Hair pigmentation and graying are important topics for the understanding of the physiology of aging; the differentiation of stem cells; and the mechanisms underlying disease processes such as progeroid syndromes, vitiligo, and hypothyroidism. Although hair graying, or canities, is a common process occurring in people as they age, an unknown percentage of individuals experience premature graying from familial inheritance or pathologic conditions. We review the physiology of hair pigmentation and the mechanism underlying physiologic graying, and we explore the etiology of pathologic causes of premature graying, pathologies associated with premature graying, and the limited available treatment options for hair graying.

Pigmentation of the Hair Follicle

The hair follicle is an organ composed of melanocytes and keratinocytes; it undergoes a cyclic process of degeneration and regeneration regulated by endocrine and paracrine mediators. Normal hair follicles undergo a 3-phase cycle characterized by a period of growth called the anagen phase, a period of involution called the catagen phase, and a period of rest called the telogen phase; after the telogen phase, the hair is shed and a new anagen phase commences.

Hair graying is a physiologic process that occurs with age in both men and women. The average age of onset of hair graying is 34 to 44 years depending on race, with an estimated 50% of men and women being 50% gray by 50 years of age. Premature hair graying has been defined as graying that occurs in patients younger than 20 years and appears to most often result from an autosomal-dominant genetic inheritance; however, it can be caused by an underlying pathology such as a segmental progeroid syndrome, vitiligo, hormonal imbalance, vitamin deficiency, or medications. The evidence for hair graying from oxidative stress has led to the investigation of premature graying as a risk factor for age-related pathologies such as coronary artery disease and osteoporosis. Although treatment of premature hair graying has advanced little over the years, recent research has expanded our knowledge of melanocytes, melanocyte stem cells, and the process of hair pigmentation, which will hopefully open the door to future treatment.
stem cell factor, which is released from the dermal papilla and acts via the receptor tyrosine kinase c-kit, causing melanocyte proliferation and increased melanogenesis. Neuroendocrine factors also play a role in hair pigmentation with adrenocorticotropic hormone, beta endorphin, thyrotropin-releasing hormone, alpha-melanocyte-stimulating hormone, and the thyroid hormones triiodothyronine (T3) and levorotatory thyroxine (T4) having been shown to promote melanogenesis.

Physiologic Graying

As individuals age, the melanin content of the hair follicle decreases, causing graying and eventual whitening of the hair. The loss of melanin has been linked to a decrease in the number of melanocytes in the hair follicle, as well as a possible decrease in the activity of the enzymes involved in melanogenesis. It has been shown that as the hair follicle ages there is ectopic differentiation of the stem cells into melanogenic melanocytes. With loss of the stem cells, the mature melanocytes in the hair bulb that are responsible for pigmenting the hair follicle are not replaced after apoptosis, leading to decreased melanocytes in the hair bulb and decreased pigment in the subsequent anagen phase of the follicular cycle. This ectopic differentiation of the stem cells is promoted by endogenous and exogenous oxidative species that accumulate in hair follicles with age.

Pathologic Causes of Premature Graying

Premature graying is associated with a variety of pathologic conditions including segmental progeroid syndromes, vitiligo, hypothyroidism, vitamin B12 deficiency, and medications. The mechanism underlying the disease phenotype is mutation of DNA repair enzymes that are involved in preventing damage from oxidative radicals. Given that oxidative stress induces ectopic differentiation of melanocytic stem cells, thereby decreasing the pool of stem cells available to replace apoptotic melanogenic melanocytes, it reasons that the deficient DNA repair enzymes in the segmental progeroid syndromes allow the accumulation of oxidative damage to stem cell DNA, leading to ectopic differentiation and the premature loss of the stem cell pool.

Vitiligo is an idiopathic depigmentation disorder characterized by the loss of melanocytes in the skin.
as well as in the overlying hair, leading to the development of hypopigmented macules and follicles. The mechanism for melanocyte loss is still unclear; however, it has been shown that epidermal melanocytes in patients with vitiligo are more sensitive to oxidative stress than their healthy counterparts. The depigmentation of the hair follicle in patients with vitiligo is partly related to the decreased ability of the differentiated and undifferentiated melanocytes to reduce oxidative species, leading to ectopic differentiation of the stem cells and apoptosis of the differentiated melanocytes.

Hair follicle depigmentation has been reported in patients with hypothyroidism and vitamin B₁₂ deficiency. The decreased T₃ and T₄ found in hypothyroidism have many effects on the hair follicle, including premature graying, alopecia, and changes in hair morphology. Evaluation of the role of the thyroid hormones on hair growth and pigmentation has shown that T₃ and T₄ directly act on the hair follicle to increase melanogenesis as well as the anagen phase of the hair cycle. The absence of the thyroid hormone's stimulatory effect on melanogenesis is suspected to play an important role in the pathogenesis of premature graying in hypothyroidism. Vitamin B₁₂ deficiency causes premature graying by an unknown mechanism, which is of particular interest given B₁₂ deficiency is known to cause hyperpigmentation of the skin.

Premature graying also has been reported as a side effect of chemotherapeutic and antimalarial agents. Imatinib mesylate, dasatinib, pazopanib, and sunitinib are inhibitors of the receptor tyrosine kinase family with utility in the treatment of a wide range of malignancies, including chronic myeloid leukemia, gastrointestinal stromal tumors, and renal cell carcinoma. These drugs may inhibit the receptor tyrosine kinase c-kit found in melanocytes, preventing stimulation of the melanocytes and melanogenesis. Chloroquine has been found to preferentially interfere with the production of pheomelanin, the melanin responsible for yellow and red pigments, by an unknown mechanism.

**Premature Graying as a Risk Factor for Age-Related Pathologies**

A number of studies have sought to assess the relationship between premature hair graying and the risk for myocardial infarction, osteoporosis, and shortened life span. After controlling for established coronary risk factors, the Copenhagen City Heart Study found an increased risk for myocardial infarction in men with moderately and completely gray hair compared with men with no gray hair; however, the same study found no relationship between gray hair and early mortality. Other studies have confirmed the relationship between premature hair graying and cardiovascular disease. Studies investigating the association between hair graying and low bone mineral density have produced varying results. After several studies asserted a relationship between premature graying, defined in these studies as almost total graying by 40 years of age and low bone mineral density, more recent studies have found no such relationship, casting doubt that premature graying is a risk factor for low bone mineral density.

**Treatment**

Treatment of premature hair graying is dependent on the cause of the graying. Drug-induced hair graying can be reversed by removal of or dose alteration of the offending agent, while graying due to vitamin B₁₂ deficiency and hypothyroidism has the potential to be reversed with vitamin and hormone replacement, respectively. Topical tacrolimus has been shown to promote repigmentation of the skin in pediatric patients with vitiligo. Although its mechanism of action is not fully understood, tacrolimus has been shown during in vitro studies with murine melanocytes to stimulate tyrosinase expression as well as the differentiation and migration of melanocytic stem cells from the hair follicle to the perifollicular epidermis. It remains to be seen if tacrolimus can stimulate hair follicle pigmentation in pediatric patients with hair graying due to vitiligo. Unfortunately, there currently is no silver bullet for preventing or treating premature graying hair and most men and women must rely on hair colorants to achieve restoration of hair color.

**Conclusion**

Hair pigmentation is a complex process that involves neuroendocrine factors to promote differentiation of immature melanocyte stem cells into mature melanocytes capable of pigmenting the hair follicle. Both the stem cells and the differentiated melanocytes are constantly under stress from oxidative species, which can alter the function of and decrease the pool of both immature and mature melanocytes. Aging is associated with the accumulation of oxidative radicals, and thus the physiologic graying of hair. Conditions that increase the amount of oxidative stress on the stem cells and melanocytes, such as progeroid syndromes or vitiligo, and decrease the melanogenic capabilities of the melanocytes, such as chemotherapeutic and antimalarial agents, can lead to the early loss of melanocytes, and hence premature graying. Despite the recent girth of research on hair pigmentation and graying, treatment and prevention remains elusive.
REFERENCES


