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# Medication-Induced Repigmentation of Gray Hair: A Systematic Review

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## Keywords

Gray hair · Treatment · Repigmentation · Medication

## Abstract

Hair graying is a common sign of aging resulting from complex regulation of melanogenesis. Currently, there is no medical treatment available for hair repigmentation. In this article we review the literature on medication-induced hair repigmentation, discuss the potential mechanisms of action, and review the quality of the literary data. To date, there have been 27 studies discussing medication-induced gray hair repigmentation, including 6 articles on gray hair repigmentation as a primary objective, notably with psoralen treatment or vitamin supplementation, and 21 reports on medication-induced gray hair repigmentation as an incidental finding. Medications noted in the literature include anti-inflammatory medications (thalidomide, lenalidomide, adalimumab, acitretin, etretinate, prednisone, cyclosporin, cisplatin, interferon- $\alpha$ , and psoralen), stimulators of melanogenesis (latanoprost, erlotinib, imatinib, tamoxifen, and levodopa), vitamins (calcium pantothenate and *para*-amino benzoic acid), a medication that accumulates in tissues (clofazimine), and a medication with an undetermined mecha-

nism (captopril). Diffuse repigmentation of gray hair can be induced by certain medications that inhibit inflammation or stimulate melanogenesis. There is also low-quality evidence that some vitamin B complex supplementation can promote gray hair darkening. While these compounds are not currently indicated for the treatment of gray hair, their mechanisms shed light on targets for future medications for hair repigmentation.

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## Introduction

Hair color has long been a symbol of youth and health, with graying signifying advanced age. Topical means of hair coloring such as permanent hair dyes are affordable and easy to use; however, they can cause irritation of the scalp, allergic reactions, and damage to the hair shaft [1]. Semipermanent and temporary hair dyes are gentler, but since they do not penetrate the hair cortex, they do not camouflage gray hair as well [1].

An optimal therapy would permanently reverse the gray back to its original hair color, without causing damage to the hair shaft or scalp irritation. In a quest for de-

velopment of this type of therapy, anecdotal reports of medications associated with hair repigmentation have been described. Unfortunately, many cases are not definitively reproducible, and little is understood about the pathophysiology behind hair repigmentation.

### *Clinical Presentation*

Graying of hair, also called canities or achromotrichia, is part of the natural aging process. It has been reported that worldwide 6–23% of people have 50% gray hair by 50 years of age [2]. Graying typically begins in the mid-30s for Caucasians, the late-30s for Asians, and the mid-40s for Africans [3–5]. Premature hair graying is considered when the onset of gray hair begins before the age of 20 years in Caucasians, before the age of 25 years in Asians, and before the age of 30 years in Africans [5, 6].

In men, gray hair typically begins at the temples and sideburns, then spreads to the vertex and lastly the occiput. In women, graying develops at the boundaries of the scalp and moves towards the vertex. Progression of hair graying depends on genetic factors; however, early onset of gray hair does not necessarily correlate with rapid progression [7].

Some causes of premature hair graying are reversible, such as nutritional deficiencies. Vitamin B12, iron, and copper deficiency, as well as severe protein malnutrition, have been linked to hair hypopigmentation [4, 8, 9]. Other risk factors significantly associated with premature gray hair include a vegetarian diet and atopy [10].

### *Pathophysiology*

The human hair shaft is composed of two main concentric regions: an inner cortex surrounded by an outer cuticle. In a small proportion of hairs, another innermost layer, the medulla, may be present [3]. Within the unit, there are 5–6 different subpopulations of melanocytes [11]. Melanogenically-active melanocytes are located at the infundibulum, sebaceous gland, and hair bulb around the dermal follicular papilla. Additionally, undifferentiated inactive melanocytes are located in the upper hair follicle reservoir near the arrector pili muscle insertion site, within the outer root sheath of the hair follicle, and in the hair bulb matrix [11]. Active melanocytes produce and transfer melanin to the keratinocytes of the hair shaft cortex, with a small amount also transferred to the medulla, and rarely to the cuticle [5]. The role of the inactive melanocytes is poorly understood, but they are thought to act as a stem cell reserve which can be induced to become melanin-producing cells if the skin is wounded [3, 5].

Hair melanogenesis is tightly linked to the stages of the hair cycle and is actively pigmented during anagen (growth) but not in catagen (involution) or telogen (quiescence) [4, 5]. Anagen for human scalp hair on average lasts 3.5 years, which requires the small population of follicular melanocytes to produce large amounts of melanin [12]. Follicle-based melanocytes are larger than epidermis-based melanocytes, with a more extensive Golgi apparatus and rough endoplasmic reticulum, thus producing larger melanosomes [13]. Follicular melanin also degrades more slowly than melanin in the epidermis. Because of this, the pigmentation at the distal and proximal ends of the hair shaft is similar [11]. The specific hair color is controlled by the type of melanin pigment produced by follicular melanocytes, including black-brown eumelanin and reddish-brown pheomelanin [4].

Numerous factors control stimulation of melanogenesis at the level of the hair follicle, including melanin-stimulating hormone, ACTH, endothelin-1, prostaglandins, leukotrienes, neutrophils, fibroblast growth factor, nitric oxide, and catecholamines [6]. In contrast, inhibitors of melanogenesis include sphingolipids, bone morphogenetic protein 4, and autoimmune processes (such as vitiligo and alopecia areata) [3, 4, 11, 14]. Certain compounds or diseases can affect the production of these factors and alter hair pigmentation. Conditions occasionally associated with darkening of hair color include Addison's disease, neurodermatitis, porphyria cutanea tarda, and inflammatory scalp conditions [3, 15–17]. Conversely, conditions linked to hair lightening or graying include cystic fibrosis, celiac disease, hyperthyroidism/hypothyroidism, vitiligo, alopecia areata, and genetic diseases such as Werner syndrome, Louis-Bar syndrome, Waardenburg syndrome, or Griscelli syndrome [3, 14, 18, 19].

The development of gray hair is ultimately due to a decrease in the number of melanocytes. This can be either due to a defect in the melanocytic stem cells or destruction of the follicular stem cell population [3–5, 20]. A common issue leading to follicular melanocyte death is oxidative stress due to the development of reactive oxygen species (ROS) from hydrogen peroxide build-up (a natural product of the hair growth process) or ultraviolet (UV) light [3, 4, 20, 21]. Antioxidants such as Bcl-2, catalase, and methionine sulfoxide reductase are naturally produced by melanocytes to protect against ROS damage. These protective molecules are notably absent in gray hair follicles [20, 21]. For example, studies on BCL-2-deficient mice have noted the development of gray hair by the second hair cycle [20, 21]. Interestingly, melanocytes in the outer root sheath appear to be less affected by ROS dam-

age, and they may be a pigment source for reversal of hair color [20]. Other causes of oxidative stress, including pollution, emotional stress, alcohol consumption, and cigarette smoking, have been linked to the premature development of gray hair [22, 23].

Hair graying is a complex process regulated by multiple intrinsic and extrinsic factors, with treatment options for hair repigmentation currently being investigated. In this systematic review, we identify medications linked to gray hair repigmentation to further delineate potential targets of hair repigmentation therapy.

## Methods

A systematic literature search was performed using PubMed and CINAHL ending in May 2019. The search terms were: ((grey OR gray) AND hair) OR canities OR achromotrichia) AND (treatment OR repigmentation OR reversal OR darkening OR therapy). All clinical trials, retrospective studies, case series, and case reports on gray hair and medication-induced color change in humans were included. Excluded were articles written in a language other than English; articles not about hair; review articles; and reports on patients starting with a hair color other than gray or white, or grey hair related to chronic nutritional deficiencies or diseases such as vitiligo or Griscelli syndrome. The quality of the evidence for each article was determined using the Oxford Centre for Evidence-Based Medicine criteria [24].

## Results

Two hundred and forty-one articles were evaluated and 27 were included in this systematic review. These consist of 4 prospective cohort studies, 3 retrospective cohort studies, 1 case series, and 19 case reports. This includes an aggregate of 133 patients with medication-induced gray hair repigmentation. Of these studies, 3 prospective studies and 1 case series focused specifically on premature hair graying, while the remaining articles investigated patients with age-related canities. Overall, the quality of the evidence is low, given that most cases were documented as solitary case reports, or in studies which were not reproducible. A summary of the articles and their level of evidence quality is found in Table 1.

The medications reported in the literature can be divided into five categories: anti-inflammatory medications (thalidomide, lenalidomide, adalimumab, acitretin, etretinate, prednisone, cyclosporin, cisplatin, interferon- $\alpha$ , and psoralen), stimulators of melanogenesis (erlotinib, imatinib, latanoprost, tamoxifen, and levodopa), vitamins (calcium pantothenate and *para*-amino benzoic

acid [PABA]), medications that accumulate in tissues (clofazimine), and those with a mechanism yet to be determined (captopril).

### *Anti-Inflammatory Medications*

While a majority of the anti-inflammatory medications were documented in case reports, 1 prospective cohort study and 1 retrospective study were noted in the literature, totaling 39 patients.

Psoralen plus UVA light (PUVA) was reported by Pavithran [25] to induce gray hair repigmentation directly in patients with premature gray hair. The author states that the idea stemmed from clinical experience while treating patients with PUVA for psoriasis. Because of this, a prospective study was performed specifically on healthy patients, aged 10–20 years, with premature gray hair ( $n = 37$ ). After 13 months of treatment, 46% of these patients noted complete scalp hair repigmentation, with no relapse at the 8-month follow-up [25]. Seven additional patients showed partial repigmentation, with pigmented proximal ends of the gray hair shafts or repigmentation with a diffuse or patchy light-brown color [25].

In a retrospective study on men receiving cisplatin-based chemotherapy for germ cell neoplasms, patients aged 15–54 years were observed at the time of hair regrowth for changes in hair color. Of the 69 patients, 16% noted darkening of the hair color [26]. Two patients noted reversion of the hair color within 2 years after having stopped chemotherapy.

The remaining cases of anti-inflammatory medications inducing gray hair repigmentation were noted in sporadic case reports. The retinoic acid receptor-activating medications acitretin and etretinate were associated with gray hair repigmentation in 2 patients with pityriasis rubra pilaris and 1 patient with psoriasis after 6–12 months of treatment [27–29]. A patient receiving interferon- $\alpha$  for the treatment of chronic hepatitis C described scalp hair repigmentation beginning 2 months after treatment, and persistent pigmentation after having discontinued the therapy [30]. Single case reports on a variety of other anti-inflammatory medications known to inhibit proinflammatory cytokine activity (including thalidomide, lenalidomide, adalimumab, cyclosporin, and prednisone) have also been linked to hair repigmentation after 2–24 months of treatment [31–37].

### *Stimulators of Melanogenesis*

Five medications thought to stimulate melanogenesis were documented in 1 retrospective study and 6 case reports of hair repigmentation. In a retrospective study

**Table 1.** Summary of the articles describing medications associated with gray hair repigmentation

Study [Ref.], year	Study type (quality)	Patients, <i>n</i>	Patient characteristics	Medication
<b>Anti-inflammatory medications</b>				
Lovering et al. [32], 2016	Case report (5)	1	75-yo F with gray hair and multiple myeloma	Thalidomide 200 mg daily for 2 yrs, then 100 mg every other day for maintenance
Tintle et al. [33], 2015	Case report (5)	1	75-yo F with gray hair and rheumatoid arthritis	Adalimumab 40 mg subcutaneously q2wks for 4 mo, switched to golimumab 50 mg subcutaneously q4wks for 1 yr
Ward et al. [27], 2014	Case report (5)	1	61-yo M with white hair and pityriasis rubra pilaris	Acitretin 25 mg daily
Dasanu et al. [34], 2013	Case report (5)	1	81-yo M with gray hair and multiple myeloma	Lenalidomide 10 mg daily 21 of 28 days and dexamethasone 40 mg weekly
Seckin and Yildiz [28], 2009	Case report (5)	1	70-yo F with white hair and psoriasis (not involving scalp)	Acitretin 0.3 mg/kg/day (25 mg/day)
Khaled et al. [35], 2008	Case report (5)	1	81-yo M with white hair and bullous pemphigoid (not involving scalp)	Prednisone 0.5 mg/kg/day for 2 mo, then 10 mg/day as maintenance for 20 mo
Sadighha and Zahed [36], 2008	Case report (5)	1	59-yo M with white hair and psoriasis	Cyclosporin 5 mg/kg/day for 4 mo, then reduced to 2.5 mg/kg/day
Kavak et al. [30], 2005	Case report (5)	1	59-yo M with white hair and chronic hepatitis C	Interferon (IFN)- $\alpha$ 2 6 mIU 3 $\times$ /wk and ribavirin 1,000 mg/day for 1 yr, pegylated-IFN 100 $\mu$ g/week subcutaneously and ribavirin 1,000 mg/day for 1 yr
Rebora et al. [37], 1999	Case report (5)	1	73-yo M with white hair and severe eczematous dermatitis	Cyclosporin A 5 mg/kg/day for a few days, then lowered to 150 mg/day for maintenance
Vesper and Fenske [29], 1996	Case report (5)	1	73-yo M with grey hair and pityriasis rubra pilaris	Etretinate 0.5 mg/kg/day PO
Babu et al. [31], 1995	Case report (5)	1	65-yo M with grey hair and colorectal carcinoma	5-Fluorouracil (5-FU) 1,000 mg plus leucovorin 30 mg every 4 wks with levamisole 50 mg TID every 2 wks for 3 mo; switched to cisplatin 100 mg plus 5-FU 100 mg every 4 wks
Robinson and Jones [26], 1989	Retrospective cohort study (3)	11	Men with metastatic germ cell neoplasms, all with alopecia from chemotherapy, median age 30 yrs (15–54), 69 pts total	Cisplatin-based chemotherapy (unknown dose or duration of therapy)
Pavithran [25], 1986	Prospective cohort study (2)	17	37 patients with premature graying, aged 10–20 yrs, 1 pt with Werner syndrome, 1 pt with hyperthyroidism, 1 pt with diabetes mellitus, 2 pts with psoriasis, and 4 pts with vitiligo	8-Methoxy psoralen 0.6 mg/kg PO every other day, followed 2 h later with 10–15 min of sun exposure, 19-mo treatment period
<b>Stimulation of melanogenesis</b>				
Cheng et al. [39], 2014	Case report (5)	1	68-yo F with gray hair and metastatic adenocarcinoma of the lung	Erlotinib 150 mg daily

**Table 1** (continued)

Study [Ref.], year	Study type (quality)	Patients, <i>n</i>	Patient characteristics	Medication
Bellandi et al. [41], 2011	Case report (5)	1	65-yo F with white hair and open-angle glaucoma	Latanoprost 0.0005% eye drop per eye daily
Alexandrescu et al. [40], 2009	Case report (5)	1	76-yo F with white hair and metastatic adenocarcinoma of the lung	Erlotinib 150 mg daily
Etienne et al. [38], 2002	Retrospective cohort study (3)	9	5 men and 4 women, median age 63.4 yrs, all with grey hair and chronic myeloid leukemia, 133 pts total in study	Imatinib mesylate (dose unknown)
Hampson et al. [42], 1995	Case report (5)	1	68-yo F with white hair and breast cancer	Tamoxifen 20 mg daily
Reynolds et al. [43], 1989	Case report (5)	1	61-yo M with white hair and Parkinson's disease	Levodopa 250 mg BID for 16 yrs, then transitioned to levodopa 100 mg daily with carbidopa 25 mg daily, bromocriptine 2.5 mg daily added 5 mo later
Grainger [44], 1973	Case report (5)	1	51-yo M with white hair and Parkinson's disease	Levodopa 1.5 g daily
<b>Vitamin supplementation</b>				
Pasricha [46], 1986	Prospective cohort study (2)	4	7 women, aged 12–31 yrs, with premature gray hair followed for 3 yrs	Patients received calcium pantothenate 200 mg PO daily, with some patients also taking Basiton Forte (thiamine 10 mg, riboflavin 10 mg, calcium pantothenate 50 mg, cyanocobalamin 15 µg, sodium ascorbate 50 mg, folic acid 1.5 mg) daily and/or vitamin E 200 mg daily, gray hair was evulsed prior to starting the supplement, follow-up every 3 mo for gray hair counting and evulsion
Pasricha [45], 1981	Case series (4)	2	Pt 1: 13-yo F with diffuse graying of hair over 1.5 yrs of unknown etiology, no family Hx Pt 2: 15-yo F with progressive hair graying over 2 yrs of unknown etiology, no family Hx	Pt 1: calcium pantothenate 200 mg daily Pt 2: calcium pantothenate 100 mg daily, increased to 200 mg after 1 mo
Zarafonitis [48], 1950	Retrospective cohort study (3)	5	20 pts total (7 men and 13 women), aged 43–86 yrs, with gray hair Pt 1: 63-yo M with gray hair and lymphoblastoma cutis Pt 2: 50-yo F with gray hair and dermatomyositis Pt 3: 68-yo M with gray hair and dermatitis herpetiformis Pt 4: 57-yo F with gray hair and lymphoblastoma cutis Pt 5: 42-yo F with gray hair and scleroderma	Pt 1: Potassium <i>p</i> -amino benzoate (K PABA) 18 g daily initially, then 12–15 g for maintenance Pt 2: K PABA 24 g daily for 2 wks, then 12–14 g daily for 6 mo, then 6–8 g daily for 20 mo Pt 3: K PABA 18–21 g daily Pt 4: K PABA 14 g daily Pt 5: K PABA 12 g daily

**Table 1** (continued)

Study [Ref.], year	Study type (quality)	Patients, <i>n</i>	Patient characteristics	Medication
Brandaleone et al. [49], 1943	Prospective cohort study (2)	16	Group 1: 19 elderly (>55-yo) men and women with white/gray hair and chronic diseases (RA, parkinsonism, arteriosclerosis with hemiplegia) Group 2: 8 young pts (29–38 yo) Group 3: 6 women with premature grey hair	Group 1: 7 pts received 100 mg calcium pantothenate plus 50 g brewer's yeast for 8 mo; 5 pts received 200 mg PABA + 50 g brewer's yeast daily for 6 mo; 7 pts received 100 mg calcium pantothenate, 200 mg PABA, and 50 g brewer's yeast daily for 6 mo Group 2: 6 pts received 100 mg calcium pantothenate, 200 mg PABA, and 50 g yeast daily; 2 pts received 100 mg Ca P and 200 mg PABA Group 3: received 20 mg calcium pantothenate and 3.5 g brewer's yeast for 6–10 mo
Sieve [47], 1941	Prospective cohort study (2)	50	50 pts with gray or white hair, ages 21–55 yrs	30 pts given PABA 100 mg BID; 20 pts given PABA plus “endocrine products”
<b>Accumulates in tissues</b>				
Philip et al. [50], 2012	Case report (5)	1	45-yo M with grey hair and borderline lepromatous leprosy	Clofazimine 300 mg daily for 2 mo, then 50 mg daily for 12 mo
<b>Unknown etiology</b>				
Read [51], 1991	Case report (5)	1	65-yo F with grey hair and hypertension	Captopril 25 mg BID and slow-release verapamil 240 mg daily, added to bendrofluazide 2.5 mg daily

yo, years old; yrs, years; pt, patient; pts, patients; wks, weeks; mo, months; Hx, history; RA, rheumatoid arthritis; PO, per os; BID, bis in die; TID, ter in die.

on patients receiving imatinib for chronic myeloid leukemia, 7% of 133 patients were reported to experience repigmentation of gray hair 2–14 months into treatment [38]. Another tyrosine kinase inhibitor, erlotinib, was also reported to induce progressive hair repigmentation 3 months and 2 years after treatment in 2 separate cases of patients with metastatic lung adenocarcinoma [39, 40]. One case of erlotinib-associated hair repigmentation began after an episode of folliculitis on the scalp [39].

A case of latanoprost eye drop use was connected with diffuse scalp hair repigmentation 3 years after having started a therapy for open-angle glaucoma [41]. Another patient reported scalp hair repigmentation 2.5 years after having started tamoxifen therapy for breast cancer [42]. Lastly, 2 patients receiving levodopa for Parkinson's disease reported diffuse hair repigmentation within 8–9 months after having begun treatment [43, 44].

### Vitamin Supplementation

Studies of vitamin B supplementation with calcium pantothenate or potassium PABA are some of the earliest ones directed specifically at gray hair repigmentation. Successful repigmentation of premature gray hair in 2 healthy patients with high-dose calcium pantothenate (200 mg daily) was noted to begin as soon as 1 month after treatment [45]. A follow-up 3-year prospective cohort study of 7 women with premature gray hair, aged 12–31 years, reported that 28% of the patients noted repigmentation with 200 mg daily, while 28% noted repigmentation with 100 mg within 3 months [46]. One prospective cohort study and 1 retrospective study investigated the use of PABA for gray hair [47, 48]. In 1941, Sieve [47] performed the first documented study on repigmentation of gray hair on 50 patients with premature or age-related hair graying using PABA at 200 mg daily. He reported subjective marked hair darkening in all patients after 2 months of treatment. Another study investigated the ef-

fect of PABA at high doses (12–24 g/day) on age-related gray hair when used for the treatment of systemic diseases such as lymphoblastoma cutis, dermatomyositis, dermatitis herpetiformis, and scleroderma ( $n = 20$ ) [48]. Thirty-five percent of the patients noted hair darkening after 2–10 months of treatment. Conversely, a prospective study on the use of 100 mg calcium pantothenate with 200 mg PABA daily for gray hair (27 subjects with age-related canities and 6 with premature graying) found 6% of the patients (all age-related graying) with a definite hair color change and 21% with a slight color change on clinical evaluation after 8 months of supplementation [49]. This study also noted that the repigmented hair returned to gray after supplement discontinuation.

#### *Accumulation in Tissues*

Hair repigmentation with high-dose clofazimine during treatment of borderline lepromatous leprosy was noted as increased pigmentation of the skin initially, followed by hair repigmentation at 6 months of treatment. Increased skin pigmentation is a common side effect of clofazimine due to drug crystal accumulation in body tissues and fluids; however, it is not commonly reported to induce hair color darkening [50]. The hair repigmentation persisted for 8 months after having completed treatment.

#### *Unknown Etiology*

A case of frontal scalp hair repigmentation was described 1 year after adding captopril and slow-release verapamil to a patient's hypertension regimen. The connection between these medications and hair repigmentation is yet to be determined [51].

## **Discussion**

As evidenced by the many cases of gray hair repigmentation in the literature, the development of gray hair may not be an irreversible process. The implication of hair pigmentation reversibility could have a noteworthy impact on the quality of life of a significant number of patients, and clinicians should be made aware of this. Most medications linked to repigmentation play an anti-inflammatory role, while fewer compounds affect melanogenesis, provide vitamin supplementation, or act on an unidentified target in the hair pigmentation process. While there are over 130 cases of medication-induced gray hair repigmentation reported in the literature, it is noteworthy that many of the medications mentioned have been used by

millions of patients and only a small minority of patients have experienced hair repigmentation. This may be partially due to a lack of patients reporting hair color changes, but might more likely be due to the complex nature of hair follicle pigmentation regulation, which highlights that targeting one mechanism may not be enough to manipulate it.

Given that the data on gray hair repigmentation mainly stems from case reports, the overall quality of evidence is low. Because of this, the strongest data derive from prospective and retrospective cohort studies on PUVA, imatinib, and cisplatin-based chemotherapy, as well as on the supplemental vitamins calcium pantothenate and PABA. Given the nature of these medications, their indication, and associated side effects, conducting trials with these toxic medications solely for the purpose of reversing hair color is prohibitive. Nonetheless, the information analyzed provides possible mechanisms of hair repigmentation that can be applied to new medications in the future, hopefully without similar adverse systemic effects.

The anti-inflammatory medications listed in this review inhibit proinflammatory cytokines. Adalimumab, thalidomide, and lenalidomide block tumor necrosis factor- $\alpha$  [52]. Similarly, cyclosporin inhibits the production and activity of IL-2. Acitretin and etretinate bind the retinoic acid receptor and inhibit expression of IL-6. Prednisone, psoralen, cisplatin, and interferon- $\alpha$  have more generalized anti-inflammatory activities by decreasing immune cell activation and cytokine expression [52]. Proinflammatory cytokines such as tumor necrosis factor- $\alpha$ , IL-6, and IL-1 are known inhibitors of melanogenesis [6]. These cytokines are produced by many cells, including macrophages, which are located around the hair follicle in the perifollicular connective tissue sheath [53]. While the hair follicle is thought to be an area of immune privilege, aging melanocytes may play a role in increasing inflammation around the hair follicle bulb. Residual melanocytes in age-related graying hair bulbs are found to have blunted dendrites, defective melanosome transfer, and failure of precortical keratinocytes to receive melanin granules [5]. Defective compartmentalization of melanogenesis leads to accumulation of ROS and attracts inflammatory cells to the hair follicle [5]. The broken-down immune barrier of the hair follicle allows proinflammatory cytokines to access and further inhibit melanogenesis. It is possible that inhibition of these cytokines may break the feedback inhibition on hair pigmentation, allowing melanogenesis to resume.

While suppression of inflammation within the hair follicle appears to play a role in promoting repigmenta-



tion, the fact that hair repigmentation does not occur in 100% of patients treated with these medications signifies that repigmentation is a multifactorial process controlled by both inhibition of inflammatory cytokines and melanogenesis stimulation. Medications such as psoralen, imatinib, erlotinib, latanoprost, tamoxifen, and levodopa are associated with stimulation of pigmentation. Prostaglandins such as latanoprost have previously been shown to cause periocular and iris hyperpigmentation when used for glaucoma [54]. In vivo studies have shown that PGF<sub>2α</sub> analogs promote melanocyte dendricity and melanogenesis [55]. Similarly, estrogens increase skin and hair pigmentation by stimulating melanin release by melanocytes [56]. Tamoxifen, a selective estrogen receptor modulator, may act as an agonist in this process leading to increased pigmentation in rare cases. Furthermore, levodopa, a metabolite of melanin production, may also lead to hair pigmentation when circulating blood levels reach a certain threshold [52]. While we can hypothesize mechanisms for these medications to promote hair follicle repigmentation, the fact that there are only sporadic cases with the use of these commonly prescribed medications points to the fact that the process of hair repigmentation is not a simple one. Many of the solitary case reports could actually be coincidental timing of medication initiation and sporadic hair repigmentation instead of true causation. In the literature, there are reports of a 21-year-old male and a 67-year-old male with sporadic hair repigmentation without changes in medication or health status [57, 58]. Intermittent melanogenesis dysfunction may be related to a problem in the hair growth cycle, such as incomplete catagen signaling [57].

The cohort study on PUVA in patients with premature gray hair showed promising results. However, these findings may be due to the fact that patients with premature gray hair typically have a smaller percentage of gray hairs. Furthermore, the process of premature hair graying may be more amenable to reversal than age-related hair graying. As noted above, age-related gray hairs have defective melanocytes, which may not be as abundant in premature gray hair [5]. Nonetheless, psoralen may influence hair follicle pigmentation through multiple pathways. Its anti-inflammatory properties include alteration in cytokine and cytokine receptor expression, which may reduce inflammation and melanocyte destruction within the hair follicle. Furthermore, psoralen stimulates melanocyte proliferation and transfer of melanosomes to keratinocytes, which could lead to increased hair pigmentation [52].

Tyrosine kinase inhibitors such as imatinib and erlotinib also showed promise for repigmentation in the lit-

erature. A known side effect of these medications is folliculitis. Postinflammatory hyperpigmentation of the area may incite hair repigmentation in some cases. However, imatinib is also reported in the literature to cause hyperpigmentation of the oral mucosa, skin, and nails [59]. Imatinib inhibits c-Kit, which plays a key role in melanocyte homeostasis [59]. In vivo studies have shown that inhibition of c-Kit influences the number, size, and dendricity of melanocytes, which may influence hair pigmentation in rare cases [60].

Calcium pantothenate and PABA supplementation initially were studied to repigment hair having grayed due to specific vitamin deficiencies. Pantothenic acid (vitamin B5) deficiency is rare in the developed world and is unlikely to be the cause of gray hair in the USA [61]. While it is considered safe to take doses of up to 5 g/day, larger doses can cause diarrhea and abdominal pain. PABA, another member of the vitamin B complex family, has been reported to be useful in sclerotic skin disorders such as scleroderma, morphea, and Peyronie's disease at doses up to 12 g/day without adverse effects [52]. Larger doses lead to an upset stomach, nausea, and hypoglycemia, which can be serious. While studies such as the cohort study by Sieve in 1941 noted impressive hair repigmentation, these trials have not been replicated or verified. With the validity of these studies in question, it is unlikely that vitamin supplementation truly impacts hair repigmentation in the absence of severe vitamin deficiencies. Due to the absence of more recent and repeatable data on vitamin supplementation for gray hair treatment, the use of these vitamins is not strongly supported solely for use for gray hair reversal.

Medications currently in development for gray hair repigmentation target both inhibition of inflammation and stimulation of melanogenesis. Harris [62] reports on a new combination compound, RT1640 (cyclosporin A, minoxidil, and a pigment-promoting drug), which induces gray hair repigmentation in a mouse model. An increase in pigmentation of gray mouse hairs was associated with increased melanocyte progenitor cell counts in up to 80% of hair bulbs. Furthermore, hair was shaved after treatment discontinuation and noted to regrow with continued repigmentation. Similarly, an  $\alpha$ -melanin-stimulating hormone agonist, palmitoyl tetrapeptide-20, was found to preserve follicular melanocyte function and increase pigmentation during melanogenesis in a mouse model [63]. Saha et al. [64] describe the use of C18:0 sphingolipid-rich placental extract to induce microphthalmia-associated transcription factor (Mitf) and activate quiescent melanocyte stem cells in gray-haired mice. There was significant growth of dense black hair on mice treated with this ex-

tract, suggesting reactivation of melanocyte stem cells. Lastly, in a mouse model, flavonoids such as sterubin, luteolin, and hydroxygenkwanin have recently been shown to regenerate pigmented hair when applied during wound healing [65]. Flavonoids are antioxidants and anti-inflammatory compounds which scavenge free radicals and promote melanogenesis through the Wnt signaling pathway. As evident by many of these investigational treatments, inhibiting inflammation as well as promoting melanogenesis may be the key to hair repigmentation.

## Conclusions

Gray hair is a natural course of aging; however, it may not be an inevitable or permanent process. Medications which target inflammatory cytokines, such as psoralen

and cyclosporin, or stimulate melanogenesis, such as imatinib or latanoprost, have been reported to induce gray hair repigmentation in rare cases. While the evidence for these medications is of low quality, and the ability to effectively study them for gray hair treatment is difficult, their limited success sheds light on possible mechanisms to target for future development of hair repigmentation medications.

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