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Review Article

Melanocyte dysfunctions: future and promise of stem cells

Sharique A Ali, Gulafsha Kassab*, Tasneem Husain

*Department of Biotechnology and Zoology, Saifia College, Barkatullah University, Bhopal 462001, India; *Present Address: Department of Biotechnology, Government Arts and Commerce College, Sagar, India*

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Abstract: Human melanocytes (MCs) and melanocyte stem cells (McSCs) are integral to skin pigmentation and appendage pigmentation, originating embryonically from neural crest cells. In adult skin, McSCs residing in the epidermis sustain the continuous regeneration of functional melanocytes, a process vital for skin homeostasis and repair. Advances in McSC research have unravelled their pivotal roles in combating disorders such as vitiligo, hair greying, impaired wound healing, and melanoma. Previous studies have significantly advanced our knowledge of the cellular and molecular characteristics of this unique stem cell population. However, a comprehensive understanding of their characteristics in melanocyte dysfunctions leading to conditions like vitiligo is still lacking. Dysfunction or depletion of McSCs is linked to these conditions, highlighting their significance in maintaining skin health. Cutting-edge technologies like single-cell RNA sequencing, spatial transcriptomics, gene editing, and whole-genome sequencing have deepened our understanding of McSC biology and their regulatory microenvironment. This review delves into the latest discoveries, offering a comprehensive perspective on McSCs and their therapeutic potential. By identifying specific molecular signals and crosstalk mechanisms, McSC research opens avenues for regenerative medicine applications, including skin repigmentation, tissue repair, and cancer treatment. The field's progression sets the stage for transformative breakthroughs in skin regeneration and broader regenerative therapies.

Keywords: Melanocyte stem cell, hair greying, melanoma, microenvironment, homeostasis

Introduction

Melanocytes are the cells responsible for producing melanin, the pigment that gives color to our skin, hair, and eyes. They play a crucial role in protecting the skin from harmful ultraviolet (UV) radiation from the sun, regulating skin color, and influencing the development of certain sensory and neurological functions. Dysfunction of melanocytes can lead to a range of disorders, from hypopigmentation and hyperpigmentation to skin cancers and neurological disorders. Animals have more pigments than humans, including melanin, carotenoids, oxyhaemoglobin, reduced haemoglobin, and the complexity and diversity of vertebrate skin structure, all of which contribute to the animals' richer skin color [1]. Melanocytes are a type of specialized dendritic cell with the remarkable ability to synthesize melanin pigment through diverse chemical and enzymatic pathways. Generally, melanin in animals is classified into two main types: eumelanin, a dark-coloured, black or brown insoluble pigment found in dark skin and black hair; and pheomelanin, a light-coloured, red, or yellow pigment that contains sulfur and is soluble in alkaline conditions [1, 2].

Melanocytes and their precursor cells, the melanoblasts, have emerged as valuable models in both developmental and structural biology. These cells have attracted significant attention from researchers and clinicians worldwide, who seek innovative strategies to address biological, pathophysiological, and technological challenges with therapeutic relevance. Extensive research on pigmentation disorders is currently underway using various animal melanocyte models, offering crucial insights into the genes, proteins, and signalling pathways involved in dermatological conditions [1, 3].

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Melanocyte stem cells (McSCs) are a type of skin stem cells, derived from the neural crest in vertebrates [4]. During embryogenesis, neural crest cells migrate along the dorsolateral pathway - linking the somite to the non-neural ectoderm - to differentiate into melanoblasts. These melanoblasts then undergo a remarkable migratory process, ultimately populating the developing hair follicles (HFs) and epidermis. Within the basal layer of the epidermis, melanoblasts further differentiate into melanocyte precursor cells, which represent an intermediate stage before maturing into fully functional melanocytes (MCs) [1]. Impairments in melanocyte function can contribute to several conditions, including vitiligo, melanoma, and albinism.

Recent progress in cellular and molecular biology has significantly enhanced our understanding of melanocyte dysfunctions, paving the way for innovative treatment approaches. In particular, the development of stem cell (SC) technology has opened new avenues of hope for clinical researchers and dermatologists in addressing various skin-related disorders, including vitiligo, melasma, and other hormone-associated conditions.

In this review, we discuss the recent advances that underscore the pivotal role of McSCs in pigmentation and the promising potential of stem cell-based approaches in treating melanocyte dysfunctions. Ongoing research aims to address existing challenges, paving the way for effective regenerative therapies for pigmentation disorders. This review also provides a comprehensive overview of melanocyte biology, associated dysfunctions, and the possible therapeutic applications of stem cells. However, several areas warrant further exploration to enhance our understanding and treatment approaches.

Synthesis and function of melanocyte

Melanogenesis is the biochemical process through which melanin is synthesized [5]. This pathway takes place within melanocytes, specifically inside specialized cytoplasmic structures called melanosomes. There are two main forms of melanin: pheomelanin and eumelanin, each differing in colour and synthesis pathway. Melanin offers several health benefits, such as absorbing and scattering UV radiation, neutralizing free radicals, facilitating redox reactions, and storing ions [6]. The type of melanin produced depends on the availability of substrates and the activity of enzymes involved in melanogenesis (**Figure 1**).

Tyrosinase (TYR) initiates the conversion of tyrosine into L-3,4-dihydroxyphenylalanine (DOPA), which is rapidly oxidized to form DOPAquinone. When DOPAquinone interacts with cysteine, it generates 3- or 5-cysteinyl-DOPAs that undergo further oxidation and polymerization to produce pheomelanin, a yellow-red, soluble pigment [7]. In the absence of thiol-containing compounds like cysteine, glutathione, or thioredoxin, DOPAquinone instead follows a pathway that leads to the formation of eumelanin, a brown-black pigment. DOPAquinone spontaneously cyclizes into DOPAchrome, which can lose a carboxyl group to form 5,6-dihydroxyindole (DHI). DHI then oxidizes and polymerizes into dark, insoluble DHI-melanin. However, in the presence of DOPAchrome tautomerase (TYRP2/DCT), DOPAchrome is converted into DHI-2-carboxylic acid (DHICA) (Del Marmol and Beerman, 1996). Tyrosinase and TYRP1 further process DHICA to produce DHICA-melanin, a lighter brown pigment. Human skin contains a mixture of melanin types, and the relative proportions of these determine visible skin pigmentation [2, 8].

Melanocyte stem cell

Melanocytes, along with their precursor cells, the melanoblasts, have long served as valuable models in developmental and structural biology research [9]. These cells have garnered significant attention from scientists and clinicians worldwide, who seek innovative strategies to address biological, pathological, and technological challenges that have become increasingly relevant to therapy. Extensive studies on pigmentation disorders are being conducted using various animal melanocyte models, offering important insights into the genes, proteins, and signalling pathways involved in skin-related conditions [1, 10-12]. More recently, stem cell (SC) technology has brought new hope to clinical researchers and dermatologists, presenting promising avenues for treating a range of skin disorders such as vitiligo, melasma, and hormone-related pigmentation issues [13].

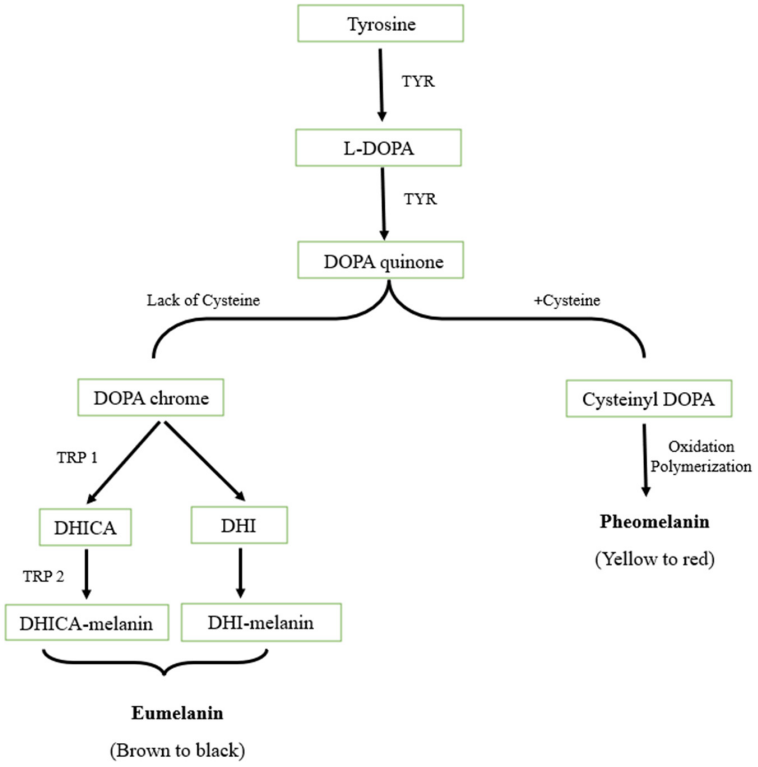

Figure 1. A simplified diagram of melanin synthesis in melanocytes during melanogenesis. Tyrosine is transformed into melanin - a polymer composed of the pigments eumelanin (black-brown) and pheomelanin (yellow-red) - through the action of key enzymes including tyrosinase (TYR), tyrosine-related protein 1 (TYRP1), and tyrosine-related protein 2 (TYRP2).

Consequently, gaining deeper insight into melanocyte-derived stem cells and their niches could pave the way for developing novel treatments for various pigmentation disorders. These stem cells give rise to transient amplifying cells as well as fully differentiated melanocytes. The study of melanocyte stem cell biology is still in its early stages, and much remains unknown, particularly regarding how these cells function within their native environments, how external factors regulate their quiescence or activation, and how adaptable this cell population is. Additionally, the precise microanatomical location of melanocyte stem cells across different species such as mice, flies, zebrafish, and humans is only beginning to be explored in depth [14, 15].

Melanocyte stem cells (McSCs) in hair follicles

In vertebrates, melanocytic cells originate from the trunk region of the neural crest. Between embryonic days 8.5 and 10 (E8.5-E10), the temporary expression of Kit ligands promotes neural crest cell migration along the dorsolateral pathway, leading to the formation of melanoblasts. These melanoblasts initially migrate into the dermis. By approximately E13.5, they transition from the developing dermis into the epidermis. From there, they move through the basal layer of the epidermis toward the developing hair follicles (HFs), ultimately populating both the epidermis and HFs. This migration results in the formation of spatially distinct melanocyte populations, including melanocyte stem cells (MSCs), follicular melanocytes (MCs), and epidermal melanocyte stem cells (McSCs) [16, 17]. Melanocytes have a dual origin from the neural crest and, aside from the primary source described, may also arise from Schwann cell progenitors via the ventral migratory pathway [18].

The hair follicle (HF) is a functional skin appendage responsible for regulating hair growth. It is divided into two main regions: a permanent section and a transient one. The permanent region, located in the upper portion of the HF, comprises the infundibulum and the isthmus. At the base of the isthmus, the outer root sheath (ORS) extends outward to form the follicular bulge, which is considered the primary niche for hair follicle stem cells (HFSCs) [19]. During HF development, the permanent portion remains unchanged, with no regeneration or programmed cell death. In contrast, the lower segment of the HF undergoes dynamic morphological changes throughout the hair cycle, including phases of growth, regression, and rest (**Figure 2**).

Melanocyte stem cells (MSCs) within the hair follicle undergo cyclical phases of activation, regression, and quiescence in alignment with the hair cycle. During the anagen (growth) phase, quiescent MSCs are activated and

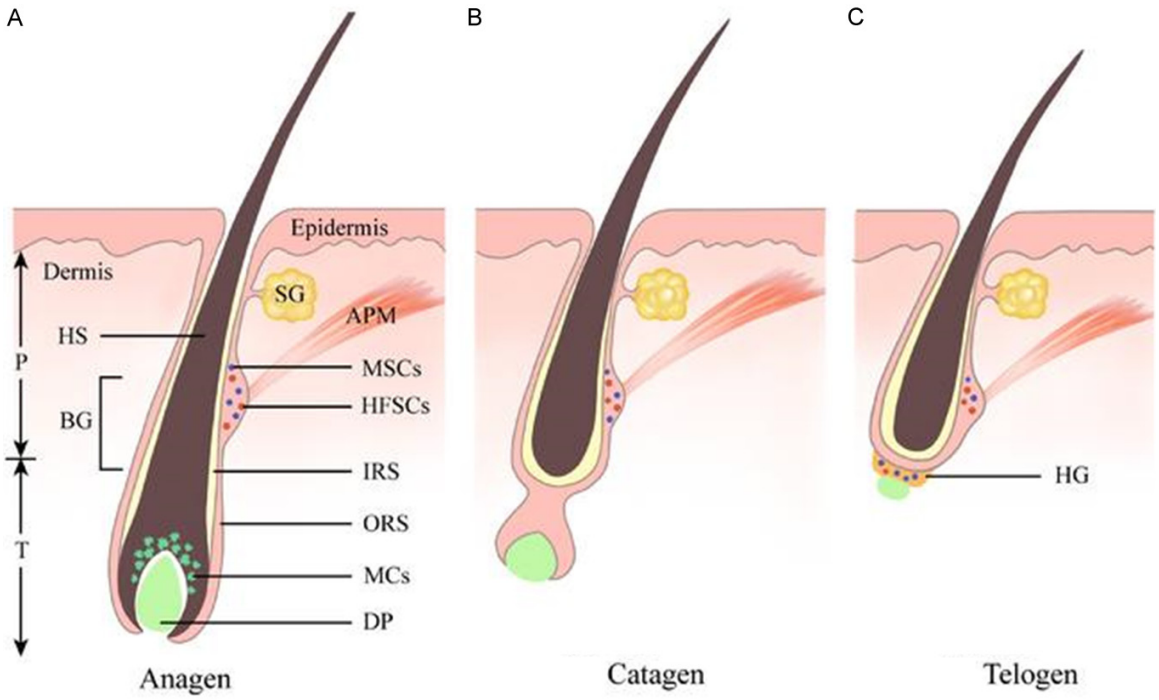

Figure 2. A schematic illustration depicting the structure of the hair follicle and the behaviour of melanocyte stem cells (MSCs) and their progeny throughout the hair cycle. A. In early anagen, quiescent MSCs (represented as blue dots) located in the follicular bulge become activated, migrate down the outer root sheath (ORS), and differentiate into mature melanocytes (green dots) within the follicular bulb. B. During the catagen phase, mature melanocytes and transitional follicular cells undergo apoptosis, while quiescent MSCs remain in the bulge. C. In the telogen phase, MSCs stay dormant in both the bulge and the hair germ (HG) until the cycle restarts with a new anagen phase. APM: arrector pili muscle, BG: bulge, DP: dermal papilla, HFSCs: hair follicle stem cells, HS: hair shaft, IRS: inner root sheath, P: permanent portion, SG: sebaceous gland, T: transient portion. Adapted from Huang et al., 2024 [22].

migrate from the bulge region to the hair follicle (HF) bulb, where they differentiate into mature melanocytes (MCs). In the catagen (regression) phase, these differentiated MCs undergo apoptosis, leaving behind only quiescent MSCs in the bulge. In the telogen (resting) phase, MSCs remain dormant, primarily residing in the bulge and the hair germ (HG) area.

Contrary to earlier assumptions that MSCs are mainly located in the bulge, Sun et al. demonstrated that during telogen, MSCs are predominantly found in the HG, with only a few remaining in the bulge (**Figure 2**). As the hair re-enters the anagen phase, MSCs in the HG become activated and give rise to transit-amplifying cells - intermediate progenitors capable of migration. These cells travel downward to the follicular bulb, where they mature into melanocytes, and upward to the bulge, where they retain self-renewal potential. In the absence of differentiation signals within the bulge, most of these transit-amplifying cells can revert to a stem cell state and migrate back to the HG during the next telogen phase, ensuring a reservoir of MSCs for the subsequent hair cycle [20].

Biological features of melanocyte stem cells (MSCs)

Melanocyte stem cells (MSCs) are small, oval-shaped cells that lack melanin granules and exhibit a slow proliferation rate [21]. Their biological traits are essential for understanding their roles in skin pigmentation, hair coloration, and regenerative potential. MSCs display unique molecular signatures, characterized by low expression levels of both housekeeping and pigment-related genes. This marked difference in gene expression suggests that MSCs are in an immature state. A 5-bromo-2-deoxyuridine labelling experiment confirmed that MSCs located in the bulge region remain undifferentiated, become active only during the

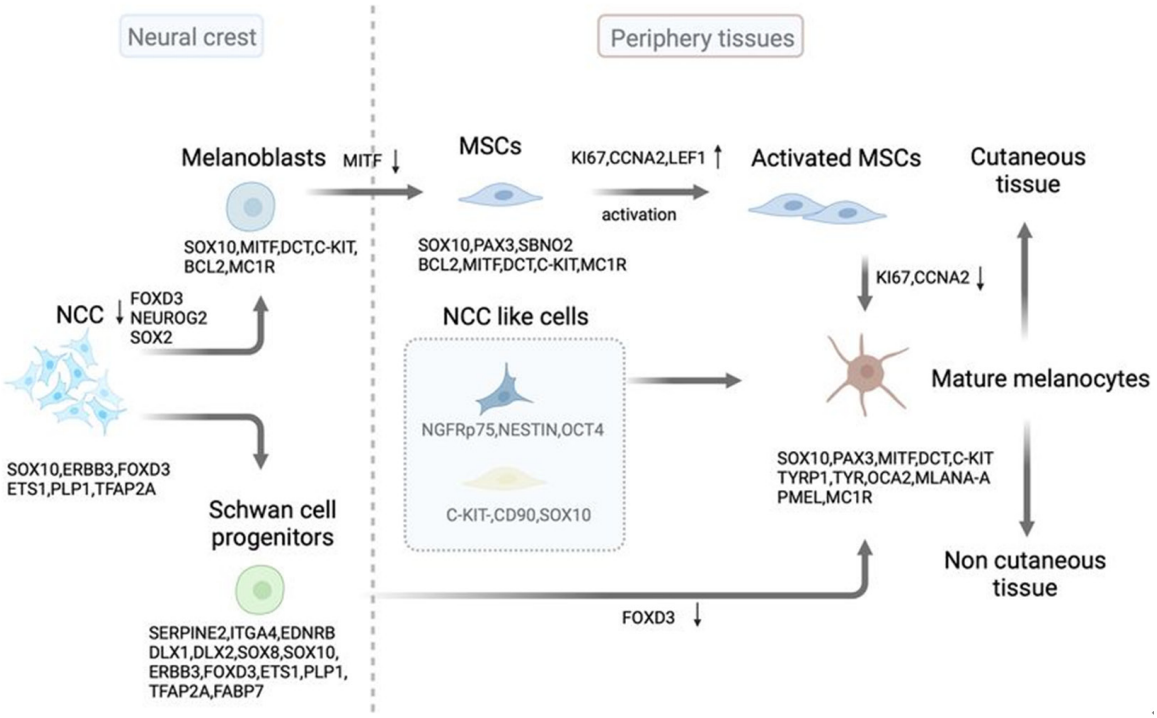

Figure 3. Origin and development of melanocytes in mammals, melanocytes originate from neural crest cells (NCCs), with melanoblasts lineages emerging through the downregulation of transcription factors such as FOXD3 and NEUROG2 and/or SOX2 in progenitor cells. The melanocytic lineage maintains expression of SOX10, which subsequently triggers the activation of key melanogenic markers including MITF, DCT, and C-KIT. As melanoblasts migrate and colonize developing embryonic hair follicles, some differentiate into pigment-producing melanocytes responsible for colouring hair during the first hair cycle. Others downregulate MITF and become melanocyte stem cells (MSCs), which localize to the hair follicle bulge and secondary hair germ. These MSCs sustain the melanocyte population by generating transit-amplifying cells that proliferate and mature into functional melanocytes during each hair cycle. Additionally, Schwann cell progenitors - also derived from SOX10-expressing NCCs - can contribute to the pigmented cell population by repressing FOXD3. In the skin, neural crest-like progenitor cells also retain the capacity to differentiate into mature melanocytes (Adapted from Cui and Man, 2023) [27].

early anagen phase, possess self-renewal capabilities, and provide differentiated melanocytes (MCs) to the hair follicle [22].

Melanocytes (MCs) serve as a valuable model for exploring the molecular basis of various cellular regulatory mechanisms, as defects in the regulation of their survival, proliferation, migration, or differentiation are often visibly reflected through changes in coat color. This makes them particularly useful for studying stem cell regulation as well, especially since impaired maintenance of melanocyte stem cells (MSCs) has been linked to the development of gray hair [23]. Over 90 different genetic loci associated with coat color mutations have been identified in mice [24]. Key regulators such as Pax3, Sox10, Mitf, Kit (formerly c-Kit), and Ednrb play crucial roles in the development of immature melanocytes, or melanoblasts (Mbs) [24]. These melanoblasts originate from the neural crest, migrate through the epidermis, and ultimately localize within newly forming hair follicles (HFs) (**Figure 3**).

Once melanoblasts reach the hair follicle (HF), they differentiate into two distinct populations: mature melanocytes (MCs), located in the hair matrix and responsible for hair pigmentation, and melanocyte stem cells (MSCs), situated in the lower permanent portion of the HF, where they maintain and regenerate the MC population during future hair cycles. In previous studies, we identified MSCs as label-retaining cells (LRCs) and demonstrated that, unlike other MC subsets, they can survive even when Kit signalling - a pathway typically crucial for MC proliferation and survival - is inhibited using a specific antagonistic antibody against Kit [25]. However,

except for this phenomenon, little is known about MSCs.

The regulation of melanocyte stem cells is a complex process, influenced by a multitude of signalling pathways. At the heart of this process lies the WNT/β-catenin pathway, which plays a crucial role in melanocyte development and homeostasis. This pathway's activity is finely tuned, allowing McSCs to self-renew and differentiate into functional melanocytes. The KITL/KIT pathway, on the other hand, regulates melanocyte growth and survival, ensuring that these cells can respond to environmental stimuli, such as UV radiation. The interplay between these pathways is delicate, and any disruption can have significant implications for skin homeostasis.

The dysregulation of McSCs is a key factor in the development of skin disorders, such as vitiligo and melanoma. When McSCs are depleted or dysfunctional, the skin's ability to regulate pigmentation is disrupted, leading to characteristic symptoms of these conditions. Furthermore, the loss of McSCs can also contribute to the development of alopecia, highlighting the importance of these cells in maintaining skin and hair health.

To harness the therapeutic potential of McSCs, it is essential to understand the mechanisms underlying their regulation. By exploring the complex interplay of signaling pathways, researchers can develop innovative treatments for skin disorders. For instance, stem and gene therapy could be used to repopulate areas of the skin where McSCs are lacking, restoring skin pigmentation and function. Ultimately, a deeper understanding of McSCs will enable the development of more effective treatments for a range of skin conditions.

Melanocyte dysfunctions

Melanocyte dysfunction (MD) is caused by genetic mutations; inherited genetic alterations can impair melanocyte function. UV light, when exposed over an extended period of time, can cause melanocyte destruction. Hormonal imbalances and hormonal changes can both affect melanocyte activity. Too far, melanocyte stem cells have been investigated most extensively in mice; while substantial data exist in other taxa, this review focuses mostly on murine systems. One advantage of researching mouse melanocytes is that growth and apoptosis coincide with the hair follicle's growth cycle. Melanocyte stem cells (McSCs) are essential for maintaining pigmentation in both hair and skin, while also contributing to critical skin functions. Throughout the hair cycle, McSCs give rise to mature melanocytes (MCs), which synthesize melanin and deliver it to the hair shaft. They are considered a crucial reservoir of MCs for the hair pigmentary system [26, 27].

Additionally, McSCs serve as the primary source of epidermal melanocytes (MCs). In mice, factors such as UV exposure or the expression of Kit ligand can stimulate McSCs in the hair follicle (HF) bulge to migrate upward along the outer root sheath (ORS) to the epidermis, where they differentiate into mature MCs [28]. Beyond their role in normal hair and skin pigmentation, McSCs also contribute to repigmentation following stress or injury. These regenerative capabilities make McSCs a promising target for clinical therapies aimed at treating depigmentation conditions like vitiligo, which is characterized by the loss or dysfunction of epidermal melanocytes [29].

In vitiligo, McSCs located in hair follicles (HFs) can be activated by UV exposure or certain medications, prompting them to migrate to the epidermis, proliferate, and differentiate into epidermal melanocytes (MCs). These MCs then produce melanin, leading to the repigmentation of depigmented areas [30]. This type of repigmentation, which starts around the openings of hair follicles, is referred to as the "perifollicular repigmentation pattern". The identification of a "medium-sized spot repigmentation pattern" further suggests that McSCs in the dermis and exocrine sweat glands may also differentiate into epidermal MCs and contribute to vitiligo repigmentation [31]. The diversity in repigmentation patterns primarily reflects the various sources of residual melanocytic precursor cells, or McSCs, within the epidermis and hair follicles. As such, vitiligo repigmentation offers an excellent model for exploring McSC differentiation and functional mechanisms.

Understanding melanocyte dysfunctions

Melanocyte dysfunctions can arise from various factors, including genetic mutations, envi-

ronmental stressors, and disruptions in key signalling pathways. When melanocytes are dysfunctional, they can lead to a range of skin disorders, such as vitiligo, melanoma, and alopecia. In vitiligo, for instance, the loss of melanocytes results in characteristic white patches on the skin, while melanoma arises from the uncontrolled growth of melanocytes. Understanding the underlying mechanisms of melanocyte dysfunctions is crucial for developing effective treatments. This involves exploring the complex interplay of signaling pathways, including WNT/β-catenin, KITL/KIT, and EDNs/EDNRB, which regulate melanocyte development, growth, and survival. By gaining insights into these mechanisms, researchers can identify potential therapeutic targets and develop innovative treatments to restore skin pigmentation and function.

Stem cells in vitiligo re-pigmentation

Follicular and epidermal melanocytes are evolutionarily related, with epidermal melanocytes emerging from follicular ones [32]. Hair follicle melanocytes play an important role in the repigmentation of vitiliginous lesions. The migration of precursor melanocytes - later identified as melanocyte stem cells (MSCs) - within the central region of the hair follicle has been linked to the re-pigmentation process triggered by both chemical and physical stimuli [33]. Cui et al. found that in vitiligo-affected skin, DOPA-positive melanocytes were selectively destroyed, whereas DOPA-negative melanocyte stem cells located in the outer root sheath (ORS) of the hair follicle remained intact [34].

Melanocyte stem cells (MSCs), which are dormant melanocyte precursors, have been detected in the lesional epidermis of vitiligo patients even after 25 years [35]. Similarly, Song et al. [36] identified a reservoir of melanocytes in the outer root sheath (ORS) of white hairs within depigmented skin. It is believed that MSCs contribute to vitiligo repigmentation by dividing and migrating from the hair follicle surface into the surrounding epidermis. Nishimura et al. demonstrated that hair follicle stem cells (HFSCs) located in the bulge region can ascend into the epidermis, initiating peri-follicular repigmentation that spreads outward in a concentric fashion, ultimately leading to diffuse repigmentation [22]. However, this process occurred only when the epidermis expressed steel factor (SLF), the ligand for the c-Kit receptor. These findings suggest that SLF plays a critical role in establishing new pathways between the follicular ORS and the epidermis, thereby facilitating the migration of melanoblasts into unoccupied epidermal niches.

Hair follicle - localization of melanocyte stem cells (MSCs)

Melanogenesis is essential for hair pigmentation [37]. Melanocyte activity in hair follicles and melanin transfer to hair shafts are necessary to keep normal hair colour. Melanocyte activity is controlled by a number of signalling pathways and variables. The microenvironment within the hair follicle is an essential regulator because it contains chemicals secreted by neighbouring cells, including keratinocytes and dermal papilla cells [38-40]. Signalling molecules such as melanocyte-stimulating hormone (MSH), stem cell factor (SCF), endothelin-1, and WNT play key roles in regulating melanocyte activity and melanogenesis during hair development. As hair pigmentation occurs, mature melanosomes are transferred from melanocytes to keratinocytes in the cortical and medullary regions of the hair shaft, imparting color to the hair. While various transport proteins and structural components are involved in the transfer and distribution of melanosomes to both skin and hair keratinocytes, the precise mechanisms behind these processes remain unclear.

Disruptions in melanogenesis and pigmentation processes can lead to hair greying. With age, both the number and functionality of melanocytes decline, leading to reduced melanin synthesis and distribution. Preclinical studies, particularly in rodents, have shown that impaired self-renewal of melanocyte stem cells is a key contributor to hair greying. As melanin levels decrease, hair gradually loses its colour, resulting in the appearance of grey or white strands. Additionally, factors such as genetics, environmental stressors, oxidative damage, and inflammation can affect melanocyte function and melanin production, contributing to premature greying [41, 42].

Conclusion

Melanocyte stem cells (McSCs) play a vital role in sustaining melanocyte populations in healthy

adult skin and its appendages. Research into McSCs has provided valuable insights into the molecular pathways involved in normal melanocyte development, as well as in conditions such as melanoma and vitiligo. While earlier studies have identified the location, origin, and markers of McSCs in human skin, a comprehensive understanding of their characteristics is still lacking. In this review, we highlight recent advances in melanocyte biology from both basic and clinical research. However, due to space limitations, we are unable to provide an exhaustive overview of all key molecules involved in melanogenesis. Defining the specific signalling pathways and mechanisms of communication among human McSCs is essential for advancing skin regeneration research. This can be achieved through technologies such as single-cell RNA sequencing (scRNA-seq), gene editing, spatial transcriptomics, and whole-genome sequencing. The repigmentation of skin and hair is anticipated to be an early milestone in the application of stem cells, ultimately laying the groundwork for regenerative therapies in tissue and organ restoration.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Sharique A Ali, Department of Biotechnology, Saifia College, Barkatullah University, Bhopal 462001, India. ORCID: 0000-0002-0378-7385; E-mail: drshariqueali@yahoo.co.in

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