



(REVIEW ARTICLE)



From hair colour to diagnosis

V. Broshtilova^{1,2,*}

¹ Department of Dermatology and Venereology, Military Medical Academy, Sofia, Bulgaria.

² Department of Infectious diseases, Parasitology and Dermatology, Faculty of Medicine, "Prof. Dr Paraskev Stoyanov", Varna, Bulgaria.

GSC Advanced Research and Reviews, 2021, 07(02), 068–072

Publication history: Received on 10 April 2021; revised on 11 May 2021; accepted on 13 May 2021

Article DOI: <https://doi.org/10.30574/gscarr.2021.7.2.0107>

Abstract

Hair pigmentation contributes extremely to the visual appearance and human-to-human communication, thus exerting enormous sexual and social impact. Follicular melanogenesis depends on genetic, biochemical and physical phenomena as well as proper epithelial-melanocytic interaction. Shades of grey, yellow, brown, red, and black produced by melanin define the exact determination of hair colour. Versatile clinical conditions depend on genetic melanogenetic changes, pigment transfer to bulb keratinocytes defects and impaired signal transduction pathways. Herein, an update of recent scientific advances on follicular melanogenesis and its pathological-driven compartmental changes reflecting specific disease phenotypes, are presented.

Keywords: Follicular melanogenesis; Skin colour changes

1. Introduction

The whole range of human hair colour depends on two-type melanin synthesis – eumelanin and pheomelanin. The hair follicle pigmentary unit includes follicular melanocytes, keratinocytes and dermal papilla fibroblasts. The process of follicular melanin synthesis includes the production by follicular melanoblasts, the transfer of melanosomes into cortical and medulla keratinocytes and re-distribution of melanin granules into the hair shaft cortex and paracortex. The complex regulation of this activity depends on plenty of enzymes, structural and regulatory proteins, transporters, and receptors, activated or suppressed during different phases of hair life cycle and on specific levels of hair follicle. The hair pigmentation reservoir of dormant stem melanoblasts settles at the upper hair paracortex and physiologically activates in final stage of telogen as well as in pathological conditions necessitating hair re-growth

2. Melanocytes and melanogenesis

Follicular melanogenesis is strictly depending on anagen hair growth cycle. It is connected to the availability of melanin precursors, and the intrinsic signal transduction pathways and hormonal signals [1]. The most important regulators are adrenocorticotrophic hormone, melanocyte stimulating hormone, c-Kit, and the endothelin receptors with their ligands. In contrast to epidermal melanogenesis, follicular melanin synthesis is active only during anagen phase, thus being cycling-dependent [2]. Complex genetic control, regulated by more than 150 alleles at over 90 loci, is available to assure time-limited production of a wide range of enzymes, structural proteins, transcriptional regulators, transporters, receptors and their ligands. In this way, well-controlled step-wise regulation activities in different compartments are perpetuated in the following order: cellular synthesis in follicular melanocyte, organ distribution in hair follicle, and developmental steps from neural crest to melanoblast migration into the targeting skin with differentiation and proliferation of mature melanocytes.

* Corresponding author: Valentina Broshtilova

Department of Dermatology and Venereology, Military Medical Academy, Sofia, Bulgairia.

Stem melanoblasts originate from neural crests [3]. Their lineage differentiation depends exclusively on microphthalmia-associated transcription factor, endothelin 3, and fibroblast growth factor-2. The migrating c-kit positive melanocytes populate the stem-cell factor-supplying hair follicles. Thus, the crucial transcription factor, involved in the melanocytic recruitment of hairs is c-kit expression. Therefore, c-kit is always required during hair growth cycle for activation of follicular melanocytes [4].

Distinct anatomic compartments are affiliated to specific melanocytic populations. Dihydroxyphenylalanine (DOPA) - positive melanocytes are detected in the infundibulum and in the upper part of dermal papilla. This population forms the most important anagen melanogenetic pool [5]. Mid-to-lower outer root sheath, peripheral bulb and proximal hair matrix contain DOPA-negative melanocytes with c-kit and bcl-2 expression, which defines them as stem cells for melanin re-synthesis during the eliciting anagen [6].

The melanogenetic follicular melanocytes reside in the proximal hair bulb. Compared to epidermal melanocytes, hair bulb melanin cells are larger, more dendritic, and with greater metabolic activity depicted by more extensive organelles. The transferred melanosomes are minimally digested with perfectly kept melanin. This is another difference from the extremely degraded melanin brought to epidermal keratinocytes. A consequence of this differential process is the possibility of eumelanin whites to have black hair, fair skin, and blue eyes [7].

3. Eumelanin and pheomelanin

Tyrosine is converted to DOPA via tyrosinase. Once formed, DOPA is proceeded either to eumelanin or pheomelanin depending by the local concentrations of hydrogen ion, metal cations, and thiols [8]. The regulation of this process depends strongly on species-specific tyrosinase proteins (TRP), which are highly conservative and biochemically stable. They assure eumelanin synthesis through appropriate processing of tyrosinase, stabilization of its enzymatic activity, and maintenance of melanosome structural integrity. The degradation of these proteins regulates the further steps of eumelanin synthesis by increasing intra cellular pH and inducing melanosome formation [9].

Melanosomes appear to be rather similar in follicular and epidermal melanocytes. They are larger and more electron-dense in black-hair follicles; smaller in brown-hair bulb and poorly melanized and often only presented by melanosomal matrix in blond. Red-hair pheomelanosomes have vesicular matrix with irregularly flocculent material. Interestingly, eumelanin and pheomelanin can co-exist in a certain human cell, however, they can only be produced in different hair cycles [10].

4. Follicular melanogenesis regulation

Normal follicular melanogenesis is crucially dependent on stem cell factor/ c-kit transduction pathway. It enhances melanin synthesis by binding of locally produced proopiomelanocortin (POMC) - derived ACTH and MSH [11]. Endorphin/ opiate receptor system can also stimulate follicular and epidermal melanogenesis by inducing dendricity and transporation of melanosomes. These intrinsic hormonal regulatory pathways are strongly dependent on environmental and genetic background [12]. Thus, families with POMC gene mutation cannot produce eumelanin and exhibit a red-hair phenotype. Decreased tyrosinase activity, inhibited by the melanogenetic factor ASP, switches the synthesis of eumelanin to pheomelanin. Other inhibitors of melanogenesis include melatonin, interleukin-1, and interleukin-6, tumor necrosis factor alpha, transforming growth factor beta, interferon gamma, glucocorticosteroids, thyronine, dopaminergic and cholinergic agonists [13].

The absence of lysosomal enzymes can affect the formation of melanosomes. The lack of the enzyme papain-like lysosomal cysteine protease cathepsin L (CTSL) exhibits vacuolation of melanocytes, causing instability of melanosome formation and improper dendritic transportation [14].

5. Greying of hair (Canities)

A single hair follicle exhibits approximately seven to fifteen melanocyte replacement cycles during the average “grey-free” life span. The age of greying is hereditary-predisposed and depends also on racial background. Usually, it is mid-30s in Whites, late-30s in Orientals, and mid-40s for Africans [15]. By 50 years of age, 50% of people have 50% gray hair. Canities is due to either gradual loss of pigment over several cycles, gradual loss of pigment along the same hair shaft, or the full de-pigmentation of hair fiber. Marked reduction of the number of active melanocytes is seen in the grey

anagen hair follicles. True gray hairs show sparse tyrosinase activity, while truly white hair bulbs are broadly negative [16].

There may also be some specific melanosome transfer defect involved. Keratinocytes in grey hairs lack melanine granules. Follicular melanocytes are spheroid and lack organelles, contain less number of smaller melanosomes and a few dendrites. Furthermore, the melanin granules are additionally packed in autophagolysosomes, thus suggesting to be defective and functionally inactive. Melanocytes in greying and white hair bulbs may be vacuolated, a common cellular response to increased oxidative stress, and may disappear very rapidly.

The beard and moustache areas commonly become grey earlier than scalp hairs. On the head, the temples are first to be affected, followed by the crown and occipital zone. Rapid “overnight” greying, although highly-dramatized, does not certainly occur. The phenomenon is due to selective breakage and shedding of pigmented hairs with retaining of non-pigmented hairs, as in an abrupt diffuse alopecia areata. Usually greying is progressive and irreversible. Anecdotal case reports of re-pigmentation can be due to alopecia areata re-growth, Addison disease and vitiligo. P-aminobenzoic acid supplementation, however, may cause darkening of grey hair.

5.1. Premature greying

The definition of this condition is greying before the age of 20 years in Caucasians and 30 years in Africans. Usually it is genetically-linked in autosomal dominant trait. Certain autoimmune disorders such as pernicious anemia, hyperthyroidism, and sometimes hypothyroidism can enhance greying in genetically-predisposed patients. Premolar hypodontia and palmoplantar hyperhidrosis can be associated with premature greying in Boeoeck syndrome. Other progeria conditions such as Werner's syndrome may cause greying as early as 2 years of age [17]. Myotonia and muscle wasting is being preceded by greying. Rothmund-Thomson syndrome is constantly presented with premature canities. It is also a common feature of 5p (cri-du-chat) syndrome.

5.2. Poliosis

A localized patch of white hair is called poliosis. Usually it affects a group of neighboring follicles. Interestingly, the melanogenesis is missing both in follicles and adherent epidermis.

5.3. Hereditary defects

In autosomal recessive oculocutaneous albinism melanocytes are structurally normal but enzymatic inactive. The melanocyte system is never completely devoid of melanin. In White patients the hair is typically yellowish-white, yellowish-red or vibrant red. In Africans the hair colour is white or yellowish brown.

Piebaldism (partial albinism) is an autosomal dominant abnormality, presented by patches of skin, devoid of pigment. The white frontlock is usually the only sign. Morphologically abnormal melanocytes with premelanosomes are detected in the affected follicles. The same biochemical changes are described in Tietz's syndrome together with deaf mutism and eyebrow hypoplasia. Dystopia cantharum with lateral displacement of medial canthi, hypertrophy of the nasal root and hyperplasia of the inner third of the confluent eyebrows is associated with piebaldism in patients with Waardenburg's syndrome [18].

The Vogt-Koyanagi-Harada syndrome consists of bilateral uveitis, labyrinthine deafness, tinnitus, vitiligo, poliosis, alopecia areata and meningitis. Usually it is triggered by acute febrile illness. Poliosis occur in 60% of patients with tuberous sclerosis. Multiple neurofibromatosis may demonstrate a patch of poliosis together with cafe-au-lait macules, and axillary and perineal freckling.

Chediak-Hagashi syndrome is an autosomal recessive defect of the membrane-bound organelles, represented by oculocutaneous hypopigmentation and improper phagocytosis. The hair is silvery-blond and sparse.

Phenylketonuria is an autosomal recessive disorder of phenylalanine hydroxylase deficiency and consecutive lack of tyrosine. Decrease pigmentation of skin, hair and eyes is associated with mental retardation, eczema and dermatoglyphism. Proper food supplementation reverse the original hair colour in 2 months. Methionine error metabolism seen in homocysteinuria causes keratinization changes with paling of hair. Raised serum levels of methionine in “oast-house” disease presents with lightening of hair and recurrent facial oedema [19].

5.4. Acquired defects

Vitiligo is the most common auto-inflammatory condition due to damage of melanocytes. Permanent pigmentary loss can occur in all diseases that may destroy the melanocytes, e.g. herpes zoster, acute pityriasis lichenoides, connective-tissue syndromes. Dental treatment may cause white patches on the beard area. X-irradiation often terminates with permanent hair loss.

5.5. Drug – and chemical- induced hair colour changes

Topically used, dithranol and chrysarobin stain light-colored hairs mahogany brown. Resorcin changes the hair colour into yellow or yellowish-brown. Peroral chloroquine modifies pheomelanin synthesis turning blond or red-hair hair into silvery white. Colour change affects first the temples and eyebrows in a patchy pattern. Some anti-psychotic drugs, interfering with keratinization, cause hypopigmented and sparse hair. Minoxidil darkens hair by converting vellus into terminal hairs. Hydroquinone suppresses tyrosine activity to cause hypopigmentation of hair and skin. In argyria, scalp hair becomes silver. Darkening of hair is seen in Parkinson's disease under bromocriptin and carbidopa therapy [20].

Many inorganic elements can be bound by the hairs. Exposure of copper in industrial conditions, swimming pools or tap water stains the hair green. Cobalt workers get bright blue hair, while handlers of indigo adopt deep blue discoloration. Grey-hair heavy smokers can become yellowish. The same discoloration can be seen under picric preparations.

5.6. Colour changes due to nutritious deficiency

As a prosthetic group of tyrosinase, copper deficiency causes achromotrichia. This is the pathological mechanism seen in Menkes' kinky hair syndrome [21]. Normal black hairs become brown to reddish, and the brown ones – blond – in patients with kwashiorkor. Intermittent protein malnutrition leads to “flag” sign-alternation of abnormal white and black bands along the hair shaft. The same phenomenon has been described in ulcerative colitis and after extensive bowel resection. Severe iron deficiency anemia can cause lightening of hair colour.

6. Conclusion

Follicular melanogenesis is extremely complicated molecular, biochemical and neuroendocrinological–depending process regulated by a plenty of intrinsic and exogenous factors. Hair colour contributes enormously to the visual appearance and self-estimate, and exerts outstanding psycho-emotional impact on the individual. A great scientific effort has been recently dedicated to elucidate the intimate nature and regulation mechanisms for follicular pigmentation control. Moreover, hair colour changes are outermost sign of specific systemic disorders that may be easily recognized and properly verified by exploration of key morphological characteristics.

Compliance with ethical standards

Acknowledgments

All my mentors and co-workers are highly acknowledged.

References

- [1] Ancans J, Tobin DJ, Hoogduijn MJ, Smit NP, Wakamatsu K, Thody AJ. (2001). Melanosomal pH controls rate of melanogenesis, eumelanin/pheomelanin ratio and melanosome maturation in melanocytes and melanoma cells. *Exp Cell Res*, 268, 26–35.
- [2] Arck PC, Overall R, Spatz K. (2006). Towards a “free radical theory of graying”: melanocyte apoptosis in the aging human hair follicle is an indicator of oxidative stress induced tissue damage. *FASEB J*, 20, 1567–1569.
- [3] Commo S, Bernard BA. (2000). Melanocyte subpopulation turnover during the human hair cycle: An immunohistochemical study. *Pigment Cell Res*, 13, 253–259.
- [4] Christoph T, Muller-Rover S, Audring H et al. (2000). The human hair follicle immune system: cellular composition and immune privilege. *Br J Dermatol*, 142, 862–873.

- [5] Gilhar A, Landau M, Assy B, Shalaginov R. (2001). Melanocyte-associated T cell epitopes can function as autoantigens for transfer of alopecia areata to human scalp explants on Prkdc (scid) mice. *J Invest Dermatol*, 117, 1357–1362.
- [6] He L, Eldridge AG, Jackson PK, Gunn TM. (2003). Accessory proteins for melanocortin signaling: Attractin and mahogunin. *Ann N Y Acad Sci*, 994, 288–298.
- [7] Costin GE, Valencia JC, Vieira WD, Lamoreux ML, Hearing VJ. (2003). Tyrosinase processing and intracellular trafficking is disrupted in mouse primary melanocytes carrying the underwhite (UW) mutation. A model for oculocutaneous albinism (OCA) type 4. *J Cell Sci*. 2003, 116, 3203–3212.
- [8] Dupin E, Le Douarin NM. (2003). Development of melanocyte precursors from the vertebrate neural crest. *Oncogen*, 22, 3016–3023.
- [9] Gillbro JM, Marles LK, Hibberts NA, Schallreuter KU. (2004) Autocrine catecholamine synthesis and the beta 2 adrenoceptor signal promote pigmentation in human epidermal melanocytes. *J Invest Dermatol*, 123, 346–353.
- [10] Hara M, Yaar M, Byers HR, Goukassian D, Fine RE, Gonsalves J, Gilchrist BA. (2000). Kinesin participates in melanosomal movement along melanocyte dendrites. *J Invest Dermatol*, 114, 438–443.
- [11] He L, Eldridge AG, Jackson PK, Gunn TM, Barsh GS. (2003). Accessory proteins for melanocortin signaling: Attractin and mahogunin. *Ann NY Acad Sci*, 994, 288–298.
- [12] Jimbow K, Park J, Kato F, Hirosaki K, Toyofuku K, Hua C, Yamashita T. (2000). Assembly, target-signaling and the intracellular transport of tyrosinase gene family proteins in the initial stages of melanosome biogenesis. *Pigment Cell Res*, 13, 222–229.
- [13] Kushimoto T, Valencia JC, Costin GE, et al. (2003). The melanosome: An ideal model to study cellular differentiation. *Pigment Cell Res*, 16, 237–244.
- [14] Marles LK, Peters EM, Tobin DJ, Hibberts NA, Schallreuter KU. (2003). Tyrosine hydroxylase isoenzyme I is present in human melanosomes: A possible novel function in pigmentation. *Exp Dermatol*, 12, 61–70.
- [15] Nakamura M, Tobin DJ, Richards-Smith B, Sundberg JP, Paus R. (2002). Mutant laboratory mice with abnormalities in pigmentation: Annotated tables. *J Dermatol Sci*, 28, 1–33.
- [16] Oyeaug L, Plante E, Vage DI, Omholt SW. (2002). The regulatory basis of melanogenic switching. *J Theor Biol*, 215, 449–468.
- [17] Slominski A, Paus R.(1993). Melanogenesis is coupled to murine anagen: Toward new concepts for the role of melanocytes and the regulation of melanogenesis in hair growth. *J Invest Dermatol*, 101, 90–97.
- [18] Stenn KS, Paus R. (2001). Controls of hair follicle cycling. *Physiol Rev*, 81, 449–494.
- [19] Slominski A, Wortsman J, Przemyslaw M, Schallreuter K, Paus R, Tobin D. (2005). Hair follicle pigmentation. *J Invest Dermatol*, 124, 13–21.
- [20] Ito T, Ito N, Bettermann A, Tokura Y. (2004). Collapse and restoration of MHC class-I-dependent immune privilege: exploiting the human hair follicle as a model. *Am J Pathol* 164, 623–634.
- [21] Lerner AB, Fitzpatrick TB. (1950). Biochemistry of melanin formation. *Physiol Rev*, 30, 91–126.