

GREY8

DERMA INSIGHTS



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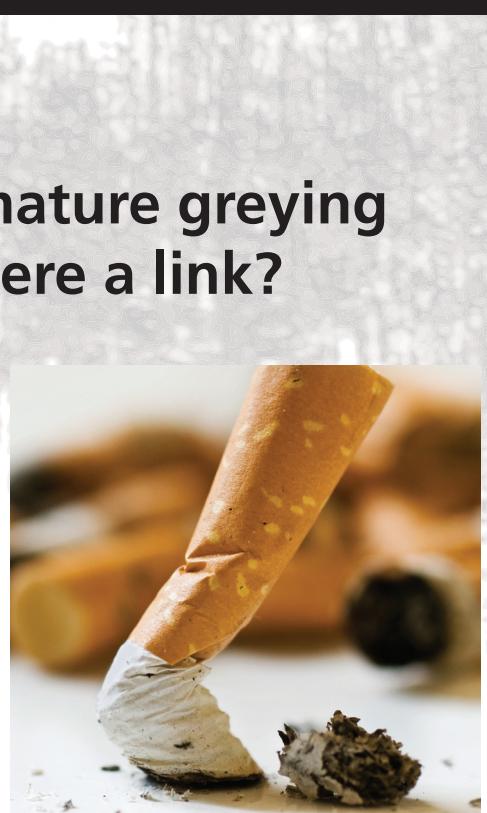
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Section 1: KONNECT

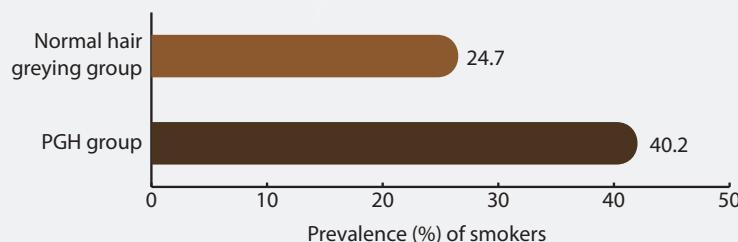
Smoking and premature greying of hair (PGH): Is there a link?

Smoking is a common preventable cause and/or risk factor for several significant systemic diseases, having effect on almost all body organs, and hair are no exception. It has been observed that smoking exerts adverse impact on hair health through its effects on the follicular growth cycle and fiber pigmentation. The effect could not only be consequence of its systemic effects but an outcome of the direct exposure also since ambient tobacco smoke exposure can result in nicotine accumulation in the hair follicles and the hair shaft. These effects of smoking could accentuate the process of premature greying of hair (PGH; defined as the first appearance of grey hair before the age of 30), thereby resulting in a higher prevalence of hair loss and PGH in smokers as compared to non-smokers.¹ A cross-sectional observational study suggested a significant relation between onset of grey hair before the age



of 30 and cigarette smoking. The results showed that the prevalence of smokers in the "PGH" group was higher (figure 1), and smokers had earlier onset of hair greying. Using multiple logistic regression with conditional likelihood, smokers were found to be 2.5 times more prone to develop PGH.²

Figure 1 Prevalence of smokers in the "PGH" vs. normal hair greying group



Source: Zayed AA, Shahait AD, Ayoub MN, Yousef AM. Smokers' hair: Does smoking cause premature hair graying? *Indian Dermatol Online J.* 2013; 4(2): 90–92.

In all, smoking is associated with negative effects on hair health as evidenced in PGH and hair loss. Dermatologist and physicians alike should therefore assess the smoking status in patients presenting with the complaint of PGH, and promote smoking cessation by offering an opinion

Smokers are 2.5 times more prone to develop PGH

on the detrimental effects of smoking on not only hair but overall health also.

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Section 2: CLINICAL VIGNETTES

Targeting melanogenesis in premature greying of hair

Hair colour is a known phenotypic variable that mainly depends on the amount of melanin pigment, and fabrication of this pigment takes place in melanosomes through a complex biochemical pathway (melanogenesis).¹ The melanocyte interacts with endocrine, immune, inflammatory and central nervous systems, and its activity is also regulated by a myriad of extrinsic factors like UV radiations and smoking.² Nevertheless, an understanding and comprehension of this mechanism (melanogenesis) also presents an opportunity to facilitate understanding of the pathogenesis of pigmentation disorders and development of potential therapeutic options.

The process of melanogenesis involves different stages, from melanocyte embryogenesis to melanosome transfer to neighbouring keratinocytes. The development of grey hair is believed to occur either from insufficient melanin formation due to melanocyte degeneration or a defect in melanosomal transfer.³ Melanin synthesis occurs in melanosomes, the specific cytoplasmic organelles produced by melanocytes. These melanosomes are transferred from melanocytes to keratinocytes via the shedding vesicle system, which generates pigment globules containing multiple melanosomes in a unique manner.⁴

Phenotypic diversity of pigmentation is generally not due to a variation in melanocyte number, but to the size and number of melanosomes, the amount and type of melanin, and melanin transfer and distribution in keratinocytes. It has been shown that grey hairs undergo a marked reduction in melanogenically-active melanocytes in the hair follicle. The net effect of this reduction is that fewer melanosomes are incorporated into cortical keratinocytes of the hair shaft. Besides, there appears also to be a defect



of melanosome transfer, as keratinocytes may not contain melanin despite their proximity to melanocytes with remaining melanosomes. Eventually, no melanogenic melanocytes remain in the hair bulb, and there is a decrease of melanin synthesis with decrease in tyrosinase activity. Studies have shown that remaining melanocytes not only contain fewer melanosomes, but the residual melanosomes may be

The development of grey hair is believed to occur either from insufficient melanin formation due to melanocyte degeneration or a defect in melanosomal transfer

packaged within autophagolysosomes; suggesting that they are defective, possibly with reactive melanin metabolites. It has been observed that melanocytes in greying hair bulbs are frequently highly vacuolated, a common cellular response to increased oxidative stress.⁵

The process of synthesis of melanin involves several important enzymes like

Table 1: Effects of factors secreted by keratinocytes after exposure to UV radiation, with paracrine action

	Melanocyte proliferation	Dendricity	Melanin synthesis	Melanosome transfer	Survival / Cytoprotection
ACTH	↑		↑		↑
α-MSH	↑	↑	↑		↑
bFGF	↑↑				
ET-1	↑	↑	↑		
GM-CSF	↑		↑		
NO			↑		
NGF		↑			↑
PGE2/PGF2α		↑	↑	↑	
IL-1	↓	↑	↓		
TNF-α			↓		
BMP-4			↓		

Abbreviations: ACTH (adrenocorticotrophic hormone), α-MSH (melanocyte-stimulating hormone), bFGF (basic fibroblast growth factor), BMP-4 (bone morphogenic protein-4), ET-1 (endothelin-1), GM-CSF (granulocyte-macrophage colony-stimulating factor), IL-1 (interleukin 1), NO (nitric oxide), NGF (nerve growth factor); PGE2/PGF2α (prostaglandin E2 and F2α), TNF-α (tumor necrosis factor-α).

Source: Videira IFDS, Moura DFL, Magina S. Mechanisms regulating melanogenesis. *An Bras Dermatol*. 2013;88(1):76-83.

tyrosinase and tyrosinase-related protein (TRP) 1 and 2. Melanocytes produce several molecules and/or intrinsic factors like peptides, cytokines, prostaglandins, and leukotrienes, which act via an autocrine or paracrine way on keratinocytes. Keratinocytes also produce several factors in response to UV radiation exposure, with paracrine action on melanocytes, which may stimulate or inhibit melanogenesis.

(Table 1).² Amongst these many factors having an effect on melanin synthesis, α -MSH is an important intrinsic factor, which exerts its effect mainly as an agonist of Melanocortin 1 receptor (MC1-R).

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Section 3: OPINION

Treatment options currently available for PGH

Premature greying of hair (PGH) is quite common in dermatology clinical practice. However, even though many patients visit dermatology clinics for the treatment of PGH, very few treatment options had been available for them that could be termed satisfactory, thereby showing the paucity of effective evidence-based treatment options for them.^{1,2}

Such a paucity of systemic or topical therapies in PGH rendered camouflage techniques using hair colorants as the mainstay of therapy, though different options had been proposed based on the extent of greying; for instance, plucking out of hair alone is often adopted as an option if less than 10% of hair are affected. Alternatively, an individual

may choose to colour only the grey hair, especially in the beginning when greying is confined to a small region like the temples in men or the perimeter in women.² This is because greying in men usually begins at the temples and in the sideburns, while in women it usually starts around the perimeter of the hairline; gradually, the grey works its way back through the top, sides, and back of the hair.³

Both temporary and permanent hair colours are available for use in persons with PGH, while it has been observed that permanent hair dye is the one that is most frequently used as a hair colorant. These dyes and colours provide a good means of camouflage against PGH; but a major disadvantage associated with the use of permanent hair colour is damage to the

hair shaft, which occur due to oxidation reaction. Hence, there is a need of identifying more effective and long-lasting treatment options for this bothersome and disfiguring condition (PGH) that often causes significant interference with social adjustment and acceptance. Herein, an improved understanding of the pathophysiology of hair greying might possibly reveal promising targets for intervention based on hair follicle melanocyte biology.

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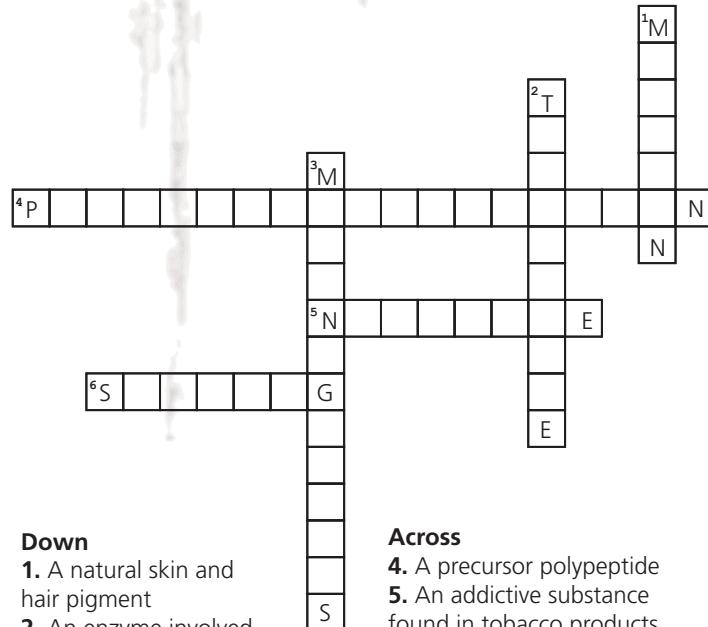
Section 4: GREY MATTER

GREY QUOTE

I've always said that
gray hair looks good on
everybody but yourself.
To me, it makes me
look old.

Kenny Rogers

CROSSWORD



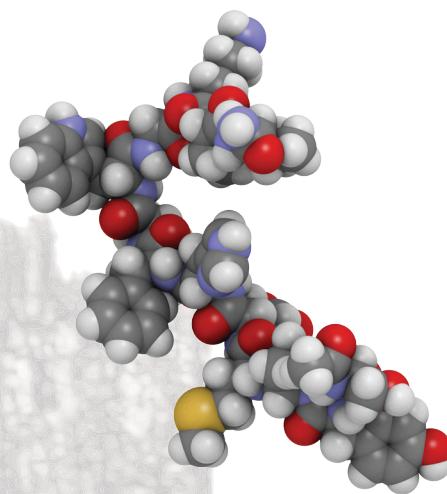
Across

- | | | |
|------|---|---|
| Down | | Across |
| 1. | S | 4. A precursor polypeptide |
| 2. | | 5. An addictive substance found in tobacco products |
| 3. | | 6. A risk factor for premature greying of hair |

Alpha-MSH biomimetic tetrapeptide

Harmonious synthesis and distribution of melanin in the skin and hair contribute to the expression of beauty and the maintenance of health.¹ As this process is disrupted in PGH, various peptides and related compounds have been under testing that might be useful in increasing the melanin levels. For instance, certain analogs of α -melanocyte stimulating hormone (MSH) and oligopeptides with the sequences derived from the hormone were shown to promote melanin synthesis in cells and *in vivo* models. Proopiomelanocortin (POMC)-derived peptide hormones, such as α -MSH, β -MSH, and adrenocorticotropic hormone (ACTH), induce the expression of many key enzymes involved in melanin synthesis, including tyrosinase (TYR), tyrosinase-related protein 1 (TYRP1), and dopachrome tautomerase (DCT).¹ α -MSH is an endogenous neuropeptide derived from POMC, and is primarily a pigmentary hormone of the vertebrates.²

ACTH, α -MSH, and β -MSH are agonists of the melanocortin 1 receptor (MC1R), a G protein coupled receptor. Binding of α -MSH to MC1R at the plasma membrane of melanocytes leads to activation of adenylate cyclase resulting in production of cyclic adenosine monophosphate (cAMP). Subsequently, protein kinase A (PKA) is



activated and in sequence phosphorylates cAMP response element-binding protein (CREB). In the nucleus, phospho-CREB binds to cAMP response element (CRE) on the promoter of microphthalmia-associated transcription factor (MITF) in DNA and induces the mRNA expression of MITF. This MITF plays a primary role in inducing melanogenic enzyme gene expression in response to various stimuli, and thus the regulation of melanogenesis.¹

Melanosome biogenesis occurs through four morphologically distinct stages, wherein in the last stage mature melanosomes are transferred from a single melanocyte through dendrites to the cytoplasm of 30–40 neighbouring keratinocytes, resulting in the spread of

melanin pigments throughout epidermis. Keratinocytes release several cytokines, including α -MSH and endothelin-1, that stimulate melanocytes to promote melanogenesis and melanosome biogenesis.¹

α -MSH is thus a well-tolerated immunomodulator with cytoprotective and anti-inflammatory effects, known to stimulate melanogenesis and proliferation of follicular melanocytes. Since human hair follicles locally synthesize α -MSH, pharmacologically more easily handled α -MSH-related peptides may imitate this endogenous regulation, and may show a favourable clinical use.³ Evidence suggests potential cosmetic application of α -MSH agonists to promote hair pigmentation and thus, reduce the hair greying process.⁴

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* Data on file



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