uhara H, *et al*. Elucidation of melanogenesis cascade for identifying pathophysiology and therapeutic approach of pigmentary disorders and melanoma. Int J Mol Sci 2020;21:6129.
3. Ohbayashi N, Fukuda M. Recent advances in understanding the molecular basis of melanogenesis in melanocytes. F1000Res 2020;9:F1000 Faculty Rev-608.
4. Videira IF, Moura DF, Magina S. Mechanisms regulating melanogenesis. An Bras Dermatol 2013;88:76-83.
5. D'Mello SA, Finlay GJ, Baguley BC, Askarian-Amiri ME. Signaling pathways in melanogenesis. Int J Mol Sci 2016;17:1144.
6. Wang F, Ma W, Fan D, Hu J, An X, Wang Z. The biochemistry of melanogenesis: An insight into the function and mechanism of melanogenesis-related proteins. Front Mol Biosci 2024;11:1440187.
7. Thawabteh AM, Jibreen A, Karaman D, Thawabteh A, Karaman R. Skin pigmentation types, causes and treatment-a review. Molecules 2023;28:4839.
8. Kondo T, Hearing VJ. Update on the regulation of mammalian melanocyte function and skin pigmentation. Expert Rev Dermatol 2011;6:97-108.
9. Yamaguchi Y, Hearing VJ. Physiological factors that regulate skin pigmentation. Biofactors 2009;35:193-9.
10. Moreiras H, Seabra MC, Barral DC. Melanin transfer in the epidermis: The pursuit of skin pigmentation control mechanisms. Int J Mol Sci 2021;22:4466.
11. Mazur E, Kwiatkowska D, Reich A. Photodynamic therapy in pigmented basal cell carcinoma-a review. Biomedicines 2023;11:3099.
12. Le L, Sirés-Campos J, Raposo G, Delevoye C, Marks MS. Melanosome biogenesis in the pigmentation of mammalian skin. Integr Comp Biol 2021;61:1517-45.
13. Nguyen NT, Fisher DE. MITF and UV responses in skin: From pigmentation to addiction. Pigment Cell Melanoma Res 2019;32:224-36.
14. Zhilnikova MV, Troitskaya OS, Novak DD, Atamanova VV, Koval OA. Uveal melanoma: Molecular and genetic mechanisms of development and therapeutic approaches. Mol Biol (Mosk) 2024;58:189-203.
15. Wang F, Ma W, Fan D, Hu J, An X, Wang Z. The biochemistry of melanogenesis: An insight into the function and mechanism of melanogenesis-related proteins. Front Mol Biosci 2024;11:1440187.
16. Seberg HE, Van Otterloo E, Cornell RA. Beyond MITF: Multiple transcription factors directly regulate the cellular phenotype in melanocytes and melanoma. Pigment Cell Melanoma Res 2017;30:454-66.
17. Kumari S, Thng ST, Verma NK, Gautam HK. Melanogenesis inhibitors. Acta Derm Venereol 2018;98:924-31.
18. Shibahara S, Takeda K, Yasumoto K, Udono T, Watanabe K, Saito H, *et al*. Microphthalmia-associated transcription factor (MITF): Multiplicity in structure, function, and regulation. J Investig Dermatol Symp Proc 2001;6:99-104.
19. Snyman M, Walsdorf RE, Wix SN, Gill JG. The metabolism of melanin synthesis -from melanocytes to melanoma. Pigment Cell Melanoma Res 2024;37:438-52.
20. Cestari TF, Dantas LP, Boza JC. Acquired hyperpigmentations. An Bras Dermatol 2014;89:11-25.
21. Markiewicz E, Karaman-Jurukovska N, Mammone T, Idowu OC. Post-inflammatory hyperpigmentation in dark skin: Molecular mechanism and skincare implications.

Clin CosmetInvestig Dermatol 2022;15:2555-65.
22. Rao M, Young K, Jackson-Cowan L, Kourosh A, Theodosakis N. Post-inflammatory hypopigmentation: Review of the etiology, clinical manifestations, and treatment options. J Clin Med 2023;12:1243.
23. Marçon CR, Maia M. Albinism: Epidemiology, genetics, cutaneous characterization, psychosocial factors. An Bras Dermatol 2019;94:503-20.
24. Wei AH, Zang DJ, Zhang Z, Liu XZ, He X, Yang L, *et al*. Exome sequencing identifies SLC24A5 as a candidate gene for nonsyndromic oculocutaneous albinism. J Invest Dermatol 2013;133:1834-40.
25. Bergqvist C, Ezzedine K. Vitiligo: A review. Dermatology 2020;236:571-92.

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