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Role Of Autophagy In The Aetiopathogenesis Of Premature Graying of Hair: A Narrative Review Of Literature

Wafaa Mohamed Abd-Elmaged[1], Khalda S. Amr[2], Hoda A. Ahmed[2], Dina Ayman[1], Amr Abdelhamed[1]

1- Dermatology, Venereology and Andrology Department, Faculty of Medicine, Sohag University, Sohag 82524, Egypt.
2- Medical Molecular Genetics Department, Human Genetics & Genome Research Division (HGGR), National Research Centre (NRC), Cairo 12622, Egypt

Abstract:

A well-known disorder that causes severe psychological stress and cosmetic impairment is premature greying of the hair (PGH). On the clinical profile and aetiology, there are extensive yet unclear data available. Numerous external and endogenous variables contribute to PGH. Genetics or inheritance, oxidative damage from UV rays, pollution, emotional issues, and inflammatory reasons are only a few of the many causal variables. PGH may be significantly impacted by autophagy. The aetiopathogenesis of PGH is explained by a number of factors, although the precise mechanism is yet unknown. Additionally, other therapy approaches have been used with mixed outcomes. This review article seeks to maximise the most current and widely recognized theories about the aetiopathogenesis and pathophysiology of PGH, which may aid in identifying the most effective treatment options and providing the most acceptable outcomes.

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*Correspondence : dinaayman92@gmail.com

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Introduction:

Age-related physiological changes, such as hair greying (canities), are common. Recent epidemic-ologic studies of men and women of different ethnicities found that 74% of adults between the ages of 45 and 65 had grey hair, with a mean intensity of 27%. .(1)

Aetiopathogenesis of Premature Graying of Hair:

The aetiology of PHG is a combination of acquired environmental variables, inflammation, and psych-ological stress, along with a genetic component with an assumed autosomal dominant pattern of inheritance .(2) Additionally, PHG may be influe-nced by other environmental factors, such as UV radiation and climate, as well as medicines, smoking, trace elements, and nutriti-onal deficiencies .(3) As a component of several premature ageing syndromes, atopic diathesis, Addison's disease, vitiligo, hypothyroidism, or hyperthyroidism, as well as other organ-specific autoimmune illnesses, it may also manifest itself .(4) PHG has also been demonstrated to be a significant indicator of osteopenia, poor bone

mineral density, and a risk factor for coronary artery disease .[5]

The strongest correlations between PHG and personal and family history were found. Every examined relative's family history of PHG was discovered to be substantially correlated with their own personal history of PHG. The mother, father, and siblings showed the highest connections for PHG family history, while the maternal and paternal grandparents showed significantly weaker but still significant associations. [4]

Interferon regulatory factor 4 gene (IRF4), which has been linked for the first time to grey hair, was discovered by researchers at University College London. Melanin synthesis and storage are controlled by the IRF4 gene .[6] The maintenance and development of melanocyte stem cells is also significantly influenced by the genes PAX3 and MITE. Greying may also be caused by defective melanosomal transfer to cortical keratinocytes or melanin incontinence brought on by melanocyte degeneration .[7]

Numerous studies have found connections between autophagy and the regulation of melanocyte proliferation, senescence, and death, as well as melanoma cell growth. By transferring cytoplasmic material to the lysosome for digestion, autophagy is a process of cellular self-digestion .[8] The autophagic machinery's proteins play important roles in melanogenesis, melanosome transfer, and pigmentation. They make it easier for developing melanosomes to move around within melanocytes on microtubules and actin filaments. When the melanosomes are transported to keratinocytes, autophagy prevents the transferred melanin from accumulating too much .[9]

LC3, a mammalian counterpart of the yeast protein Atg8, is one of numerous proteins that are known to be crucial for the autophagic process. After being created in a soluble cytosolic form (LC3-I), Atg7 and Atg3 catalyse an autophagy-specific conjugation reaction that changes LC3-I into a membrane-bound form (LC3-II). Following that, LC3-II is attracted to the autophagosomal membrane. The presence of LC3-II both inside and outside of autophagosomes has been demonstrated by immunoelectron microscopic examination .[10]

Autophagy

Delivering cytoplasmic components to the lysosome for destruction is a part of autophagy. Macro-autophagy, micro-autophagy, and chaperone-mediated autophagy are the three different processes of autophagy according to their mechanisms. Macro-autophagy is controlled by proteins (ATGs) and depends on the sequestration of material into double-membraned vesicles (autophagosomes) in the cytoplasm. Lysosomal enzymes break down the cargo in autophagolysosomes, which are formed when these vesicles join lysosomes. In order to catabolize processes or provide energy, lysosomes release breakdown products. In contrast, in mammals, endosomal-lysosomal fusion triggers micro-autophagy, which involves the invagination of the late endosomal membrane to trap cytoplasmic material that is subsequently eliminated in late endosomes or in lysosomes. Lysosomal membrane invagination in yeast is a characteristic of micro-autophagy. .[11]

Numerous instances in the skin illustrate the two main relationships between autophagy and ageing: **(1)** Autophagy slows down ageing, and **(2)** As people get older, autophagy activity decreases. Autophagy delays ageing in both cell-autonomous and non-autonomous ways by maintaining intracellular homeostasis and promoting the growth of specific cell defense mechanisms .[12]

Autophagy in Melanocytes:

Skin's melanocytes create melanin and distribute it to nearby keratinocytes, which are found either in hair follicles, where it is used to determine hair colour, or in the interfollicular epidermis, where it is used to decide complexion. Age spots (lentigo senilis), pallor, and variations in hair colour are all signs of ageing, suggesting that melanocyte function varies as we get older. Greying of the hair is the most significant consequence of melanocyte failure in ageing. It is believed that

the deterioration of the hair follicle pigmentary unit with ageing is caused by the depletion and form changes of the follicular melanocytes, which feed the pigment to the hair, as well as a rise in redox stress. [13]

Microtubule-Associated Proteins 1 Light Chain 3B:

Proteins linked with microtubules Light chain 1A/1B The MAP1LC3B gene in humans produces the protein 3B (hereinafter referred to as LC3). A crucial protein in the autophagy mechanism is LC3. The most widely utilised indicator of autophago-somes is LC3. [14]

LC3 role in autophagy*:*

During autophagy, autophagosomes take up cytopl-asmic elements such cytosolic proteins and organelles. Concurrently, a cytosolic version of LC3 (LC3-I) interacts with phosphatide-ylethanolamine to generate LC3-phosphatidyl-ethanolamine conjugate (LC3-II), which is drawn to autophagosomal mem-branes. As autophago-somes and lysosomes combine to form autolysosomes, lysosomal hydrolases deg-rade intra-autophagosomal components. Concurren-tly, LC3-II in the autolysosomal lumen is broken down. Due to this, the autophagosomal marker LC3-II's lysosomal turnover reflects starvation-induced autophagic activity, and the immunoblotting or immunofluorescence detection of LC3 has evolved into a useful method for monitoring autophagy and activities related to autophagy, such as autophagic cell death. [15]

LC3 role in melanogenesis:

Although LC3 has been found on melanosomes inside of melanocytes, its functional significance is yet unknown. Based on enhanced LC3 flux, a study linked the removal of melanosomes from kerati-nocytes to autophagy.. [16]

It is proved that LC3B is necessary for the mobil-ization of melanosomes on microtubules. Highlig-hted the role of the ATG4B protease in the dissociation of LC3B from melanosome membranes as a result of its switch from microtubule to actin tracks. As a result, the actin-rich dendrites that transport melanosomes to keratinocytes do not inc-lude the LC3B unique to melanocytes. It's interesting how the biology of melanosomes and autophagic apparatus interact. [9]

Because of the complicated interactions between the two cytoskeletal tracks and the molecular motors, it is unknown how the peripheral melanosomes in all previous cases are redistributed to the center. It has been carefully investigated if LC3B knockdown may have an impact on microtubule structure directly. High-resolution imaging, which shows no observable changes in the position of other organelles on LC3B knockdown, provided strong support for the hypothesis that LC3B is involved in melanosome movement. Perinuclear clustering appears to be the most favored steady-state organization upon disruption of melanosome trafficking. The melanosome may construct complexes with kinesin and dynein using a variety of adaptors by using LC3, just like the autophagosome can. The specific mechanism behind LC3B-mediated melanosome migration needs to be further clarified .[9]

The atypical intermediate melanosome clustering phenotype for ATG4B knockdown has suggested that ATG4B regulates melanosome trafficking. According to biochemical and mutagenic tests, ATG4B is involved in delipidating LC3B from the melanosome membrane. The function of LC3 in melanosome anterograde migration. A thorough knowledge of the LC3B movement of melanosomes on microtubules will be made possible in the future with the careful rebuilding of kinesin and dynein translocon complexes. One could argue that the mobilization and transfer of melanosomes by LC3B to keratinocytes is an indirect method of cellular removal. The epide-rmal desquamation process results in the slough-hing off of melanosomes from keratinocytes. It's interesting to note that because heteropolymeric melanins generated within melanosomes are known to require harsh conditions for degradation, the cell may experience issues with melanosome breakdown. [17]

Future research must focus on how LC3 distin-guishes between the two routes—clearance by

vesicular trafficking and degradation by lysosomal fusion–mechanistically. An autophagic effector known as WD repeat domain, phosphoinositide interacting 1 (WIPI1) has previously been connected to transcriptional control of melanosome formation. Recent research demonstrated how important LC3 and ATG4B are to melanosome dynamics. One crucial aspect of preserving cellular homeostasis may be the interaction between two crucial pathways. As a method of cellular clearance and turnover, organelle trafficking intersects with the autophagic machinery, offering a fresh perspective on vesicular dynamics. [9]

Conclusion:

In dermatology practice, premature greying of the hair is a prevalent issue. Its pathophysiology is complicated, and treating it is difficult. It is regarded as a valuable resource for future studies and clinical trials to determine the precise aetiopathogenesis and pathophysiology, which will aid in developing the best course of treatment with the greatest effectiveness and the fewest side effects.

Abbreviations:

PGH: Premature graying of hair.
LC3B: Microtubule-Associated Proteins 1 Light Chain 3B.

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