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Age-related graying of the hair — a brief summary of potential mechanisms

Monika Armatys[1], Agata Kłosowicz[2], Anna Wojas-Pelc[2]

[1]*Medical student, Collegium Medicum, Jagiellonian University, Cracow*
[2]*Department of Dermatology, University Hospital in Cracow*

ABSTRACT

Graying of the hair is one of the most eye-catching phenotypic changes related to the chronological aging. During the last decades, scientists have engaged in research that has increased our understanding of different mechanisms of aging of a hair follicle, however many aspects of this process remain unclear. Progressive hypopigmentation of the hair shaft has been associated with decrease in number of melanocytes and tyrosinase hypoactivity in the hair bulb along with the depletion of melanocyte stem cells (MSCs) in the bulge area. Pathogenesis of graying may involve oxidative damage and incompetent MSCs maintenance. Moreover, other factors such as defective melanosomal transfer as well as insufficient neuroendocrine stimulation of MSCs and melanogenesis are hypothesized to play an important role.

Key words: graying, hair follicle, melanocytes

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INTRODUCTION

Hair pigmentation loss is one of the most eye-catching phenotypic changes related to the chronological aging. Although graying is not a severe skin condition, it may have an impact on one's self-esteem, psychological health and social interactions [1, 2]. The aim of this paper is to summarize in a concise manner the mechanisms behind progressive hypopigmentation and eventual loss of the hair pigment due to the process of aging. White hair or hypopigmentation can also be a sign of various pathological conditions, such as genetic syndrome [3], autoimmune diseases, hormonal imbalance, nutritional and micronutrient deficiencies [4]. If this condition occurs in young patients (under 20 years of age in Caucasians, 25 in Asians and 30 in Africans), it is referred to as premature hair graying [5]. However, both, pathologically-induced and premature hair graying, exceed the scope of this review.

BACKGROUND

Hair color is the result of many factors, such as distribution, type and proportions of the pigment — melanin — along with physical properties of the hair shaft [1]. Depending on genetic and environmental factors, it is individually unique and dynamically changes throughout the lifetime [6]. In medical literature, we will find numerous descriptions of pathologically- or drug-induced hair color changes [7].

Melanin, next to carotenoids and hemoglobin, is one of the most important skin pigment classes [2]. For hair pigmentation most crucial is the ratio between eumelanin and pheomelanin. Their proportion may vary, even within the same cell, based on the activity of main melanogenic enzymes: tyrosinase, gp75, dopachrome tautomerase and on the concentration of tyrosine and cysteine [5, 6]. Melanin is known for its protective role against UV damage and active oxygen species [8, 9] ,however, in certain conditions (*e.g.* UVR exposure), it can act as photosensitizer producing ROS and causing cell death, especially pheomelanin, which is more susceptible to photodamage [8]. Melanin is being produced by specialized cells — melanocytes, inside lysosome-like cell organelles — melanosomes. Melanocytes are neural crest-derived cells, located in various regions of the human body: skin's epidermis, hair follicle, the uvea, the inner ear, vaginal epithelium, meninges, bones and heart. Within hair follicle, they can be found in anagen bulb, epithelial part of a hair, right above the papilla. Single melanocytes, similar to the epidermal ones, can also be found in the infundibulum and the sebaceous gland [10]. Follicular melanocytes are larger and more dendritic than epidermal

Address for correspondence:
Agata Kłosowicz, MD, Department of Dermatology in the University Hospital in Cracow, Kopernika, 31–501 Krakow, Poland, e-mail: agata.klosowicz@viamedica.pl

melanocytes. Melanogenesis in follicular melanocytes is periodical, synchronized with hair growth cycle, unlike in epidermal ones, which synthesize melanin continuously.

Melanocyte stem cells (MSCs) are amelanogenic precursor cells of melanocytes, settled in the bulge, the subbulge area and sweat glands [1–5]. These cells migrate from neural crest to specified locations during embryogenesis. The process of migration and devotion to melanocyte lineage is strictly regulated by signals from developing skin such as KIT/SCF interactions [6], MITF, SOX10, PAX3, FGF-2, ET3 [11]. Some of these cells undergo a processes of proliferation and differentiation into mature melanocytes; the rest of them create a quiescent fraction of melanoblasts, to eventually differentiate in the future and provide melanogenically active melanocytes. MSCs do not synthesize melanin and are more susceptible to damage and apoptosis.

The hair follicle pigmentary unit, located in the bulb, comprises five keratinocytes and one melanocyte providing them with pigment or one keratinocyte and one melanocyte in the hair bulb matrix [6]. This unit's melanogenic activity is regulated by fibroblasts and endocrine, paracrine and autocrine hormones *e.g.* α-MSH and ACTH.

MECHANISMS

The visual effect of "graying" of the hair is a result of hypopigmentation and eventual pigment loss in the hair. The age of onset varies between individuals and is estimated to be 34 ± 9.6 years in Caucasians and 43.9 ± 10.3 years in Africans [12].

OXIDATIVE STRESS — 'FREE RADICAL' THEORY

Melanocytes are particularly prone to endogenous and exogenous oxidative damage [13]. Mitochondria are especially susceptible to ROS because their DNA is less protected than genomic DNA. In result, generated mutations lead to cell death [6]. Melanocytes have naturally high levels of BCL-2 (antiapoptotic oncogene) and it is speculated that in areas of ROS generation *e.g.* during melanogenesis, BCL-2 prevents apoptosis by regulating anti-oxidant pathways [6]. Factors such as inflammation [14], psycho-emotional stress [15], UV-light [16] or smoking [17] can also trigger oxidative stress. Oxidative stress-induced hair follicle changes include apoptosis and decrease in number of melanocytes in the bulge and the bulb regions, absence of oxidative stress-protectors (*e.g.* BCL-2) and melanocyte growth factors (*e.g.* c-Kit), higher frequency of associated mitochondrial DNA damage [13], ectopic differentiation of MSCs in the hair bulb below Auber's line [13, 18] and loss of responsiveness to stem cell factor (SCF) stimulation during migration and pigmentation [13]. Further identification of massive H_2O_2-concentrations in the gray hair shaft and low levels of catalase, methionine-S-sulfoxide reductase A and B (MSRA and MSRB) suggested that the lack of melanin is caused by oxidative damage to tyrosinase and the consequent impairment in its function [19].

EXHAUSTION AND INCOMPLETE MSCS MAINTANANCE IN THE BULGE

Melanocytes are melanogenically active during anagen phase, however, their activity and function during catagen and telogen phases remain unclear [5]. Maintenance of differentiated melanocytes is partly regulated by KROX20+ hair shaft progenitors. These hair precursor cells produce a protein called stem cell factor that is showed essential for hair pigmentation [20]. Some dendritic melanocytes with undetectable melanogenic enzymes are present in catagen hair follicle [21]. One possible explanation is that melanocytes undergo de-differentiation during catagen phase, only to re-differentiate during the next anagen phase [22]. Another scenario identifies these cells with immature melanocytes derived from MSCs reservoir area since mature melanocytes are removed by apoptosis each cycle [22]. Dysregulation of signaling pathways (*e.g.* NOTCH [23, 24], TGF-β [25]) and transcription factors (*e.g.* MITF [26, 27], SOX10, PAX3 [28]) disrupts equilibrium between maintenance and differentiation of MSCs [28]. Hair follicle can produce intensely pigmented hair at a rate of 1 cm per month for up to 3–5 years, which shows how impressive the synthetic capacity of melanocytes is [5, 6]. An average human scalp hair follicle experiences around 7–15 melanocytes replacements, before reaching the point of exhaustion of this synthetic capacity, which equals about 45 years [5, 6, 22]. Hypopigmentation and loss of melanocytes seem to be temporally preceded by loss of melanocyte stem cells [15]. This may suggest that graying of the hair arises from MSC [26]. Physiological aging of MSCs can be associated with defective migration [6], ectopic melanocyte pigmentation or differentiation within the niche [13, 18, 26]. BCL-2 deficiency is especially dangerous for MSCs, as it tremendously accelerates their aging process [26]. Additionally, an increase in the incidence of hair graying has been linked to progressive telomere loss on mice with increased age [29].

DEFECTIVE MELANOSOMAL TRANSFER

Observations of melanin debris deposits in the hair bulb and surrounding tissues suggest defects in melanosomal transfer of the pigment to keratinocytes [2]. In hypopigmented hair melanocytes change their morphology — they are more vacuolated and contain fewer and smaller melanosomes [22]. Melanosomes can be found inside autophagolysosomes, probably due to their defect or a melanin/melanin metabolites leakage [2, 6, 22]. This eventually leads to degeneration and apoptosis of melanocytes. Interestingly, an increase in dendritic cells was reported in a surround-

ing area, possibly because of melanocytes' degenerative changes [2, 22].

NEUROENDOCRINOLOGICAL FACTORS

Hair follicle not only is a target of various neurohormones, neuropeptides, neurotrophins or neurotransmitters but also constitutes a source of para- and autocrine neuroendocrine factors. Insufficient neuroendocrine stimulation of MSCs and melanogenesis of hair follicle may result in progressive hair depigmentation. In order to reduce oxidative damage, hair follicle developed its own equivalent of hypothalamic-pituitary-adrenal axis, that is responsible *e.g.* for α-MSH up-regulation, which activates cytoprotective and antioxidative mechanisms [30]. Apart from α-MSH and ACTH, there are multiple molecules impacting hair follicle and pigmentation *e.g.* TSH, cortisol, catecholamines, histamine or β-endorphin [30]. It is speculated that MSC activity might be also modulated by sympathetic nerves innervating their niche [31, 32]. Hyperactivity of neuronal activities, under extreme stress, leads to burst release of the neurotransmitter noradrenaline and result in MSC depletion and ectopic differentiation [32]. Whether this mechanism is also responsible for senescing hair graying remains unclear. However, there are reported cases of patients with fewer gray hair on the sympathectomized side of the scalp than on the normal side after a cervical sympathectomy [32–34].

DISCUSSION

Our understanding of the mechanisms that lead to aging in a hair follicle has increased significantly over the last decades, yet many aspects of this complex process remain unclear. The loss of hair pigmentation may result from numerous mechanisms linked to melanocytes, MSCs and melanogenesis. Further research on this cell lineage development, proliferation, differentiation and maintenance will be beneficial not only for finding new treatment strategies against graying but also to gain a better understanding of the pathogenesis other skin conditions such as melanoma.

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