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Melanogenesis and its associated signalings

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ABSTRACT

Introduction: Melanogenesis is the mechanism of melanin formation in the skin or hair, which is produced by melanosomes in melanocytes. Melanin is the main coloring pigment of the skin, hair and eyes, and also functions as a photoprotection against ultra-violet (UV) exposure.

Methods: A total 20 relevant literatures which focused on skin pigmentation and melanogenesis were used to construct this review. The articles were published from 1998-2018. Most of the literatures were basic research and the clinical information were extracted from their discussion.

Result: The process of melanogenesis starts from the migrational process of melanoblasts which are precursors of melanocyte cells originating from the neural crest into the epidermal layer and hair follicles. Many factors play a role in melanogenis both intrinsically and extrinsically, the dominant intrinsic factor is Melanocyte Stimulating Hormone-α (α-MSH) while the extrinsic factor that plays a role is UV ray.

Conclusion: Melanogenesis is a complex process which influenced by a wide array of internal and external factors with α-MSH and UV ray act as the main regulators. Due to delicate nature of this process, defect in a certain stage could result in significant medical condition.

Keywords: melanogenesis, melanin, melanosom, α-MSH dan UV

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INTRODUCTION

The skin is the outermost protective organ that contains epidermal units which produce skin pigment, melanin. The main components of this unit are keratinocytes and melanocytes which communicate to each other via paracrine signaling. Melanin is known as the main determinant of hair, skin, and eye colour and plays important role in photoprotections by absorbing UVR. Pigmentation has extensive genetic properties but influenced by several factors both intrinsically and extrinsically.[1]

The melanin generating process is known as melanogenesis which comprised of several crucial stages. The process of melanogenesis involves many proteins and amino acid derivatives, which play important role from embryogenesis to the transfer of melanosomes to keratinocytes.[1,2] MSH is one of the melanocortin peptides that produced by proteolytic cleavage of protein pro-opiomelanocortin (POMC). It is the main endocrine factors that strongly induced melanogenesis and produced by pars intermedia of hypophysis in very small amount. Increased production of this hormone usually marked pathogenic condition.[3-5] However, several studies reported that MSH and other peptides can be produced by organs other than the pituitary (i.e the skin). In this case, it is believed that epidermal keratinocytes are the source of this peptide, but some other cells that also capable of producing MSH includes melanocytes and Langerhans cells. Considering this findings, it is postulated that the pigmentation induction by UV exposure is mediated by melanocortin peptides such as MSH[6] with intricate interaction between central pituitary gland and skin tissues. In this review, melanogenesis will be discussed in more detail including the signaling pathways that regulate it.

Embryologic Development of Melanocyte

Embryologically, the development of melanocytes occurs through several stages from the neural crest until when it migrated to the final target where it becomes the precursor of melanocytes. In the course of the migration to melanin production in the skin, they affected by several important regulatory proteins such as Wnt, endhotelin, steel factor and others.[1,7] The migration occurs through several stages of the cycle and proliferation which will eventually form clusters of melanocytes populations in the epidermis and hair follicles.[1,5]

Melanocytes originate from the neural crest in the vertebrae. During its development, melanoblasts, the precursor cells of melanocytes, will migrate through the dorsolateral pathways

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to the epidermis, eyes, ears and leptomeningen.[2,7] Other than migrating through the dorsolateral pathway, cutaneous melanocyte migration can also occurs through the ventral pathway which plays a role is the Schwan cells development along the nerve of the skin.[3,7] In addition, melanoblasts also migrate to the iris, leptomineningen and to the ear[3]. Some abnormalities could be emerged if aberrations occur during the embryogenesis process of melanocytes such as melanomas of the eye, Ota nevus or multiple melanositic congenital nevus if deviations occur in leptomeningen.[3,7-9]

Melanogenesis in the Melanosome

Melanosomes are specific intra cytoplasmic organelles that function as a compartment of melanin pigment synthesis, storage and transport.[1,3] Melanosomes are very closely related to lysosomes. Through compartmentalization, both protect cytoplasmic melanin through various processes such as protection against pro-enzymes and protease while melanosomes provide protection to melanin precursor such as phenol and quinone which can easily oxidize lipid membrane.[3]

Melanosomes are produced both by melanocytes and retinal pigment cells. Cellular melanosome located in their cytoplasm. During melanogenesis, the transfer process of mature melanosomes to epidermal keratinocytes and hair matrix occur continually because of the importance of this process.[2,3] In its development, melanosomes require tyrosinase (TYR) and tyrosinase related proteins (TYRP-1 and TYRP-2). These three enzymes are needed in the process of melanogenesis in the endoplasmic ribosome reticulum and transportation to the Golgi complex to go through the glycosylation process, where these processes are needed in the process of melanogenesis through its processing in the ribosome-endoplasmic reticulum and its subsequent transportation to the Golgi complex to be glycosylated, where these processes are essential for the structure and function of melanosomes.[1,10] In its development melanosomes through four stages namely:[2]

1. Phase I: premelanosomes are small dots or vesicles with an amorphous matrix
2. Phase II: melanosomes begin to have a clear form. Fibril matrix structures are formed and tyrosinase can be detected but the synthesis of melanin has not yet occurred. At this stage, pheomelanosomes begin to synthesize melanin, but not for eumelanasomes.
3. Phase III: Melanin production begins and pigments deposited on protein fibrils. Pheomelanosum continues to synthesize melanin, while eumelanosomes are just starting to synthesize melanin.
4. Phase IV: Pheomelanosomes and eumelanosomes are filled with pigments. At this stage, there is no tyrosinase activity and melanosomes are ready to be transported to keratinocytes

There are variation in melanosomes in melanocytes and keratinocytes in determining individual skin color in cutaneous pigmentation. Light-skinned individuals have predominant melanosomes in their melanocytes in stages I and III, while keratinocyte's melanosomes usually at stage III. In individuals with lighter skin color, melanosome degradation occurs more quickly and the number of melanosomes per cell is less than 20. The distribution in keratinocyte lysosomes is also between 2-10 groups.[2,3,11] Meanwhile, darker-skinned individuals usually have melanosomes in stage IV. Melanosomes in keratinocytes are also in stage IV and tend to be slow-moving. The melanosomes per cell generally in excess of 200 and its distribution in keratinocyte's lysosomes is only one.[3,14]

Melanosome Transfer to Keratinocyte

Melanosome transfer to keratinocytes is not only to protect DNA from UV damage but it also the main pathological process in pigmented skin disorders such as melasma, aging spots and vitiligo. There are three theoretical mechanisms proposed to explain this melanosome transfer: 1) Direct inoculation of melanosomes into keratinocytes through the nanotubular membrane filopodia melanocytes, 2) Through the phagocytosis pathway, where the melanocytes secrete melanosomes and then engulfed by keratinocytes, 3) Partial cytophagocytosis in which the transfer of melanosomes to keratinocytes occurs through the end of melanocyte dendrites containing melanosomes and located close to kertinocytes.[15,17] Molecular mechanism of how the transfer of melanosomes from melanocytes to keratinocytes is still under investigation. In one of the researches, Ando et al,. proposed a model of melanosome transfer through the vesicle decay system, which can be separated into following stages:[2]

1. Pigment bubbles containing multiple melanosomes and some mitochondria are formed in the philopodia of dendrit melanocytes
2. The bubbles are released through dendrites to the extracellular space
3. Pigment bubbles will be captured by the keratinocyte microvilli which will then be joined with protease activated receptor -2 (PAR-2)
4. Degradation of pigement bubbles

5. A melanosome will be released into the keratinocyte cytosol and reach the perinucleus

Melanin Biogenesis and Its Regulation

Melanin protects against UVR exposure by photoabsorption or by neutralizing free radicals in both skin and hair. Melanin is a polymeric pigment complex and has two forms: eumelanin with predominantly blackish brown pigment and pheomelanin with dominant reddish yellow pigment. Both of these types differ in their photoprotective properties or their structure in melanosomes.[3,16,20]

Melanin Biosynthesis Pathway

Skin, hair and eye colors are resulted from melanin accumulated in keratinocytes produced by specific cells, melanocytes. Melanocytes play an important role not only in determining the type of melanin but also in its distribution which will affect the color of the tissue. In addition to the tissue color, it also protects the tissue by photoprotection mechanism. The melanin pigment in human skin consists of a mixture of eumelanin and pheomelanin. The ratio of both depends on the ethnicity or race of the individual.[2,20] The ratio of eumelanin to total melanin determines the visible skin color while the ratio between eumelanin and pheomelanin determine the hair color.[2]

The process of melanin biosinthesis (eumelanin and pheomelanin) requires tyrosinase to convert tyrosine as the precursor of melanin. Tyrosinase is an enzyme that dependent on copper and plays a crucial role in the initial catalysis process to convert tyrosine to L-3,4-dihydroxyphenylalanine (DOPA) and subsequently oxidizes it to DOPAquinone (DQ).[2,3] In the presence of cysteine, DQ will be converted to cysteine DOPA and then further oxidized and polymerized into reddish yellow pheomelanin and soluble melanin. If there is no thiol compound (cysteine and glutathione or thioredoxin) DQ will spontaneously convert into DOPAchrome which has a blackish brown color. DOPAchrome will spontaneously decarboxylated into 5,6-dihydroxyindole (DHI) which is immediately oxidized to polymerize into blackish brown pigment.[5,6] However, in the presence of DOPAchrome tautomerase (TYRP2/DCT), it will convert DOPAchrome to DHI-2-carboxyl acid (DHICA). Then, tyrosinase and TYRP1 will convert it to melanin which has light brown in color. DHI melanin and DHICA have blackish brown color and are called eumelanin.[1-3,20]

Some pigmentary disorders in the skin can occur due to interference with this biosynthetic pathway. Copper deficiencies in melanin biosynthesis would result in Menkes Kinky hair syndrome. The molecular basis of this process is a defect in ATP7A which impairs the transfer process of copper to melanosomes. Other disorder such as oculo cutaneous albinism type 1 (OCA1) is an abnormality due to the absence of pigment in the skin, hair and eyes, which occurs because of the lack or absence of tyrosinase during the process of melanin biosynthesis. Patients with OCA 1 are more susceptible to skin cancer due to sunlight exposure.[1,3,7] The melanin biosynthetic pathway is described below in Figure 1.

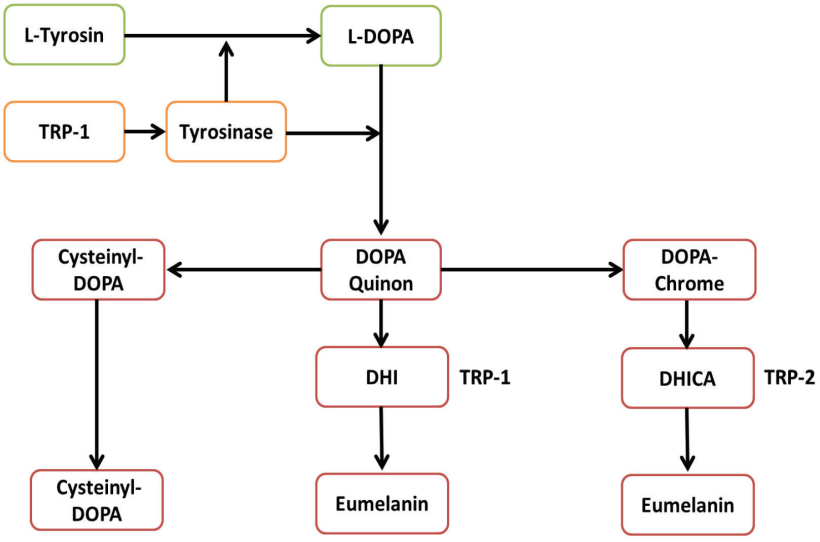

Figure 1. Biosinthetic pathway of melanin[20]

The Regulation of Melanin Biosynthesis

The ratio between melanin eumelanin and pheomelanin was found to be higher in individual skin types V and IV than in types I and II. Pheomelanin is more common in individuals with red hair, while eumelanin is more common in individuals with hair color other than red.[3,17-19] The amount of melanin produced in each individual is determined by many complex and interrelated factors: such as the level of enzyme activity, transporters and the balance of enzymes or protein structures, all of which are involved in the process of melanogenesis. Proteins that play a role in controlling the transition of eumelanin and pheomelanin are: α-MSH, agouti signaling protein (ASIP), endothelin-1, basic fibroblast growth factor (bFGF), and UVR as the external factor.[3,7]

Melanocyte-Stimulating Hormone as the Main Regulator of Skin Pigmentation

Melanocortin receptors (MC-Rs) are transmembrane seven paired G protein which have

five sub-types namely: MC1-R, MC2-R, MC3-R, MC4-R, and MC5-R. MC-Rs are encoded by genes that located in chromosome 16q24.3 and the main regulator of pigmentation. MC-Rs are expressed by melanocytes, melanoma cells, monocytes, endothelial cells and keratinocytes.[5,19] The MC1-R binding with α-MSH activates adenylate cyclase which in turn increases intracellular cyclic adenosine monopospate (cAMP). An increase in cAMP activates protein kinase A (PKA) which then further activates tyrosinase, the most important enzymes in melanogenesis. This mechanism indicates that α-MSH plays a crucial role in melanogenesis.[5,12] However, several studies also found that α-MSH could also reduce melanogenesis. This effect is likely due to the presence of phosphorylation and degadration of microphtalmia-associated transcription factors (MIFT). In the melanoblast differentiation, MIFT induces three enzymes that play a role in the regulation of melanin synthesis, namely: tyrosinase-related protein-1 (TRP-1), tyrosinase-related protein-2 (TRP-2) and 3,4-dihydroxyphenylalanine (DOPA) chrome. Therefore, it is logical that MIFT degradation would result in decrease in melanogenesis.[5,7,13]

Protein kinase-C (PKC) is also an intracellular protein activated by α-MSH in the melanogesis. This mechanism also proves that MSH is able to regulate tyrosinase which plays a role in melanin biosynthesis.[5] PKC is a serine or threonine kinase that is involved in diverse cell functions including growth factors, transformation and differentiation. PKC is an active enzyme in the cytoplasm that is activated by diacylglycerol, a second messenger in lipid signaling. Diacylglycerol is also released in the event of tissue due to biological stress, including UV exposure.[3,7,8] The expression of PKC in different tissues will induces functional change of melanocytes by inducing PKC-α, β, ε, Δ and ξ expression. Then, these receptor components activate PKC-β which plays a role in phosphorylation of tyrosinase.[8] In the biosynthesis of melanin, tyrosinase will catalyze tyrosine conversion to L-3,4-dihydroxyphenyaalanine (DOPA) and DOPAquinone which are two main steps in the biosynthesis process.[1,3,8] In addition to melanin biositesis, PKCs also play important roles in inducing dendrites and protecting melanocytes from UV exposure as well as facilitating the transfer of melanosomes to keratinocytes.[8]

CONCLUSION

Melanogenesis is a complex interaction between stimulation and inhibitor factors as well as endogenous and environmental factors. The process of melanogenesis starts from embryogenesis to the transfer of melanosomes to keratinocytes. α-MSH is an endogenous factor that plays a dominant role in the regulation of melanogenesis, where the process will produce melanin through the mechanism of transcription, translation and post-translation. Melanin is produced from interaction of various cellular and molecular signalings which involve melanogenesis enzymes such as tyrosinase, TRP, and PKC-β with dermal cells such as fibroblasts, keratinocytes and melanocytes. A slight change in this process will result in abnormalities of skin phenotypes. Aside from those internal factors, ultra violet exposure is the most important external factors that regulate the rate of melanogenesis.

CONFLICT OF INTEREST

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