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REVIEW

Gray Hair: From Preventive to Treatment

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Abstract: Aging is an inevitable natural process, with gray hair being one of its most visible signs. Hair graying holds psychosocial importance and is an excellent model for studying human pigmentation and aging in an accessible mini-organ. This phenomenon results from decreased melanin production in hair follicles, influenced by genetic, environmental, and lifestyle factors. Gray hair often poses aesthetic concerns and can be accelerated by environmental stressors, lifestyle choices, and nutritional deficiencies. Given the variation in onset and prevalence of gray hair, this study explores the underlying biological factors—namely, genetics, oxidative stress, and hormonal changes—to inform better prevention and treatment strategies. Recent advancements in prevention and treatment, such as topical melanin stimulants, antioxidants, dietary supplements, and low-level laser therapy (LLLT), offer promising approaches to managing gray hair. Understanding gray hair comprehensively—encompassing biological, psychological, and social dimensions—provides valuable insights into the aging process and can enhance overall well-being while addressing the stigma associated with aging. Our comprehensive analysis reveals that while graying correlates with certain health conditions, its primary significance is physiological rather than pathological. This understanding is essential for healthcare providers and the public to approach graying with scientific objectivity rather than social prejudice.

Keywords: aesthetic, oxidative stress, preventive, curative, aging, hair graying

Introduction

Hair graying is a prominent sign of aging, commonly attributed to a decrease in follicular melanocyte stem cells (MSCs) or their dysfunction, affecting melanin production and transforming hair into gray.[1] All races experience the process of hair aging, but the characteristics and patterns of hair aging vary across different races, because differences in melanin levels among races lead to variations in the greying process.[2,3] Premature graying before age 30 can significantly affect self-esteem and body image, as gray hair is commonly associated with aging. This early onset can be particularly distressing for younger individuals, impacting their self-confidence and social perceptions.[4–8]

Hair graying, also known as canities or achromotrichia, is a natural part of aging, but its onset and progression can be influenced by intrinsic and extrinsic factors. Psychological stress is widely recognized as a major contributor to premature hair graying (PHG), supported by numerous studies in both humans and animal models.[1,9–11] The underlying mechanisms involve the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis, mediating stress response and influencing hair follicle biology. Hair follicles are innervated by sympathetic and sensory nerves that project to regions such as the infundibulum, isthmus, and bulge, with nerve distribution dynamically changing across the hair cycle, particularly with increased longitudinal fibers during early anagen.[4] Stress-induced sympathetic activation can deplete melanocyte stem cells in the follicular bulge through norepinephrine signaling, reducing melanin production and irreversible pigment loss. In addition to stress, genetic predisposition plays a central role in determining the age of onset and rate of hair graying. Hair pigmentation is regulated by melanogenesis within the follicle and modulated by various factors, including melanocyte-stimulating hormone (MSH), adrenocorticotropic hormone (ACTH), endothelin-1, prostaglandins, leukotrienes, fibroblast growth factors, nitric oxide, catecholamines, as well as essential vitamins and minerals.[12] Furthermore, exposure to genotoxic agents such as chemotherapy drugs (eg, busulfan and mitomycin C),

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environmental toxicants, oxidative stress, and radiation can also contribute to PHG by damaging melanocytes or disrupting melanogenic signaling.[11]

Hair color is determined by melanin content in the follicles.[13,14] A deficiency in melanin leads to graying, with mechanisms including melanin dysfunction and loss influenced by genetic, physiological, environmental, lifestyle, nutritional status, and medical factors.[15] Reactive oxidative stress (ROS) increases damage to tissues and biomolecules, including proteins and Deoxyribonucleic Acid (DNA). As hair grows, melanin synthesis in the follicle releases high levels of ROS.[13,16] Research has shown that hydrogen peroxide (H_2O_2) accumulates in gray hair follicles, causing irreversible tyrosinase inactivation by oxidizing methionine residues. In gray hair follicles, various stressors impair the antioxidative system, leading to increased ROS and premature senility of MSCs.[4,17] Conversely, black hair follicles can express high B cell lymphoma/leukemia type 2 (BCL2) levels, enabling survival under ROS.[16] Aging increases oxidative stress, impairs antioxidant defenses, elevates ROS, and disrupts MSCs function by altering hair follicle structure and microenvironment, ultimately impairing melanin synthesis.

Recent advancements in preventing and treating gray hair include topical treatments that stimulate melanin production, antioxidants to combat ROS, and dietary supplements rich in vitamins and minerals.[18] Low-level laser therapy (LLLT) is also emerging as a potential treatment to improve hair health and pigmentation.[19] Integrating these new approaches aims to provide more effective solutions for managing gray hair. Innovations such as the synthetic biology approach for colorant production and novel extraction techniques for natural dyes are being explored to develop safer and more effective treatments.[5,20,21]

Understanding the biology of hair graying is essential for developing effective therapies and gaining insights into aging and overall health. This research can help reduce stigma by fostering a more informed and positive view of natural changes. Identifying genetic, environmental, and psychological factors enables preventive strategies such as stress management, nutritional support, and toxin avoidance. Therapeutically, advances may lead to treatments that restore melanocyte function or stimulate melanogenesis through drugs, supplements, or stem cell approaches. Integrating scientific knowledge with cultural perspectives can help address the psychological impact of graying and improve quality of life.

Myths Surrounding Gray Hair

The emergence of gray hair has long been surrounded by various myths and misconceptions, which often blur the line between scientific fact and folklore. One common myth is that stress or shock can instantly turn hair gray. However, the rare condition known as canities subita (also called Marie Antoinette syndrome, Thomas More syndrome, or nocturnal aging phenomenon) describes a rapid, but not instantaneous, whitening of the hair that occurs over a short period following severe psychological trauma. Instead, stress can exacerbate underlying genetic or environmental factors, contributing to the gradual graying process.[22]

Another prevalent myth is that pulling out gray hair will result in more gray hairs growing back. This belief is unfounded, as graying is determined by the overall activity of melanocytes in the hair follicle and not by individual hair removal. However, pulling out gray hair can damage the follicle and potentially lead to other hair health issues. The belief that people with darker skin gray less than those with lighter skin is a myth.[2] While different ethnic groups may start graying at various ages (African populations typically in their mid-40s, Asians in their late 30s, and Caucasians in their mid-30s), these differences are due to genetics and biology, not skin color.[7] Gray hair is universal across all ethnicities, though it may be less noticeable or occur later in some groups.

Some also believe certain foods or supplements can reverse gray hair and restore its original color. While a balanced diet rich in essential vitamins and minerals is vital for overall hair health, no conclusive evidence exists that any specific food or supplement can reverse graying once it has occurred.[23,24] Nutritional deficiencies can contribute to premature graying, but addressing these deficiencies typically helps maintain hair health rather than restore lost pigmentation.[25] The repigmentation of white or gray hair is observed in patients receiving various medications.[24,26]

Some shampoos, conditioners, and topical treatments claim to permanently reverse gray hair, relying on marketing strategies and unproven claims rather than scientific evidence.[27] However, these claims usually lack substantial scientific

support. Most products marketed for this purpose only temporarily cover gray hair or improve hair appearance without addressing the underlying biological processes.[6,7]

Mechanism of Gray Hair Formation

The formation of gray hair results from a decline or loss of melanin production in hair follicles. Melanin, the pigment responsible for hair color, is synthesized by melanocytes within the follicle. With aging or exposure to environmental stressors, melanocyte function can deteriorate, reducing melanin levels and causing hair to appear gray. Hair graying (canities) is among the most visible signs of aging. Due to its broad psychosocial and commercial relevance, it has drawn significant attention from skin biologists, dermatologists, trichologists, and the cosmetic industry.[15,28]

The process of pigmentation in hair differs from that in the skin. In hair, each melanocyte works in conjunction with five keratinocytes to create what is known as the "hair follicle-melanin unit". By contrast, in the skin, one melanocyte is linked to 36 keratinocytes, forming an "epidermal-melanin unit". Unlike skin, where pigment production is a constant process, hair pigmentation is closely tied to the phases of the hair growth cycle. During the anagen phase, hair is actively pigmented, but this pigment production halts in the catagen phase and is absent altogether during the telogen phase.[7]

Hair follicles are equipped with a reservoir of stem cells, which gives them the remarkable ability to regenerate and produce hair throughout an individual's life. Melanocytes in the hair follicle, including melanoblasts that differentiate into MSCs, migrate to the hair bulb and become active during the anagen phase. They produce melanin and possess antioxidant defenses against ROS generated during melanogenesis.[13] MSCs are necessary for replenishing their differentiated, pigment-producing progeny to maintain the coloration of the hair fiber.[29] Aging contributes to structural changes in hair follicles, such as a decline in melanocyte stem cells (MSCs) and modifications to the follicular microenvironment, impairing melanin synthesis. At the molecular level, this involves altered regulation of genes involved in pigmentation, particularly those encoding tyrosinase, a key enzyme in melanin biosynthesis. Reduced expression or activity of tyrosinase leads to diminished melanin production and, ultimately, hair graying. Alterations in other melanogenesis-related genes, such as tyrosinase-related proteins (TRPs) and melanocyte-inducing transcription factor (MITF), further contribute to graying.[13,30] The hair follicle microenvironment is crucial in regulating stem cell behavior. For instance, acute stress induced by resiniferatoxin results in the loss of MSCs from the hair follicle bulge, while differentiated melanocytes remain unaffected, leading to unpigmented hair. The β2 adrenergic receptor (ADRB2) on MSCs is critical in stress-induced hair graying. Even without stress, noradrenaline signaling can trigger graying, as shown by the appearance of white hair following resiniferatoxin injection in immune-deficient mice. Figure 1 shows how various factors regulate hair follicle pigmentation. Hormones from the hypothalamic– pituitary–thyroid (HPT) and HPA axes influence melanin production, such as thyrotropin-releasing hormone (TRH), triiodothyronine (T3), tetraiodothyronine (T4), corticotropin-releasing hormone (CRH), proopiomelanocortin (POMC), α-MSH, and adrenocorticotropic hormone (ACTH). Growth factors like nerve growth factor (NGF), Stem cell factor (SCF), and hepatocyte growth factor (HGF) support melanocytes, while transforming growth factor-β (TGF-β) and glucocorticoid receptor (GR) inhibit them. Circadian regulators, brain and muscle ARNT-like 1 (BMAL1) and period circadian regulator 1 (PER1), affect pigmentation timing, ensuring hair color precision.

Melanogenesis is the process by which melanocytes produce melanin within melanosomes, protecting against ultraviolet (UV) radiation and neutralizing free radicals. Positive regulators of melanin production include endothelins, histamine, and eicosanoids, which act through cell surface receptors. A key element in this process is the *melanocortin-1 receptor* (*MC1R*) and its ligand α-MSH, which regulate cyclic adenosine monophosphate (cAMP) levels, essential for pigmentation. L-tyrosine and L-dihydroxyphenylalanine (L-DOPA) also serve as substrates and regulators of melanogenesis.[13] With aging, graying of hair often results from weakened or defective melanocytes. Conditions like vitiligo disrupt melanin synthesis due to the absence or malfunction of melanocytes, with the disease's development involving the destruction of melanocytes and obstruction of the melanin production pathway.[32]

MITF uniquely suppresses genes related to type I innate immune signaling linked to hair graying. Research has shown that white hair follicles contain more immune cells than black hair follicles, suggesting a connection between immune system activity and the graying of hair. Additionally, dermal white adipose tissue surrounding hair follicles produces

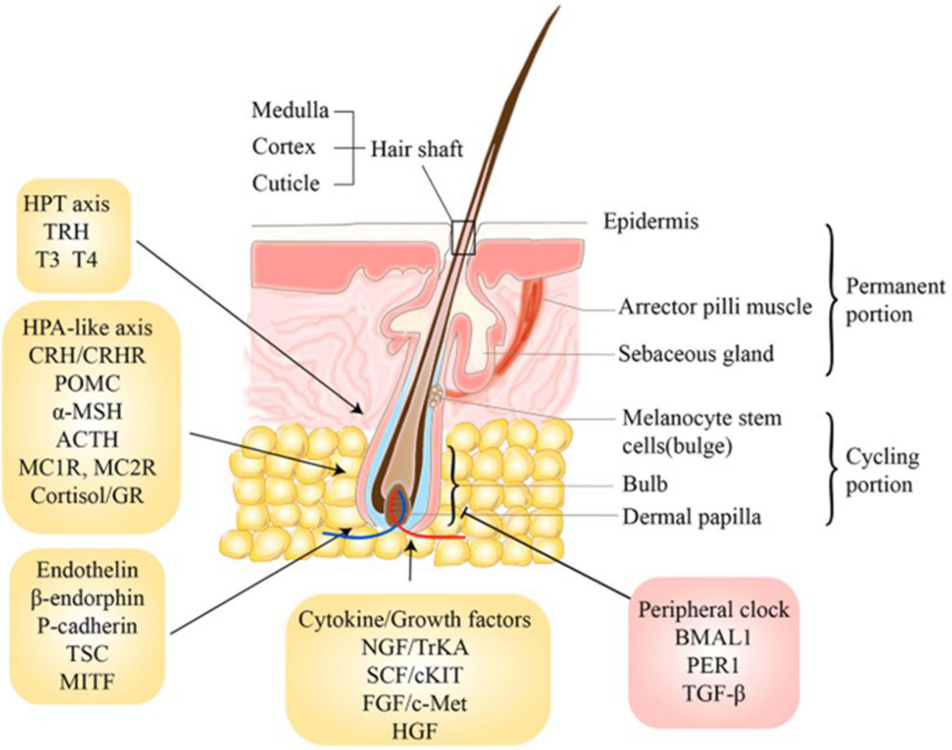

Figure 1 Schematic structure of the hair and regulators of human hair follicle pigmentation. Multiple positive (indicated by arrows) and negative (indicated by inhibitor lines) factors regulate human hair follicle pigmentation. Reprinted from *Ageing Res Rev*, volume 89, Wang S, Kang Y, Qi F, Jin H. Genetics of hair graying with age. 101977, copyright 2023, with permission from Elsevier.[31]

Abbreviations: HPT, hypothalamic– pituitary–thyroid; TRH, thyrotropin-releasing hormone; T3, triiodothyronine; T4, tetraiodothyronine; HPA, hypothalamus–pituitary–adrenal axis; CRH, corticotropin-releasing hormone; POMC, proopiomelanocortin; α-MSH, alpha-melanocyte-stimulating hormone; ACTH, adrenocorticotropic hormone; MC1R, melanocortin receptor; GR, glucocorticoid receptor; TSC, tuberous sclerosis complex; MITF, microphthalmia-associated transcription factor; NGF, nerve growth factor; TrkA, tyrosine receptor kinase A; SCF, stem cell factor; c-KIT, tyrosine-protein kinase Kit; FGF, fibroblast growth factor; c-Met, tyrosine-protein kinase Met; HGF, hepatocyte growth factor; BMAL1, brain and muscle ARNT-like 1; PER1, period circadian regulator 1; TGF-β, transforming growth factor-β.

adiponectin, which inhibits *MITF, TYRP1*, and *WNT10B* expression, reducing melanogenesis. Changes in the perifollicular microenvironment may help explain age-related hair graying.[13]

Current evidence indicates that hair graying arises from multiple interrelated biological mechanisms that differ among individuals. These include cumulative oxidative stress, DNA damage, overactivation of the mechanistic target of rapamycin complex 1 (mTORC1) signaling, melanocyte senescence, and reduced production of pigmentation-promoting factors in the hair matrix. Various regulators include genetic predispositions (including DNA repair deficiencies and IRF4 variants), peripheral clock genes, P-cadherin signaling, neuro-mediators, HGF, KIT ligand secretion, and impaired autophagic flux. These alterations result in decreased melanogenesis, mediated by MITF and tyrosinase, and hinder the transfer of melanosomes to precortical matrix keratinocytes. This process leads to depletion of melanocytes and their progenitors in the hair follicle pigmentary unit (HFPU). Hair graying becomes irreversible when bulge melanocyte stem cells (MSCs) are exhausted, which typically occurs at a later stage.[28]

Hair graying emerges from an intricate interplay of biological factors that vary among individuals, primarily driven by the accumulation of oxidative and DNA damage, hyperactive mTORC1 signaling, premature melanocyte aging, and insufficient production of pigmentation-promoting factors within the hair matrix. This process is regulated by diverse mechanisms, including genetic elements like DNA repair efficiency and IRF4 gene variations, peripheral circadian rhythm genes, P-cadherin signaling pathways, neurotransmitters, growth factors (HGF and KIT ligand), and cellular recycling processes. MSCs are particularly susceptible to genomic damage, which can lead to premature differentiation or death, ultimately depleting the melanocyte reservoir in hair follicles. This process is exacerbated by telomere shortening, which occurs naturally with age but can be accelerated by oxidative stress and environmental factors, leading

to cellular senescence and decreased melanocyte function.[28] When DNA repair pathways become disrupted, particularly those involving base excision repair and nucleotide excision repair, accumulated DNA damage triggers p53-mediated responses, which can induce cell cycle arrest, apoptosis, or premature differentiation of MSCs, directly contributing to the graying phenotype.[31,33,34]

mTORC1 is a protein complex that senses the availability of nutrients, growth Factors, and the presence of cellular stresses to coordinately regulate multiple physiological cellular processes like cell growth, proliferation, autophagy, organelle biogenesis, and Wnt signaling.[35,36] Growing evidence indicates that mTOR signaling maintains hair follicle cycling and stem cell stability, potentially as a key mediator in VDR deficiency-induced hair follicle damage and alopecia.[37] Studies using cultured human scalp hair follicles reveal that gray/white follicles show elevated mTORC1 activity, while rapamycin-mediated mTORC1 inhibition enhanced growth and pigmentation through increased α-MSH production. Conversely, reducing TSC2, a mTORC1 inhibitor, decreased pigmentation. These findings suggest that mTORC1 inhibition is a potential therapeutic strategy for hair loss and pigmentation disorders.[35]

Multiple additional mechanisms contribute to hair graying, including MSCs depletion through oxidative stress and DNA damage pathways. While neurohormonal mediators and cytokines play critical roles in regulating skin functions, their dysregulation can lead to inflammation, pigmentation abnormalities, premature aging, and skin cancers.[38] However, it is noteworthy that the regulatory mechanisms of pigmentation in the skin and hair are diverse, moving forward. Skin color is determined by melanocytes located in the outer layer of the skin, which is called the epidermis. These cells decide the skin color and guard against UV radiation.[39,40] On the other hand, hair color is controlled by the melanocyte found in the hair follicle, which forms melanin granules, giving hair its color.[21,41] Skin and hair pigmentation have certain varying factors since these two have different functions and environments. In some regulatory pathways, such as oxidative stress and hormones, both systems can interact and influence each other. Melanocytes act as neuroendocrine cells in hair follicles by synthesizing and releasing stress-related hormones and neurotransmitters such as catecholamines, serotonin, melatonin, proopiomelanocortin peptides, and corticosteroids.[42] This is distinct from skin melanocytes involved in epidermal pigmentation and immune cell communication, whose activity is regulated by Fibroblast Growth Factor (FGF) and stress signal. Hair follicle melanocytes specifically respond to stress and hormonal signals to modulate hair color.[43,44] This specific function makes hair follicle melanocytes vulnerable to stress-induced graying, differentiating these processes from overall skin dysfunction.[10,45]

Hair growth is an energy-intensive process within hair follicles beneath the skin, driven by mitochondria within the cells. During this growth phase, hair cells respond to chemical and electrical signals, including stress hormones from the body. These exposures can alter the proteins and molecules deposited in the growing hair shaft. As hair emerges from the scalp, it hardens, preserving these molecular changes as pigmentation patterns. By examining individual hairs and correlating these patterns with life events, researchers may be able to trace a person's biological history, offering insights into the relationship between stress, health, and hair pigmentation.[1]

Several factors contribute to the decreased function of melanocytes, including genetic predispositions, ROS, nutritional deficiencies, autoimmune disorders, and environmental exposures. Genetic variants can influence the timing and extent of graying, while oxidative stress from ROS can damage melanocytes. Nutritional deficiencies in vitamins B_{12} and D, minerals such as copper and zinc, and autoimmune conditions like vitiligo and alopecia areata can also affect melanocyte function. Environmental chemicals and pollutants may accelerate melanocyte degradation.[5,19] Recent studies indicate that hydrogen peroxide (H_2O_2) accumulation in scalp hair shafts causes oxidative damage within hair follicles, leading to graying. This accumulation impairs the hair's ability to produce pigment by reducing the expression of key antioxidant enzymes like catalase and methionine sulfoxide reductases A and B. Additionally, oxidative damage to tyrosinase, a critical enzyme in melanin production, further limits melanogenesis. Environmental and lifestyle factors such as UV radiation, pollution, psychological stress, alcohol consumption, smoking, inflammation, and chronic diseases exacerbate oxidative stress, complicating efforts to prevent or treat premature graying.5 Understanding the underlying mechanisms of hair graying is crucial for developing strategies to prevent or reverse age-related changes in regenerative tissues. Interestingly, hair graying induced by ionizing radiation, such as γ-rays or X-rays, has become a valuable experimental model for studying the molecular pathways involved in this process. These insights could lead to targeted interventions for mitigating or reversing the graying of hair.[11]

Gray Hair Formation: A Multifactorial Phenomenon

The appearance of gray hair, or canities, results from a progressive loss of pigmentation in hair follicles. This depigmentation is associated with genetic, physiological, environmental, lifestyle, and medical influences. Understanding how these factors interact is essential for developing effective strategies to prevent and treat gray hair. Advances in elucidating this process's molecular and cellular mechanisms hold promise for developing targeted therapeutic approaches.

Genetic Factors

Genetic predisposition plays a significant role in determining the age of onset and rate of graying. Polymorphisms in the gene encoding tyrosinase, an enzyme essential for melanin production, can affect pigmentation efficiency. Epigenetic factors, such as DNA methylation, also modulate gene expression in hair aging. Research has identified several factors associated with PHG, including a family history of PHG, a family history of depression, and iron deficiency. Conversely, a history of HSV infection is negatively associated with PHG. Factors like a history of PHG, obesity, alcohol intake, caffeine intake, hearing loss, diet, exercise, hair loss, personal mental illness, or autoimmune diseases do not show significant associations with PHG. These findings underscore the strong hereditary component of PHG.[12]

The aging process of melanocytes significantly impacts hair graying, with various essential genes (eg, *TYR, MITF, MC1R*) involved in melanocyte development and melanogenesis. Genetic variations, particularly in the *MC1R* pathway, influence hair color and graying onset, which affect heredity and ethnicity. Optimal pigmentary unit reconstruction occurs during the first 10 hair cycles, and graying typically begins in the mid-30s for Caucasians, late-30s for Asians, and mid-40s for Africans.[31]

Molecular genetics suggests that hair pigmentation is related to the *MC1R* gene. It is a G protein-coupled receptor activated by several peptides to stimulate melanogenesis. The *MC1R* gene mutation tends to produce functional variability in PHG or canities.[46]

Multiple genes influence melanocytes' function and longevity, contributing to hair graying. One key gene is BCL2, which promotes cell survival. Lower expression of BCL2 leads to increased apoptosis (cell death) of melanocytes, reducing melanin production. Another essential gene is MITF, which regulates the expression of melanogenic enzymes, such as tyrosinase. Mutations or decreased activity in MITF can impair melanin production, contributing to graying. *Interferon Regulatory Factor 4* (*IRF4*) also plays a role in pigmentation regulation; variations in this gene have been linked to early graying.[28]

Congenital hypopigmentary disorders involve hereditary pigment defects in the iris, hair, and/or skin. Gray Hair Syndromes (GHSs), including Griscelli, Chediak-Higashi, Elejalde, and Cross syndromes, are rare autosomal recessive conditions characterized by silvery gray hair and severe multisystem impairments. This report details a rare case of Griscelli syndrome and underscores the role of clinical and trichoscopic examination in diagnosing these potentially lethal genetic disorders. Timely diagnosis and treatment are crucial for improving clinical outcomes and quality of life.[47] Figure 2 illustrates key genes and molecular pathways involved in melanogenesis, highlighting the cellular mechanisms that regulate pigment production. This figure captures the intricate cellular interactions driving the process of hair coloration.

Genomic analyses have shown that demographic processes shaped the distribution and frequency of disease-associated variants over time.[48] The genetic basis of hair graying exhibits significant variation across continental populations, reflecting diverse evolutionary histories and selective pressures. Recent genome-wide association studies (GWAS) and population genetics research have revealed specific polymorphisms contributing to these differences.[2,49,50] The *MC1R* gene exhibits significant polymorphism, with 55 single-nucleotide polymorphisms (SNPs) identified across seven geographically distinct human populations. *MC1R* nucleotide diversity was notably high (10.1×10^{-4}) compared to other genes. Regarding population differences, the most significant variation was found between Asian populations and others, primarily due to the p.R163Q polymorphism. Meanwhile, the least difference was observed among populations from the United States, Northern Europe, and Southern Europe. Interestingly, Tajima's D statistical analysis indicated positive selection in European populations, suggesting this gene may have played an essential evolutionary role in this region.[51]

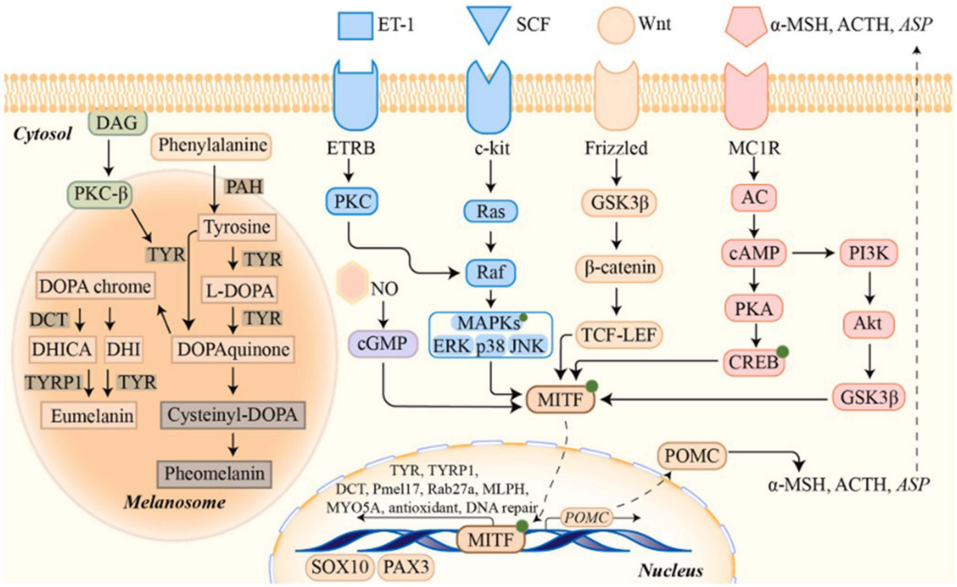

Figure 2 Main genes and molecular signaling pathways involved in melanogenesis from expression studies. Melanogenesis is the biosynthesis of melanin within melanosomes by a series of reactions. The process is initiated from either the hydroxylation of L-phenylalanine to L-tyrosine by phenylalanine hydroxylase (PAH), which is the nonobligatory step, or directly from L-tyrosine. And then L-tyrosine is hydroxylated to L-dihydroxyphenylalanine (L-DOPA) catalyzed by tyrosinase, which is the crucial rate-limiting step in melanin biosynthesis. The next step is the oxidation of L-DOPA to dopaquinone, and dopaquinone is then processed into pheomelanin in the presence of thiols, or eumelanin in the absence of thiols. Subsequently, the melanosomes containing melanin are successively transferred from melanocytes and incorporated into keratinocytes, thus generating hair pigmentation. Paracrine factors including α-MSH, ACTH, ASP, SCF, ET-1, and WNT secreted by fibroblasts and keratinocytes, bind to their corresponding receptors, and then activate multiple signaling pathways. Sequentially, the transcription of MITF is promoted, which contributes to promoting expressions of key genes related to melanogenesis such as TYR, TYRP1, DCT, Rab27a, MLPH, and MYO5A. Therefore, melanin is synthesized by elevated key enzymes, initiated from tyrosine to L-DOPA catalyzed by TYR. The next step is the oxidation of L-DOPA to dopaquinone, and dopaquinone is then processed into pheomelanin or eumelanin. With the help of transport proteins such as Rab27a, MLPH, and MYO5A, melanosomes containing abundant melanin are transported from melanocytes to keratinocytes. Reprinted from *Ageing Res Rev*, volume 89, Wang S, Kang Y, Qi F, Jin H. Genetics of hair graying with age. 101977, copyright 2023, with permission form Elsevier.[31]
Abbreviations: α-MSH, α-melanocyte-stimulating hormone; ACTH, adrenocorticotropic hormone; ASP, agonist stimulating protein; MC1R, Melanocyte-specific melanocortin-1 receptor; AC, adenylate cyclase; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; CREB, cAMP responsive element-binding protein; MITF, microphthalmia-associated transcription factor; Wnt, Wingless-related integration site; GSK3β, glycogen synthase kinase 3 beta; SCF, Stem Cell Factor; PKC, protein kinase C; cAMP, cyclic AMP; MEK, MAPK/ERK Kinase; ERK, extracellular regulated MAP kinase; ET-1, endothelin 1; ETRB, endothelin receptor type B; PAH, phenylalanine hydroxylase; L-DOPA, L-dihydroxyphenylalanine; TYP, tyrosinase; TYRP1, tyrosinase-related proteinase 1; DCT, dopachrome tautomerase (also known as TYRP2); DHICA, 5,6-dihydroxyindole-2-carboxylic acid; DHI, 5,6-dihydroxyindole; Pmel17, premelanosome protein 17; MLPH, melanophilin; MYO5A, myosin VA.

The findings indicate that polymorphisms in *IRF4* and *SLC24A4* were strongly associated with pigmentation traits, while variants in *ASIP, TYR, TYRP1, MC1R, OCA2*, and *SLC45A2* showed additional significant associations. These results underscore the role of specific genetic loci in determining pigmentation, providing valuable insights into the genetic underpinnings of hair, eye, and skin color variation in humans.[52] The melanocortin-1-receptor (*MC1R*) gene regulates human pigmentation and is highly polymorphic in populations of European origin.[53] African populations demonstrate unique genetic advantages through higher frequencies of BCL2 protective variants promoting melanocyte survival, distinct ASIP gene polymorphisms affecting melanin production, and population-specific KIT ligand variants influencing MSCs maintenance. BCL2 acts as an antiapoptotic regulatory protein that blocks cell death and is essential in regulating skin homeostasis in the outer root sheath cells of the hair follicles.[54]

Physiological Factors

Graying hair becomes more visible with age as melanin production in hair follicles declines. This results from depleted melanocyte reserves, leading to gray hair.[16] Factors like ROS and impaired antioxidant systems can accelerate the process by damaging melanocytes in the outer root sheath and bulb, disrupting the renewal and migration of MSCs.[31]

PHG can be triggered by genetics, environmental factors, or stress, which deplete the melanocyte reservoir early. As people age, more hair follicles stay in the resting phase longer, contributing to graying.[55] At the molecular level, hair pigmentation is influenced by genes and signaling pathways such as Bmpr2, Acvr2a, and the Notch 1 and Notch 2 pathways. Stem cell factor and its receptor (c-Kit) also play a role in melanogenesis during the hair growth phase.[7,55]

Physiological hair graying often follows the "three-fifty rule", where about 50% of individuals have at least 50% white hair by age 50. As melanin synthesis generates ROS, aging leads to a decline in antioxidants like catalase, glutathione, and SOD, creating an imbalance. This oxidative stress and reduced BCL2 levels diminish the anti-apoptotic capacity of MSCs. Hair graying occurs as MSCs undergo apoptosis and the stem cell pool depletes.[15,56]

In BCL2−/− mice, hair follicle morphology appears normal at birth. Still, by Day 8.5, MSCs in the hair follicle bulge have vanished, resulting in a lack of melanocytes during the second hair cycle. Research on PTEN-deficient mice (DctCrePtenflox/flox) suggests that low PTEN expression enhances AKT/ BCL2 signaling, inhibiting MSC apoptosis and preventing hair graying. However, this defect makes MSCs more susceptible to chemicals and increases melanoma risk.[57]

The ability of melanocytes to produce melanin diminishes after about ten cycles of hair follicle regeneration, leading to hair graying. Hair pulling can accelerate hair follicle cycle transitions and graying. Research by Machiko et al suggests that the proto-oncogene RET promotes hair follicle cycle transitions and MSC depletion, contributing to graying. C-Raf/ B-Raf gene double knockout mice exhibit cell cycle disruptions, with MSCs unable to enter the S phase or complete self-renewal, leading to progressive MSC loss and hair graying. Additionally, conditions like androgenetic alopecia, which involve hair follicle miniaturization and shortened hair cycles, may increase the likelihood of hair graying due to accelerated follicle cycle transitions.[58]

Immune system disturbances are associated with hair depigmentation disorders, including acute episodes of widespread alopecia areata that cause sudden graying due to pigment loss. This has led some experts to hypothesize that the autoimmune target in alopecia areata may involve the melanin pigment system.[59] Alopecia areata, a common autoimmune condition with a lifetime risk of approximately 1.7%, is characterized by immune responses to autoantigens. Research is aided by the accessibility of scalp biopsies and the use of SCID human/mouse scalp graft models, which allow disease transfer via human lymphocytes.[15,60] Canities subita, a rare condition where hair turns gray suddenly. Although the exact mechanism of canities subita is not yet fully understood, current evidence suggests a link between this condition and immune system dysregulation, particularly in autoimmune alopecia areata targeting melanocytes.[7]

Hormonal imbalances also play a significant role in hair growth and pigmentation. Disorders affecting the thyroid, adrenal glands, or pituitary glands can disrupt the levels of hormones that regulate the hair growth cycle and follicle structure. Research has indicated a potential link between endocrine dysfunction, particularly thyroid disorders, and PHG. Although specific antithyroid antibody profiles were unavailable in some studies, the high prevalence of hypothyroidism in individuals with PHG suggests a possible autoimmune component in the process.[61] Thyroid receptors are present on outer root sheath cells and play a role in regulating the frequency of the hair cycle. Hypothyroidism is associated with a decreased frequency of the anagen phase, while hyperthyroidism can result in the growth of thin hairs.[62]

PHG needs to be distinguished from other conditions causing lighter hair. Albinism can make hair white, and white hair in children might be due to neurocutaneous disorders like Griscelli, Chediak–Higashi, and Elejalde syndromes. Other conditions causing gray hair in children include Cross syndrome, Angelman syndrome, and Prader–Willi syndrome. Metabolic disorders like phenylketonuria and histidinemia can also lighten hair. Vitiligo can cause white patches in hair, known as poliosis, also seen in conditions like Piebaldism and Waardenburg syndrome.21

Nutrition Factor

Hair pigmentation, regulated by melanogenesis in follicles, is influenced by factors like MSH, ACTH, endothelin-1, prostaglandins, leukotrienes, neutrophils, fibroblast growth factor, nitric oxide, catecholamines, as well as essential vitamins and minerals.[63] Reversible hypopigmented graying has been associated with nutritional defects, especially copper and iron. The existing literature shows that PHG is associated with reduced levels of copper, and the results regarding zinc and iron are inconclusive. A study employing a young Indian population correlated PHG with lower serum ferritin, calcium, and Vitamin D3. Thus, one can prevent PHG by maintaining a balanced diet and ensuring the intake of nutrients such as B12, folate, copper, and calcium. The nutritional causes of PHG concern vitamins such as vit B9 and B12, biotin, vitamin D, and minerals, with the most common being low serum calcium, ferritin, and vitamin D3 levels.[64–67] No significant differences in serum lead and selenium levels were observed between those with and without PHG.[68] Research shows that special emphasis is placed on the incidences of hair depigmentation due to nutritional

deficiencies.[7] Nutrient deficiencies can be impaired by, for instance, malabsorption, which occurs when the body fails to digest or absorb nutrients efficiently.[69] These deficiencies are owed to defects, which comprise malabsorption, smoking, alcohol abuse, and improper diets.[63]

Sociodemographic factors, including older age, rural residence, and a positive family history, are significantly associated with PHG. Lifestyle factors, including irregular meal patterns and low fruit consumption, were also linked to PHG, with 54.1% of students with gray hair reporting poor quality of life, particularly males and rural residents.[70]

Medication-Related Factors

Chemotherapy drugs, such as busulfan and mitomycin C, are genotoxic and can cause PHG. Usually, damaged melanocytes are eliminated through apoptosis and senescence, but research by Ken et al suggests that MSCs depletion may occur due to ectopic differentiation and impaired renewal. This protective mechanism, while preventing tumorigenesis, inadvertently leads to gray hair. However, it remains unclear whether ectopic differentiation directly impacts intact MSCs or if keratinocyte stem cells help inhibit abnormal MSCs.[58]

Various drugs, including those used for Parkinson's disease, chemotherapy agents, cytostatic drugs, topical photosensitizers, resorcinol, dithranol, and frequent antibiotic use, can disrupt melanin production and influence hair pigmentation. These pharmacological effects demonstrate how external factors, such as medication, can alter the regulation of melanin and contribute to hair depigmentation.[63]

PHG has been reported as a side effect of several drugs, including chloroquine, hydroxychloroquine, imatinib (and other c-kit inhibitors), interferon, antiepileptic agents like phenytoin and valproate, and tamoxifen, among others. In most cases, drug-induced hair graying is reversible by reducing the dose or discontinuing the offending medication.[71]

Environmental Factors

Hair graying, also known as canities or achromotrichia, is a natural part of aging, but it can be accelerated by external factors such as stress, environmental toxicants, and radiation exposure. Among these, UV radiation significantly damages melanocyte DNA, accelerates cellular aging, and leads to PHG. Gray hair is particularly vulnerable to UV-A and UV-B radiation, which can cause further damage.[72] Ionizing radiation (IR), particularly at high doses (≥5 Gy), leads to irreversible DNA damage, triggering MSCs to form ectopically pigmented melanocytes (EPMs), which are associated with PHG.[11,58]

Oxidative stress is a key contributor to hair graying. ROS accumulates during the hair growth cycle, and when antioxidants like catalase and methionine sulfoxide reductase fail to neutralize these prooxidants, melanocytes are damaged, reducing pigmentation. External factors such as UV radiation, pollution, emotional stress, and inflammation exacerbate oxidative stress. Studies indicate that compromised antioxidant activity, including reduced catalase and superoxide dismutase levels, plays a crucial role in PHG.[7]

Exposure to harmful chemicals, whether through hair care products or lifestyle habits like smoking, can also accelerate hair graying. Smoking reduces blood flow to hair follicles, leading to significant melanin loss and PHG.[11,73] Similarly, hair care products containing harsh chemicals like parabens, sulfates, and silicones damage the hair cuticle and interfere with melanin synthesis, resulting in gray hair. Though these products may initially seem practical, they degrade hair health over time and contribute to untimely graying.[74]

Radiation exposure, especially from ionizing radiation, has gained attention for its impact on DNA damage, oxidative stress, and cellular senescence in melanocytes, all contributing to PHG. Sources of ionizing radiation include medical diagnostics, radiation therapy, occupational exposure, and accidental nuclear events.[11] Environmental pollutants, such as particulate matter, tobacco smoke, and heavy metals, further damage hair by triggering inflammatory responses and interfering with hair follicle function. UV exposure, exacerbated by ozone depletion, causes oxidative damage and can accelerate the aging process of hair follicles.[23,75]

Controlling ROS and stimulating melanogenesis are essential for preserving MSCs and reactivating hair pigmentation. This approach can significantly reduce hair graying (canities) within four months of consistent application.[13]

Lifestyle Factors

Chronic stress can induce inflammatory responses that damage hair follicles and disrupt the growth cycle. A significant breakthrough in understanding this phenomenon comes from a study by Zhang et al in *Nature*, which identified norepinephrine (noradrenaline) as a key factor in stress-induced hair graying. Their research demonstrated that stress causes the release of norepinephrine from sympathetic nerves, which depletes MSCs responsible for hair pigmentation.[17,76]

Zhang et al used chemogenetic techniques to show that sympathetic nerve activation directly causes MSCs depletion. They found that norepinephrine binds to the β2-adrenergic receptor (ADRB2) on MSCs, leading to altered gene expression and aberrant proliferation of these cells, ultimately resulting in their depletion. Pharmacologic and genetic interventions that suppressed MSCs' proliferation successfully preserved hair pigmentation under stress, confirming the link between norepinephrine release and hair graying (Figure 3).[17,76]

Although this study concentrated on mice, it prompts significant considerations for similar human processes, where melanocytes are found in both hair follicles and the interfollicular epidermis. The research highlights that ADRB2, while pivotal in the stress response, may have a limited role in the normal physiology of MSCs. This suggests that the mechanism by which stress induces hair graying might be an evolutionary remnant or serve a specific yet-to-be-fully-understood function in melanocyte biology. Furthermore, these findings open the door to investigating additional pathways, such as the G protein-coupled estrogen receptor (GPER). GPER has shown promise in influencing skin pigmentation and melanoma progression, indicating that alternative mechanisms may also be crucial in modulating human pigmentation and hair graying.[17,57]

Further research indicates that stress can induce hair graying after 3–5 hair cycles, with more intense stress accelerating this process in subsequent cycles. In mouse models (TyrcreERT2; Adrb2fl/fl and TyrcreERT2; GRfl/fl), sympathetic nervous system hyperactivation led to rapid MSCs depletion, making recovery from hair graying difficult. Persistent norepinephrine release under stress also results in ectopic pigmentation of melanocytes (EPMs) within the hair follicle niche, contributing further to MSCs depletion and PHG.[58]

Gray Hair: Preventive and Treatment

Prevention Strategies

Gray hair develops when melanocytes in hair follicles reduce or stop producing melanin, leading to pigment loss in new hair growth. Prevention strategies should focus on protecting melanocyte function and melanin synthesis to maintain natural hair color.

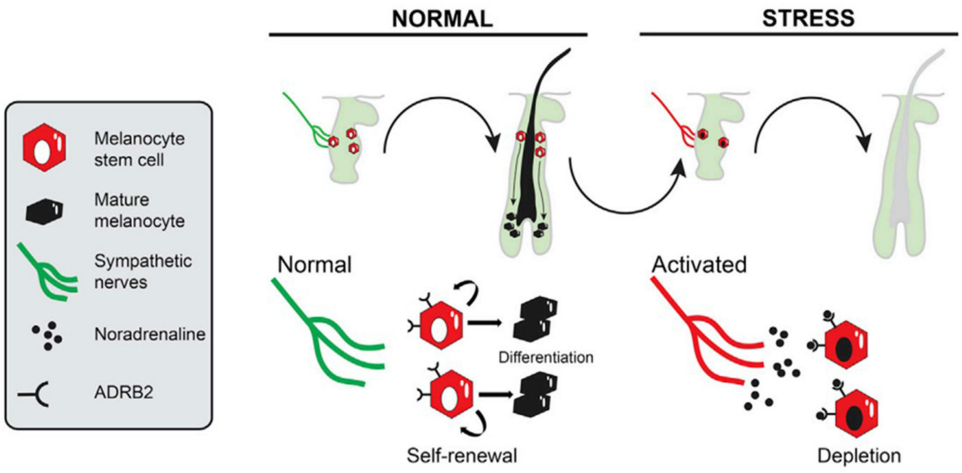

Figure 3 Stress Induces Depletion of MSCs by Sympathetic Nerve Activation Hair follicles undergo physiological cycles of regeneration. Each hair cycle produces a keratinized hair fiber, with color derived from pigment mature melanocytes produce. In mice, stress activates sympathetic nerves, releasing noradrenaline in the MSCs' niche. This results in MSCs depletion, and subsequent hair growth lacks color due to the absence of new melanocyte production. Reprinted from *Dev Cell*, volume 52(5), Huang S, Rompolas P. The psychology of gray hair. 548–549, copyright 2020, with permission from Elsevier.[17]

Nutritional Intake

The researchers highlight the importance of antioxidant-rich diets, as specific nutrients can counteract ROS.[77] Diets rich in antioxidants, vitamins, and minerals have been shown to impact hair health and potentially mitigate PHG, helping to protect against free-radical damage.[78] Antioxidants, such as those found in dark chocolate,[79] blueberries, leafy greens, pecans, beans, and artichokes, enhance melanin production and protect hair follicles from oxidative damage.[80,81] Copper is a trace element essential for melanin biosynthesis; some rich sources include shellfish, seeds and nuts, organ meats, wheat-bran cereals, whole-grain products, and chocolate. Additionally, vitamins A, C, and E play crucial roles in hair and scalp health.[25,78] Vitamin A facilitates cellular growth and differentiation, Vitamin C contributes to collagen synthesis and offers protection against ROS, while Vitamin E supports scalp health through its antioxidant properties. Adequate intake of these nutrients is associated with improved overall hair health.[23,79] Respondents with PHG show higher levels of pro-oxidants and lower levels of antioxidants than controls. The severity of graying correlates with the level of ROS. Therefore, supplementing with antioxidants is likely recommended for managing PHG.[82]

The analysis of B-complex vitamins' relationship to hair follicle metabolism reveals that out of the eight water-soluble B vitamins essential for cellular function, only four compounds - riboflavin (B2), biotin (B7), folate, and cobalamin (B12) - demonstrate a clinically significant correlation with hair loss pathophysiology. While adequate levels of these micronutrients can generally be maintained through dietary sources, biotin presents a unique case as it is endogenously synthesized, making exogenous supplementation typically unnecessary in immunocompetent individuals with normal metabolic function.[78]

Vitamin B12 deficiency can cause PGH through unknown mechanisms. About 55% of patients with pernicious anemia had graying before 50 years, compared to 30% in the control group.[7] Supplementing these essential trace elements may help reverse PHG and prevent its progression, offering a potential strategy for maintaining hair pigmentation and overall health.[83]

Beyond dietary interventions, natural ingredients have demonstrated the potential to prevent PHG. Vitamins are crucial as modulators of hair growth, highlighting their potential to promote regeneration, prevent alterations, and combat hair loss.[25] These substances are applied topically to the scalp to nourish hair follicles and may help reduce gray hair. Many phytochemicals include epigallocatechin gallate (EGCG), caffeine, capsaicin, procyanidin, onion juice, pumpkin seed oil, rosemary oil, saw palmetto, red ginseng extract, curcumin, garlic gel, and other natural products such as amino acids, marine proteins, melatonin, vitamins, and zinc, were reported to have hair growth-stimulating property.[9]

Stress Management

Norepinephrine (NA), a stress hormone, can accelerate hair graying by binding to β2 adrenergic receptors (β2AR) on MSCs. This suggests that targeting the NA-β2AR axis could be a potential strategy for preventing stress-induced hair graying. Rhynchophylline, a compound specifically targeting β2AR, shows promise in mitigating the adverse effects of NA on melanogenesis, offering a potential solution for managing stress-related hair graying.[76]

Incorporating relaxation techniques such as meditation, yoga, and deep breathing exercises is recommended to manage stress and mitigate its impact on hair health. Chronic stress can contribute to various health issues, including PHG, and can manifest as sleepless nights, anxiety, loss of appetite, and high blood pressure. Studies indicate a connection between stress and the health of stem cells in hair follicles, emphasizing the importance of stress management. Non-medical treatments like relaxation techniques generally have fewer side effects than pharmacological or surgical interventions. They are often more cost-effective, making them accessible to a broader population. However, it is essential to consider the long-term costs and effectiveness of these non-medical approaches, as they may not always yield satisfactory results in individuals with severe hair problems.[84]

Avoid Harmful Habits

Avoiding detrimental substances and practices is essential to optimize hair health and minimize adverse effects. Smoking introduces harmful chemicals that damage hair follicles and disrupt normal growth, accelerating premature graying. Similarly, excessive alcohol consumption impairs nutrient absorption and hydration, leading to poor hair health and an increased risk of hair loss and graying.[30]

Protection from ultraviolet (UV) radiation is also critical. Prolonged UV exposure can damage the hair's melanin production, causing premature discoloration. Protective measures such as wearing hats or using umbrellas during outdoor activities help preserve hair pigmentation and prevent UV-induced color loss.[85,86]

Recent research into hair care focuses on anti-aging compounds and antioxidants. Substances such as green tea polyphenols, selenium, copper, phytoestrogens, and melatonin are being studied for their potential to support hair health and counteract aging effects. While anti-aging compounds in shampoos may have limited efficacy due to dilution and short contact times, topical applications could be more effective. Antioxidants like vitamins C and E are significant for their protective role against oxidative damage.[87]

Monitoring oxidative stress markers is essential for understanding hair aging. Elevated levels of malondialdehyde (MDA) and decreased levels of reduced glutathione (rGSH) and superoxide dismutase (SOD) are linked with premature graying and systemic redox imbalance. Antioxidant supplementation may provide therapeutic benefits by addressing oxidative stress and potentially delaying or reducing the severity of premature graying.[56]

Gentle Hair Care

In selecting hair care products for sensitive hair, avoiding formulations containing harsh chemicals and synthetic additives such as parabens, petrochemicals, sulfates, and silicones is essential due to their adverse effects on health and the environment. Synthetic surfactants, in particular, contribute to pollution and can harm aquatic ecosystems.[74]

Natural and botanical ingredients are preferred alternatives. Shampoos featuring natural surfactants derived from *Schizandra mukorossi* offer advantages in biodegradability and environmental impact. These surfactants also demonstrate superior foaming and emulsification properties compared to synthetic options, thanks to their effective reduction of surface tension.[84]

Additionally, products containing APHG-1001, an extract of *Pueraria lobata*, may provide benefits such as preventing gray hair. Opting for such natural formulations ensures improved compatibility with sensitive skin and supports environmental sustainability.[18]

Clinical Considerations

For individuals concerned about hair health or experiencing premature graying (PHG), it is recommended to seek professional medical advice. Hair graying is often attributed to genetic factors and is commonly managed with temporary hair dyes, which necessitate frequent applications and may potentially damage hair follicles. Alternative treatments include hair follicle transplantation for conditions such as vitiligo and pharmaceutical agents like pifithrin-alpha and serotonin reuptake inhibitors such as fluoxetine, which may reverse graying in some cases. Continued research into the genetic and molecular mechanisms underlying hair graying is essential for developing improved prevention and treatment strategies.[31]

Consultation with a dermatologist can offer a personalized evaluation and customized management plan for gray hair. Dermatologists may employ a combination of pharmaceutical and topical interventions, though it is important to note that no current treatment provides a permanent solution for gray hair.[88]

Diagnosis of canities (premature graying) primarily involves clinical assessment. For patients without a family history of PHG, diagnostic tests for serum levels of vitamin B12, folic acid, and thyroid function are recommended. The application of trichoscopy, a non-invasive diagnostic method for examining the scalp and hair follicles, is under investigation for its utility in diagnosing canities.[47] Despite the demand for dermatological treatments, consistently effective options remain limited. Management should address underlying conditions such as vitamin B12 deficiency and hypothyroidism, which can be treated with appropriate supplementation and hormone replacement therapies. Plucking gray hairs may serve as a cosmetic solution in cases where less than 10% of scalp hair is affected, although it does not address the underlying pathology.[4,66]

Treatment Strategies

Recent research has deepened our understanding of the mechanisms behind gray hair formation. This insight offers potential for developing predictive tools and targeted interventions to address early hair aging through personalized risk assessments.

Healthy Lifestyle

A systematic approach to lifestyle modifications is essential to address ROS and support overall health effectively. A diet rich in antioxidants, vitamins, and minerals is critical for enhancing the body's capacity to mitigate oxidative stress.[77,79,89] Engaging in regular physical exercise provides significant benefits for reducing oxidative stress. Exercise promotes overall health by increasing levels of antioxidant enzymes, including superoxide dismutase (SOD) and catalase (CAT). A balanced exercise regimen, incorporating both aerobic and resistance training, effectively enhances antioxidant defenses and maintains oxidative balance.[90]

Effective stress management is integral to reducing oxidative stress. Chronic stress increases ROS production, leading to various health issues.[91] Mindfulness, meditation, and relaxation techniques are recommended to manage stress levels. Ensuring adequate sleep is crucial for recovery and maintaining oxidative balance.[84]

Monitoring and adjusting lifestyle factors play a vital role in managing oxidative stress. Tools such as oxidative balance scores (OBS) can assess the cumulative effects of diet and lifestyle on oxidative stress. Lifestyle modifications should address harmful behaviors, including smoking, excessive alcohol consumption, and obesity, which are associated with increased ROS production and cellular damage.[77]

Incorporating antioxidant-rich products into one's regimen can offer additional protection against oxidative damage. Specialized hair and skin care products formulated with antioxidants can help mitigate oxidative stress. Adopting a comprehensive approach that includes dietary, physical, and lifestyle interventions and targeted supplemental products is essential for effectively combating ROS and promoting optimal health.[23,89]

A healthy lifestyle can support curative efforts for gray hair, as it may help improve hair health and potentially slow or partially reverse graying in some cases. Ensuring a balanced diet rich in essential nutrients, including vitamins B12, B9 (folic acid), D, E, and minerals like copper and zinc, is crucial. These nutrients are key to hair pigmentation and may help when gray hair is due to deficiencies.[25,78,92]

Therapy

Hair graying, also known as canities, is primarily caused by oxidative stress, leading to increased ROS and reduced melanocytes. UV exposure, pollution, and emotional stress exacerbate this process, disrupting cellular antioxidant defenses and diminishing melanin production. Recent research has developed active ingredients that reduce ROS, protect melanocyte reservoirs, and restore hair pigmentation. In a clinical trial involving male volunteers, a significant reduction in grey hair was observed after four months of treatment, demonstrating the potential of these ingredients to combat oxidative stress and promote repigmentation.[13,72,75]

Nutritional deficiencies also play a role in hair graying. For instance, an 11-year-old boy with PHG and iron deficiency anemia experienced a return to standard hair color after iron supplementation. This highlights the potential for reversing grey hair by addressing deficiencies in essential nutrients such as iron, vitamins (B12, D, C, E), and minerals (copper, zinc). Antioxidants found in these supplements may also help mitigate oxidative stress and delay the onset of graying.[55,63,66]

Hormonal imbalances significantly influence hair pigmentation. Disruptions in thyroid hormones, such as hypothyroidism, and sex hormones, like androgens, can accelerate the graying process. Additionally, melatonin, the hormone responsible for regulating sleep, may have a protective role against hair graying. Research on triiodothyronine (T3) has shown that its topical application can promote hair growth by accelerating the transition of hair follicles from the resting (telogen) phase to the growth (anagen) phase, potentially impacting follicular melanocytes.[15]

Emerging therapies for grey hair reversal include stem cell research and LLLT. Advances in induced pluripotent stem cells (iPSCs) and hair follicle dermal papilla cells offer promise for regenerating hair follicles and restoring pigmentation in white hair. Meanwhile, LLLT, which uses low-intensity lasers to stimulate hair follicles, is being studied for its potential to reverse grey hair, although more research is needed to confirm its efficacy.[19,84,93]

Topical and oral treatments are also under exploration. Prostaglandins have been used topically to stimulate melanogenesis, while Melitane, a biomimetic peptide that activates the melanocortin one receptor, has shown promise in promoting hair pigmentation.[71] Shampoos containing antioxidants like vitamins C and E are marketed to reduce oxidative damage to hair follicles, though their short contact period raises questions about their effectiveness.[87]

Alternative approaches, including homeopathy, have been considered in treating grey hair. For example, a case study demonstrated that the homeopathic remedy Sulphur 1M led to significant recovery of grey hair. Similarly, high-dose p-aminobenzoic acid (PABA) has been reported to darken grey hair temporarily in some cases. However, results are inconsistent, and it is not widely recommended for this purpose.[94]

Recent studies suggest that the scalp microbiome may influence hair health and pigmentation. Imbalances in the microbial community on the scalp could contribute to hair aging and graying, making this an area of growing interest in grey hair research. Further investigation is needed to fully understand the relationship between microbiome and hair pigmentation.[75]

Finally, psychological stress has been shown to influence hair graying, with recent studies indicating that hair pigmentation can sometimes reverse after stress is alleviated. Molecular profiling of grey hairs revealed the upregulation of proteins related to energy metabolism and antioxidant defenses during the reversal process. These findings suggest that stress-induced graying may be temporarily reversible, providing a novel avenue for therapeutic development.[95]

Hair Coloring

Hair coloring is a popular cosmetic approach for managing gray hair, offering an immediate solution for those looking to restore their natural color or explore new shades. As a cosmetic treatment, it is widely used for aesthetic reasons and to boost self-confidence, especially when gray hair becomes a concern.[6,7]

High-quality hair dyes are commonly used to conceal gray hair, and consultation with a hair color specialist can optimize results while minimizing potential damage. Recent innovations in hair dyeing technology involve the development of surfactant-free oil-in-water emulsions that incorporate tannic acid, gallic acid, Fe(D-gluconate)2, and natural oils. These emulsions leverage the dyeing properties of the Fe^{3+}–tannin complex combined with the nourishing benefits of natural oils, offering a novel approach that eliminates the need for additional surfactants or emulsifiers.[5]

Hair dyes are categorized based on their color resistance into temporary, semi-permanent, and permanent types. Temporary dyes adhere to the hair cuticle, while semi-permanent dyes penetrate slightly into the cortex and typically last up to six washes. Demi-permanent and permanent dyes involve oxidation reactions with color precursors, allowing deeper penetration into the cortex and resulting in longer-lasting color. Differences among these dyes are related to their chromophore groups, hair fiber affinity, water solubility, and photostability, which influence their effectiveness and durability.[6,96]

Growing awareness of the adverse effects of synthetic hair dyes has led to an increased demand for safer and more environmentally friendly alternatives. While synthetic permanent dyes are effective, they may pose health risks such as allergenicity, mutagenicity, carcinogenicity, and environmental toxicity. In contrast, natural dyes derived from plant sources—including Indian gooseberry (*Emblica officinalis*), false daisy (*Eclipta alba*), lotus tree (*Zizyphus spinachristi*), and henna (*Lawsonia alba*)—are considered safer, less allergenic, and more eco-friendly. Research into these natural dyes focuses on extracting phytochemicals like quinones, tannins, and flavonoids using various techniques, including solvent, ultrasonic, microwave, supercritical fluid, and enzyme-assisted methods.[20,55]

Herbal-based dyes, utilizing natural ingredients, offer a potentially less irritating alternative to synthetic dyes. However, these natural dyes often require frequent reapplication to maintain color. Additionally, pharmaceutical formulations for addressing gray and aging hair include synthetic and natural approaches. Innovations such as Mayraki's Anti-gray Hair Color Restoring Treatment, along with anti-aging compounds like green tea polyphenols, selenium, copper, and melatonin, are being investigated for their effectiveness in improving hair health and managing premature graying.[20]

Despite their benefits, hair dyes can cause side effects, including irritant dermatitis and contact allergic dermatitis, commonly associated with p-phenylenediamine. Meta-analyses have indicated a significant risk of developing certain cancers related to hair dye use, with permanent dyes generally presenting higher risks compared to semi-permanent options. Ongoing research aims to explore anti-aging compounds and novel delivery systems, such as topical liposomal delivery of melanin, to mitigate oxidative stress and enhance overall hair health.[7]

Implications of PHG

PHG has been linked to an increased risk of coronary artery disease (CAD) in young smokers, suggesting that PHG could serve as an early indicator for clinicians to identify patients at risk for premature CAD, especially among smokers. While various risk factors for PHG have been documented, including smoking and deficiencies in vitamins (B12, folic acid, and biotin) and minerals (such as low serum calcium and ferritin), other significant factors include a family history of PHG, obesity, high blood pressure, lack of exercise, drug use, genetic syndromes, dyslipidemia, thyroid disorders, hyperuricemia, and liver function abnormalities. Among pharmacotherapeutic options, calcium pantothenate, PABA, and their combination receive a low-grade recommendation (2A). Anutailam is the only herbal agent evaluated in clinical research settings. Addressing and treating these accompanying pathologies has led to the reversal of PHG in many cases, highlighting the importance of comprehensive management.[97] The Copenhagen City Heart Study found that men with gray hair had an increased risk of myocardial infarction compared to those without gray hair.[7]

PHG typically occurs between ages 16 and 20, with females being more susceptible. Genetics significantly influence PHG, impacting social interactions as individuals with premature graying often attract attention.[98]

Perspective

Hair pigmentation is a complex process involving various cell types and their interactions within the hair follicle microenvironment. Key players include MSCs and mature melanocytes, which work alongside cells in the hair follicle bulge, bulb, and dermal papillae. Recent research has expanded our understanding by highlighting the roles of additional cells such as nerves, adipocytes, and immune cells. Fibroblasts and endothelial cells also significantly influence pigmentation, with fibroblasts affecting melanocyte proliferation and pigmentation through MAPK and WNT/β-catenin pathways, while endothelial cells stimulate and inhibit pigmentation.[4,57,99] Further studies have identified distinct melanocyte subpopulations in the human scalp using c-KIT/CD117 microbeads, revealing variations in melanosome markers and the presence of immature melanocytes.[14]

Aging has a profound impact on hair melanin and color. Research shows that increased total melanin (TM) and a higher proportion of 5,6-dihydroxyindole (DHI) units correlate with darker hair color. This change is associated with increased melanosome volume and TM but also involves complex alterations in melanosome morphology. Comparative studies between Japanese males and females reveal that both sexes experience hair darkening with age, although males tend to have darker hair at younger ages. These studies also highlight significant differences in melanosome size and pigmentation markers between sexes.[41,100]

Recent studies have explored the potential of pulsed electromagnetic fields (PEMFs) in enhancing pigmentation. In zebrafish models, PEMFs increased the expression of key melanin synthesis enzymes, such as tyrosinase-related protein 1 (TRP1) and dopachrome tautomerase (DCT), through ERK and p38 phosphorylation pathways. These findings suggest that PEMFs could be a promising approach for treating gray hair and hypopigmentation-related skin disorders.[32]

The global hair dye and color industry is valued at approximately $30 billion, with projections estimating it will reach around $42 billion by 2025. Despite this substantial market size, there is a notable lack of diversity in natural options for deep and dark pigments.[101] There is a growing interest in natural, eco-friendly hair coloring agents due to the harmful effects of synthetic dyes. Natural plant-based dyes, which utilize phytochemicals like quinones, tannins, and flavonoids, offer safer alternatives. Green, plant-based hair dyes are increasingly popular for their health and environmental benefits. They are less toxic, biodegradable, and offer antioxidant, anti-inflammatory, and antimicrobial properties. However, their industrial use faces challenges such as complex extraction processes, sensitivity to environmental factors, low dye uptake and color fastness, poor color reproducibility, reliance on transition metal mordants, and insufficient toxicological data.[20] Advances in this field include synthetic biology for dye production and encapsulation technologies to stabilize natural dyes. These innovations represent a shift towards more sustainable and less toxic hair care solutions.[20]

Current and emerging treatments for hair graying include gene therapy, targeted molecular drugs, and advanced hair transplant technologies. New hair care products incorporating peptides, growth factors, and plant extracts aim to stimulate hair growth and maintain hair health. Additionally, novel surfactant-free emulsions using tannic and gallic acids and plant oils provide effective natural alternatives to traditional hair dyes.[5] Research continues to explore various

treatment modalities, such as exogenous melatonin, which has shown promise in improving hair follicle health and quality in animal models.[102]

Emerging research into hair graying includes physical treatments like low-level laser therapy (LLLT) and electromagnetic fields (EMFs), which are being investigated for their ability to stimulate melanogenesis and treat conditions like vitiligo. LLLT, platelet-rich plasma (PRP), and stem cell therapies are newer therapies that have gained prominence in recent years. Cell-based strategies have come a long way with technological advances, especially in tissue engineering. Nanotechnology has significantly advanced in various biology-related fields, including diagnosis, drug delivery, and molecular imaging. In regenerative medicine, nanotechnology is increasingly applied to replace lost cells or tissues, such as hair follicles (HFs). "Nanopharmaceuticals" encompasses functional nanostructures for biomarker detection and nanomaterials designed for drug delivery and regenerative applications. The formulation of nano-pharmaceuticals affects their follicular penetration. Patzelt et al found that aqueous and ethanolic gels penetrate hair follicles more deeply than aqueous or ethanolic suspensions.[93]

Furthermore, understanding the relationship between hair graying and other health conditions, such as cardiovascular disease and hearing loss, is crucial for developing comprehensive treatment strategies. This holistic approach to treatment and research aims to provide effective solutions for hair graying and related conditions.[7,11]

Despite significant advances in hair graying research, several fundamental challenges remain. The precise molecular cascade leading to MSCs depletion is still unknown, and researchers find it challenging to measure the relative contributions of intrinsic aging and environmental factors on melanocyte loss. Ethnic and sex-based differences indicate genetic influences. However, the specific mechanisms remain unclear due to multiple interacting factors such as cyclical gene expression, cell-cell interactions, follicular microenvironment variability, oxidative stress, and external stimuli. Addressing these gaps requires large-scale genomic studies across populations, exploration of gene-environment interactions, and rigorous clinical trials for targeted therapies. Furthermore, investigating the potential reversibility of graying under certain conditions offers promising avenues for future treatments. This multifaceted understanding of hair-graying mechanisms is essential for developing effective therapeutic strategies.

Based on my extensive review of the literature on hair graying, I have found a significant imbalance in the research between descriptive studies and mechanistic investigations. The focus on limited populations has created significant gaps in our understanding of how genetic and environmental factors interact across different ethnic groups. Although recent advances in understanding MSCs biology are valuable, a shift in research focus toward longitudinal studies integrating genetic, environmental, and lifestyle factors is essential. Current cross-sectional studies limit our understanding of the progression of graying and the effectiveness of potential interventions. Apparent differences in graying patterns across populations and the potential link between premature graying and broader health issues highlight the need for a shift in research priorities. This shift should involve standardized assessment tools, population-specific interventions, and a more comprehensive approach to studying the potential reversibility of early-stage graying. Such an approach would lead to more effective, personalized treatments for graying.

Conclusion

In conclusion, gray hair research is advancing rapidly, offering hope for more effective therapies to prevent and manage hair aging. As our understanding of the biological mechanisms underlying hair graying deepens, we can anticipate more targeted and personalized approaches to hair care in the future. PHG has a significant psychological impact. Future treatments for PHG will likely focus on reducing oxidative stress and promoting melanocyte growth. Additional research is necessary to explore treatment modalities targeting specific genes and proteins involved in hair follicle melanogenesis. This could lead to more effective strategies for managing and potentially reversing PHG.

Data Sharing Statement

Data sharing not applicable – no new data generated, or the article describes entirely theoretical research.

Consent for Publication

The author confirms being the sole contributor to this work and has approved it for publication.

Disclosure

The author declares no conflicts of interest in this work.

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