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Review Article

Biochemical aspects of mammalian melanocytes and the emerging role of melanocyte stem cells in dermatological therapies

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ABSTRACT

Skin color in animals is richer than human beings and is determined by different types of pigments. Melanin is the key pigment responsible for the diverse pigmentation found in animal and human skin, hair, and eyes. Melanin pigment is synthesized by melanocytes and is consecutively transferred to adjacent keratinocytes; here, it acts as an internal sunscreen to defend from ultraviolet (UV) damage. Any defect in the process of melanocytes development and/or melanin synthesis results in esthetic problem of abnormal pigmentation. Clinically, abnormal pigmentation displays distinct increased or reduced pigment levels, known as hyperpigmentation or hypopigmentation. These defects affect either the melanocyte number or its function. Herein, we discuss the fundamental aspects of melanocytes/melanin biology taken together the underlying cause of pigmentary disorders. The current chapter also gives an insight into the melanocyte stem cells biology, which in turn can facilitate the development of novel treatment regimens for dermatological disorders.

Keywords: Melanin, melanoblasts, melanocyte stem cells, melanocytes, skin pigmentary disorders

Introduction

Skin color in animals is richer than human beings and is determined by different types of pigments such as melanin, carotenoids, oxyhemoglobin, and reduced hemoglobin as well as by the complexity and diversity of the structure of vertebrate integument.[1] Melanin is the key pigment responsible for the diverse pigmentation found in animal and human skin, hair, and eyes.[2] Melanocytes are the specialized dendritic cells which are endowed with distinctive and fascinating property of synthesizing melanin pigment by a cascade of chemical and enzymatic reactions. Basically, animal melanins are divided into two large groups, i.e., light-colored, red/yellow, alkali-soluble sulfur-containing pheomelanin (pheo = dusky/cloudy, predominant in red hair/freckles phenotype), whereas dark colored, black/brown, insoluble pigment eumelanin (eu = good) found in dark skin, and black hair.[3] Both types of melanin are derived by the oxidation and polymerization of the common precursor L-tyrosine or L-dopa with the involvement of crucial enzyme of melanogenesis, called as tyrosinase.[4-6]

Biological control of melanogenesis and patterns of pigmentation in the living organism is the consequence of different factors and mechanisms. Any discrepancies in the control mechanism of normal pigmentation result in the onset of disturbed melanogenesis pathways which ultimately lead to various dermatological or esthetic problems, such as hyperpigmentation or hypopigmentation.[7,8] These defects affect either the melanocyte number or its function. However, the basic biochemical, pathophysiological, genetic, as well as molecular cause of these anomalies is yet to be ascertained.[9-11] Therefore, the collective description of pigmentation disorders will help to understand the underlying mysterious molecular mechanisms/pathways of regulating the mammalian pigmentation.

Melanocytes and its precursor cells known as melanoblasts have proved as excellent models in developmental and structural biology.[12] Due to their interesting traits, melanocytes have attracted the attention of researchers and clinicians around the world, to hunt novel approaches and resolutions to the biomedical, pathophysiological, and technological problems which have now become clinically important. A lot of research is being carried out on pigmentation disorders using various animal melanocyte models, providing initial clues to recognize the several genes and proteins along with their associated signaling pathways underlying the dermatological disorders.[13,14] Of late, stem cell (SC) technology has given a new ray of hope for clinical researchers or skin biologists for the treatment of various skin-related medical conditions such as vitiligo, melasma, and other hormone-related dysfunctions.[15] Therefore, a better understanding of melanocyte-derived SC

and their niches may lead to the use of these cells in the development of potential therapeutic treatment for several pigmentation disorders.

Starting from the review of biological importance, structure and function of mammalian melanocytes, the present chapter is proposed to throw light on the interdisciplinary perspectives of melanin, its biochemical synthetic pathways and their associated enzymes with the aim of providing current knowledge through research is done so far, from a dermatological and clinical point of view. Herein, we will discuss the pathophysiological mechanisms by which melanocyte dysfunctions lead to skin pigmentation anomalies. The current chapter will also provide a deep insight into the biology of survival, maintenance, and regeneration of melanocyte SCs (MSCs) which in turn can facilitate the development of novel treatment regimens against dermatological disorders.

Structure and Functions of Mammalian Melanocytes

Melanocytes are specialized cells located in the basal layer of epidermis (the outermost layer of skin). These are rounded pigment cells which possess long, branch-like extensions known as dendrites. Melanocytes remain connected through their dendrites with approximately 30–40 keratinocytes forming epidermal melanin unit and to the fibroblasts in the underlying dermis.[16,17] The melanin pigments are synthesized through a cascade of biochemical and enzymatic reactions within specialized unit membranous subcellular organelles called as melanosomes, where a number of melanogenic enzymes and structural proteins are gathered to synthesize melanin pigments from L-tyrosine or L-phenylalanine. After synthesis, these melanin pigments have got deposited in melanosomes to form melanin granules. With the help of their dendritic processes, melanocytes transfer melanin granules to the neighboring keratinocytes where melanin has got accumulated to exert pigmented skin or hairs.[5] Apart from their physiological role in generating various skins and hair pigmentation/color, the principal function of melanocytes is to protect the skin from the genotoxic effects of ultraviolet (UV) radiations of sunlight due to their ability to absorb UV radiation and harmful free radicals.[18]

Embryonic Development of Melanocytes

The development of melanocytes lineage has long grabbed special attention of developmental biologists. Due to their ability to differentiate from single cell to multipotent SCs, they offer an outstanding model for structural and developmental purposes. Melanocytes have originated following remarkable and distinct developmental pathways from neural crest cells (NCCs) which are formed during the neurulation process in a developing embryo. The NCCs are highly migratory and capable of generating multiple cell lineage including melanocytes through migration, proliferation, and differentiation.[15,19]

On the basis of the anteroposterior position in the embryo, the NCCs can be classified into five overlapping categories, i.e., cranial, vagal, sacral, truncal, and cardiac. It is believed that the NCCs in the trunk region give rise to melanocytes, glia, and neurons along with other cells.[20] The NCCs of trunk migrate along two main routes: First one is ventrolateral route of migration followed by the cells that leave the crest early between neural tube and somites and turns into neurons as well as glia, while another is dorsolateral route opted by the late departing cells follow a pathway between the ectoderm and somites through developing dermis and develop into the melanocytes.[21] Melanoblasts along with Schwann cells, adrenomedullary cells, sensory, and sympathetic neurons have been developed from the ventrolateral migrating NCCs, whereas melanoblasts are the only descendants of dorsolaterally migrating NCCs.[22] Melanoblasts are highly proliferative, efficient of moving over a long distance in the dorsolateral route and can terminally differentiate into melanin-producing melanocytes in skin and hair.[3,20,23]

After their migration to the hair follicles (HFs), melanoblasts have got divided into two populations: The first population consists of hair matrix melanocytes, which is responsible for initial hair pigmentation while the other consists of MSCs, which are situated in the bulge region of HF.

Physiochemical Aspects of Melanin Pigment

Skin color in animals is richer than human beings and is determined by different types of pigments such as melanin, carotenoids, oxyhemoglobin, and reduced hemoglobin as well as by the complexity and diversity in the structure of vertebrate integument.[24,25] Melanin is the key pigment responsible for the diverse pigmentation found in animal and human skin, hair, and eyes. Melanin is insoluble hydrophobic pigment biopolymer with a negative charge and complex molecular structure formed by oxidative polymerization of phenolic or indolic compounds.[24,25] Several major categories of melanin exist in nature, but the most common are eumelanin (dark brown-black) which possess photoprotective properties and pheomelanin (red-yellow) which is presumed to be phototoxic.[26,27]

In mammals, melanins are dispersed through epidermal tissues and their derivatives, where the color they impart, play significant roles in thermoregulation, protection of skin hazardous effects of UV radiation, etc. Furthermore, as melanin has binding affinity for drugs and various chemicals, it proficiently strains toxic substances to defend tissues from oxidative and chemical stress.[28] Besides, melanins are also localized in other internal organs such as brain, inner ear,

spleen, and liver where they contribute in physiological process and disease resistance.[3,29]

Biogenesis of Melanin

The synthesis of melanin (melanogenesis) occurs in melanocytes through cascade of biochemical and enzymatic reactions.[5] Melanogenesis is regarded as oxidative phenomenon as it basically includes the oxidation of orthodiphenols to orthoquinones to attain a polymerization of the subunits that give rise to large pigment molecules. The biosynthetic pathway of melanin produces reactive oxygen species (ROS) and other oxidative subproducts that are potentially toxic to melanocytes. To avoid the cytotoxic effects of ROS as well as other toxic substances in the cytosol, the process of melanogenesis takes place within specialized subcellular organelles known as melanosomes.[3,30]

During melanogenesis, mixtures of eumelanin as well as pheomelanin have been produced at different ratio. The ratio is decided by tyrosinase activity and the substrate concentration of tyrosine and sulfhydryl group.[26] In mammals, melanogenesis is catalyzed by mainly three enzyme complexes which are highly similar copper containing transmembrane metalloproteins, i.e., tyrosinase (TYR), tyrosinase-related protein 1 (TRP1) or gp75, and TRP2 or DOPAchrome tautomerase (DCT). Melanin, the photosensitive polymer, is synthesized from amino acid L-tyrosine through a series of biochemical reactions. Tyrosinase is considered as the rate-limiting enzyme of melanin synthesis that catalyzes the two important reactions in the biosynthetic pathway; the first rate-limiting step of hydroxylation of L-tyrosine to 3,4-dihydroxyphenylalanine (L-DOPA) and subsequent reaction of the oxidation to L-dopaquinone. L-dopaquinone is the division point from where the pathway splits into two lines; one leading to eumelanogenesis while other leading to pheomelanogenesis within melanocytes [Figure 1a].

Sulfhydryl groups such as L-cysteine or glutathione play crucial role in pheomelaninogenesis. In the presence of sufficient concentration of sulfhydryl compound, L-dopaquinone immediately reacts with it to form 5-S-cysteinyldopa or 5-S-glutathionyldopa and quinones which are then further converted into benzothiazine afterward into benzothiazole. These products subsequently undergo oxidative polymerization resulted in the formation of pheomelanin [Figure 1a].[31,32]

During eumelanogenesis, when sulfhydryl group is not present in sufficient concentration, dopaquinone is transformed into levodopa which subsequently cyclizes to an orange colored intermediate, i.e., dopachrome by autoxidation. With the help of TRP1 and TRP2, isomerization of dopachrome to carboxylate intermediate 5,6-dihydroxyindole-2-carboxylic acid (DHICA) takes place.[33,34] TRP1 catalyzes the oxidation of DHICA to indole-5,6-quinone-2-carboxylic acid in mice, not in humans. TRP1 which has DHICA oxidase activity, converts dopachrome to DHI which finally undergoes oxidative polymerization to form eumelanin [Figure 1a].[35-37]

The cellular site of melanin synthesis, storage, and transportation is a membrane-bound subcellular organelle known as melanosome produced by melanocytes. Melanosome biogenesis is categorized into four developmental stages (I-IV). Stage I and II comprise immature, unmelanized premelanosomes, structural proteins, as well as melanin synthesizing enzymes such as TYR, TRP1, and TRP2 transported from other organelles to immature, non-pigmented Stage II premelanosomes. Melanin deposition begins at Stage III melanosomes and the organelle is fully melanized by mature Stage IV melanosomes [Figure 1b].[3,38,39] In skin, these Stage IV melanosomes further get secreted and transported from melanocytes to keratinocytes where they form a pigmented supranuclear cap around the keratinocyte nucleus to protect it from harmful effects of UV radiation-induced DNA damage.[16,40]

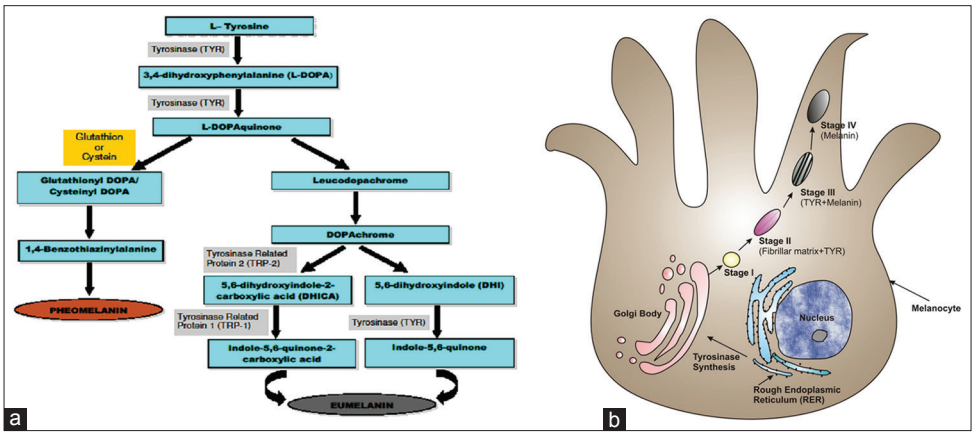

Figure 1: (a) The biochemical pathway of melanin synthesis occurs within melanosomes or pheomelanosomes, directing to the production of eumelanin or pheomelanin, (b) The developmental stages of melanosomes (I-IV) during melanin synthesis. Stage I and II comprise immature, unmelanized premelanosomes, structural proteins, as well as melanin synthesizing enzymes transported from other organelles to immature, non-pigmented Stage II premelanosomes. Melanin deposition begins at Stage III melanosomes and the organelle is fully melanized by mature Stage IV melanosomes

Melanocytes exist in all types of skin in almost similar and constant density. It is the distribution and amount of melanin that influences the color of skin. Production of melanin is principally regulated by melanocortin receptor 1 (MC1R) signaling. MC1R signaling is regulated by either alpha-melanocyte-stimulating hormone (α-MSH) which acts as agonist or agouti signal proteins (ASP in mice, ASIP in humans) which in turn plays the role of antagonist of signaling pathway.[41] When α-MSH binds to MC1R, it activates eumelanogenic pathway by activation of adenylate cyclase and eventually leads to the production of secondary messenger cAMP signaling cascade. It enhances the downstream expression of microphthalmia-associated transcription factor (MITF) required for promoter activation of all the three melanogenic enzymes (TYR, TRP1, and TRP2) with the resultant increase in eumelanin synthesis. However, binding of ASP to MC1R inhibits eumelanin synthesis by affecting the binding of α-MSH and its downstream signaling, hence promotes pheomelanogenesis.[3,42]

Pigmentary Disorders: Result of Defected Melanin Synthetic Pathway

The mechanism of melanin biogenesis as well as its distribution is highly intricate which involves various genes and enzymes; structural proteins that play key role through various complicated signaling pathways and have yet to be completely elucidated. Errors in any process may lead to hypopigmentation disorders where normal numbers of melanocytes are maintained but show rigorous defects in the site or amount of melanin. Defects in melanin synthetic pathways are either inherited or acquired. Melanocytes synthesize melanin and successively transfer it to the neighboring keratinocytes.[16] Any defect in this process of melanin transfer is also one of the causes of depigmentation. It provides important evidence for intervention of skin pigmentary disorders such as albinism, vitiligo, piebaldism, and melasma.[43]

Hypopigmentation

Mostly three possible theories have been proposed to understand the mechanism of hypopigmentation; the first one is associated with the genetic insult which results in loss of melanocytes during embryonic development (e.g., piebaldism), second by retardation/alteration in production and/or distribution of melanin (e.g., oculocutaneous albinism [OCA] and tinea versicolor), and third one is by destruction of melanocytes (e.g., vitiligo).[44,45]

Piebaldism is characterized by the presence of congenital white forelock and white macules without melanocytes with notable phenotype in skin and hair mostly on the frontal head, ventral trunk, and extremities.[46] This pathological condition is a result of mutation in the tyrosine kinase gene named "KIT gene" which after activation plays crucial role in the development as well as proliferation of melanocytes. KIT gene encodes for the SC growth factor receptor expressed in mastocytes and in melanocytes.[47]

OCA signifies the hypopigmentary disorder caused by reduced/defective melanin production within melanosomes due to disruption in the maturation and trafficking of tyrosinase enzymes which results in loss of total pigmentation of all the skin, hair, and eye. OCA is classified into four non-syndromic forms (OCA1-4) based on the gene that is mutated. OCA1 is the most severe among all the OCA caused due to mutation in TYR enzyme, in which OCA1A shows total lack in TYR function and pigment remains completely absent in the skin, hair, and eyes throughout life, while OCA1B displays decreased function of TYR protein due to which individuals are born with white skin and hair but develop some pigment with age.[48] OCA2 is caused by mutation in gene *OCA2* (also known as P gene). The *OCA2* gene is supposed to encode a transport or channel protein which is proposed to transport TYR, in which patient shows brown pigmentation.[49] OCA3 is characterized by mutation in melanin synthetic enzyme *TRP1* gene in which patients retain red hair along with reddish-brown skin.[50] The OCA4 is clinically characterized by mutation in the gene encoding the membrane-associated transporter protein or SLC45A2, located in melanosomal membrane which acts as transporter, helps in directing the traffic of melanosomal proteins and other substances to melanosomes, with patients displaying brown pigment. OCA2 and OCA4 have similar clinical characteristics but differ in responsible gene.[45]

Vitiligo is a dermatological disorder characterized by progressive loss/reduction of epidermal melanocytes number and activity which results in severe critical skin depigmentation.[3] It is usually classified into two forms: Most common, severe non-segmental form and less common segmental form. The exact cause of melanocyte loss is still unclear. Studies done across the world led researchers to ascribe these three factors; (1) cellular immunity caused by the genes that influence the autoimmunity response, (2) genetically abnormal melanocytes, and (3) an environmental or physiological factor such as oxidative stress that activates program for the destruction of melanocytes.[3,51]

Hyperpigmentation

There are various exogenously or endogenously originating risk factors which are associated with developing abnormal presence of a pigment in the skin which leads to hyperpigmentation disorders. These are either hypermelanosis, where the number of melanocytes remain unchanged, but the quantity of melanin has got increased (e.g, Addison's disease, melasma) or hypermelanocytosis where the number of melanocytes has increased (e.g., lentigines).

Melasma is an acquired pigmentary disorder characterized by irregular coloration from light to dark brown, sharply margined, and roughly symmetric patches of hyperpigmentation on the

face. Melasma is histopathologically classified into epidermal, dermal, and mixed types depending on pigment depth.[52] Increasing sun exposure increases the risk of melasma due to the overproduction of the melanin and transfer of melanosomes by hyperfunctional melanocytes.[53] Apart from sun exposure, multiple factors contribute to the onset of melasma such as pregnancy, hormone therapy, certain cosmetics, endocrine or hepatic dysfunction, autoimmune thyroid disorder, and photosensitizing drugs.[54] Transcriptomics study conducted by Kang *et al.*[55] showed the increased expression of numerous melanin synthesis-related genes such as TYR, TRP1, TRP2, and MITF in the lesional skin. Similarly, immunohistochemical staining of the lesional skin also showed higher protein expression of these genes.[55]

Lentigines are characterized by the brown spots occurring due to increased number of melanocytes in the epidermis. All forms of lentigines are found to have certain degree of increased melanocyte number and are characterized as simple lentigines except the solar lentigines (SLs) which are typified by increased melanin production.[53,56] In SL, hyperpigmented lesions commonly occur on the back of the hand, face, forearm, back, neck, and chest due to chronic sun exposure which increase in number and size upon chronological ageing.[57] Although progression from lentigines to melanoma has not been established, lentigines are independent risk factor for melanoma. The genetic effects involved in the initiation and formation of SL are not yet known completely. However, SL lesion formation is associated with increased expression of pigmentary proteins such as TYR, TRP1, proopiomelanocortin, endothelin-1 (ET-1), ET receptor B, and SC factor and its receptor (c-KIT).[58,59]

Melanocyte SC (MSCs): Potent Therapeutics Against Pigmentary Disorders

Following successful development and migration of mammalian melanocytes to their respective location, how do these cells maintain and redevelop pigmentation in life of adult animals, is one of the key questions that remains to be answered. Pigment cell research done so far in various species provides solid evidence of occurrence of reservoir of MSCs which play principal role in repigmentation of skin or hairs when needed. The detection and possible manipulation of these MSCs might retain therapeutic use for skin pigmentary disorders. SCs are unspecialized cells which confer two important properties that discriminate them from rest of the cells; first one is their ability to restore their numbers over long periods and another is their capacity to differentiate into specialized cells with specific function after getting specific signals.[60]

The HF is a skin appendage which contains epidermal keratinocytes and follicular cells, mesenchymal cells, along with the pigment-producing melanocytes. HF is dynamically remodeled mini organ, two-third of the lower HF is totally reproduced during the hair cycle (growth phase [anagen], regression phase [catagen], and resting phase [telogen]), while the leftover upper permanent portion is maintained.[61] Hence, the HF is proposed to be an ideal model system for analyzing the process of tissue replenishment/regeneration under certain physiological conditions. MSCs are unpigmented, quiescent cells, most likely situated within a specific anatomical niche, making it easy to find and isolate. During embryogenesis, the MSCs are exclusively colonized in the bulge region of HF, specifically in mice skin not in humans.[62]

However, in human skin, the immature melanocytes are maintained in the basement membrane of the interfollicular epidermis, which play a key role in the generation of skin pigmentation.[63] The MSCs become activated at new anagen phase of HF cycle, where they begin to proliferate and produce melanocyte progenitor cells. As anagen phase proceeds, these proliferative progenitor cells migrate toward the hair bulb section where they differentiate into the mature melanocytes. These mature melanocytes express all of the key melanogenic enzymes, i.e. TYR^+, $TRP1^+$, $TRP2^+$, or DCT^+ which synthesize melanin pigment and their consecutive transfer to melanosomes and finally into the adjacent keratinocytes.[64] At the onset of catagen phase, the differentiated melanocytes in the hair bulb endure apoptosis, while MSCs survive. As a result of which during telogen phase, HF holds only MSCs that remained quiescent, reactivated in the next hair cycle.[62]

Due to their extraordinary properties comprising its long lifespan, multipotency and ability to migrate quickly to new location *in vivo*, ability to be manipulated *in vivo,* as well as *ex vivo*, flexibility with respect to its differentiation choices, these prolific MSCs offer an influential SC source for regenerative medicine applications against various skin pigmentary ailments.[65] These cells can also be exploited for gene therapy through *ex vivo* gene delivery and retrasplantation. The MSCs also open new vistas to figure out underlying causes of pathological conditions triggered by the SC system including various pigmentation defects such as vitiligo, graying of hair, wound healing, and melanoma.

Vitiligo

Vitiligo is one of the hypopigmentary disorders caused by destruction of melanocytes. It is characterized by acquired, progressive, and circumscribed loss of pigmentation in hair and skin with a complete loss of melanin in patients.[66] The skin SCs can be preserved in clinical set up for a long period of time and these can be used in the medical management of vitiligo, burn, and other skin pigment-related disorders. Interestingly, the HFSCs can also be used for cell-based clinical needs, especially in vitiligo. After conventional therapies such as immunosuppressive modalities for treatment of vitiligo, repigmentation frequently begins in perifollicular area. This

is expected to occur from the reservoir of MSCs in the HF bulge.[67] It has been proposed by Tobin *et al.*[68] that although the presence of MSCs is difficult to recognize in the clinical setting, the unpigmented melanocytes have been identified in chronic recalcitrant vitiligo. Their findings strongly support the possibility of the presence of MSCs in the niche which probably provide a chance of repigmentation.

In a clinical study conducted by Parsad *et al.,*[69] it was established that on PUVA (psoralin UVA) treatment, 65.5% of 352 vitiligo patches exhibited a perifollicular repigmentation of affected areas. It is evident from another study performed by Seleit *et al.,*[70] 54% and 63% of MSCs remain present at the interfollicular and follicular areas of vitiliginous skin. Research done by several workers support the finding that MSCs reside in the outer root sheath of HF, and therefore, suspension of outer root sheath cells serves as a source of MSCs when transplanted into the vitiliginous skin.[71,72] These studies also give clue that MSCs can perhaps contribute to the regulation of immune cells and skin inflammation after wounding.

Wound healing

SCs exhibit unique property of differentiation during tissue regeneration to supply functional mature cells. In addition to their conventional role in melanocytes repigmentation, MSCs can also produce epidermal melanocytes in response to wounding.[73] In adult skin, superficial injuries that do not harm HF are healed swiftly with the regeneration of epidermal appendages. Whereas, in case of deeper wounding that disturb the HF bulges heal with scars and without structure.[74] It was proposed by Ito *et al.*[75] that during the process of wound healing, MSCs from the bulge of HF produce daughter skin cells, which later migrate to epidermis (basal layer and sebaceous gland). Chou *et al.*[76] have reported that the process of wound healing is related with MC1R–ACTH and MC1R–α-MSH signaling pathway and the MSCs migration preceded melanocyte proliferation. These studies confirm the crucial role played by MSCs in wounding after skin injury and also propose that it is the follicular MSCs which form the actual basis of epidermal melanocytes.[77]

Hair graying/canities

Premature hair graying or canities has significant undesirable effects on the appearance, self-esteem, and sociocultural acceptance of the affected persons. Hair graying offers an exceptional opportunity to learn the uncoupling of melanin production with growth of the hair shaft.[78] MSCs reside in the bulge as well as sub-bulge region of mammalian HF and remain in direct contact with HFSCs. It serves as the functional niche for MSCs and is required to maintain the growth of pigmented hairs that are activated during hair cycle.[67,79]

Nishimura *et al.*[80] have reported that the incomplete maintenance of immature precursor MSCs in the HF bulge as well as sub-bulge region and MSCs depletion are the causes of hair graying phenotype in mice. The loss of same melanocyte population was also observed in an age-correlated fashion in human HF. However, recently, it was reported by Thadani *et al.*[81] that while treating neurodegenerative disorder using MSCs, it was suddenly noticed that the gray hairs of patients have also started becoming black. They have further postulated that MSCs migrate to the dysfunctional brain and affect the NCCs through their cytokines, which in turn upregulate the melanin synthetic cycles.

Conclusion

Comprehensive knowledge of development, evolution, functioning, and disruption of pigmentary systems needs the insight into underlying cellular interactions and signaling pathways producing this system. Fundamental pathways that direct melanocytes and biogenesis of melanin as described in this chapter have got altered/dysregulated in skin pigmentary disorders such as hypopigmentation and hyperpigmentation. Despite massive research done in pigment cell biology, many aspects of melanocyte development and melanin production in normal and diseased situations are yet to be ascertained. Hence, future studies to better understand the mechanism of melanogenesis and its associated disorders to develop treatment regimens is need of the hour. Research on MSC is one of the new emerging fields, which offers novel therapeutic regimens for various dermatological disorders due to their pluripotent nature to differentiate into numerous cell types, ease of accessibility, and a distinctive immunological profile. Extensive research of MSCs throws light on hope for the MSCs as an excellent model for use as universal donors in cell-based therapies as well as regenerative medicine. These MSCs will help to explore the underlying molecular mechanism of normal melanocyte development as well as pathological conditions caused by the defects in the SC systems including several skin pigmentary defects. Hence, further studies with the aim to develop in-depth understanding of biology of MSCs system will help to develop new therapeutic strategies for various pigmentary ailments which ultimately will benefit the patients without causing any side effects.

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