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REVIEW

Autophagy Dysfunction: The Kernel of Hair Loss?

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Abstract: Autophagy is recognized as a crucial regulatory process, instrumental in the removal of senescent, dysfunctional, and damaged cells. Within the autophagic process, lysosomal digestion plays a critical role in the elimination of impaired organelles, thus preserving fundamental cellular metabolic functions and various biological processes. Mitophagy, a targeted autophagic process that specifically focuses on mitochondria, is essential for sustaining cellular health and energy balance. Therefore, a deep comprehension of the operational mechanisms and implications of autophagy and mitophagy is vital for disease prevention and treatment. In this context, we examine the role of autophagy and mitophagy during hair follicle cycles, closely scrutinizing their potential association with hair loss. We also conduct a thorough review of the regulatory mechanisms behind autophagy and mitophagy, highlighting their interaction with hair follicle stem cells and dermal papilla cells. In conclusion, we investigate the potential of manipulating autophagy and mitophagy pathways to develop innovative therapeutic strategies for hair loss.

Keywords: hair follicle, mitophagy, dermal papilla cell, hair follicle stem cell, alopecia

Introduction

The term "hair loss" refers to the gradual diminution or shedding of hair. Alopecia constitutes a multifaceted condition influenced by an array of factors such as genetics, physiology, environment, and lifestyle choices.[1,2] Alopecia transcends a mere physical concern; it alters appearance and can exert a profound impact on psychological well-being and social interactions. To elaborate, in 2014, over one million individuals sought surgical or non-surgical therapy.[3] In 2015, the global market for hair loss treatments was appraised at approximately $7.3 billion.[3] Nestled within the dermis and subcutaneous tissue, the hair follicle (HF) emerges as a complex organ embodying intricate structures and functions.[4] It houses over twenty distinct cell types that orchestrate HF cycling and hair proliferation, with the dermal papilla cell (DPC) and the HF stem cell (HFSC) playing leading roles.[5] HF cycling can be segmented into three principal stages: anagen, catagen, and telogen.[6] During the transition from late telogen to anagen phases, the interplay between DPC situated in the base of the bulge and stem cells within the bulge region is vital.[7] DPCs dispense an assortment of pro-hair growth factors, pivotal for the activation of stem cells and the commencement of a new hair cycle.[8,9] Upon signal reception, activated HFSCs proliferate until a critical population threshold is met, instigating the HF's ensuing growth phase.[10] Nevertheless, multiple factors can perturb the HF cycle, engendering a premature exit from the anagen phase and an expedited arrival of catagen and telogen stages. Outcomes like hair shaft (HS) miniaturization or a reduction in the quantity of HFs during the catagen-telogen phase potentially culminate in hair loss attributable to these malfunctions.[11]

Androgenetic alopecia (AGA), colloquially termed male pattern hair loss (MPHL) or female pattern hair loss (FPHL), reigns as the preeminent form of hair loss worldwide.[12] In men, it starts with bilateral temporal thinning of the frontal scalp and progresses to the vertex.[13] In women, it predominantly manifests as diffuse thinning atop the scalp, sans a receding hairline[14] The etiology of AGA remains incompletely deciphered, yet is principally correlated with the male hormone testosterone and its metabolite dihydrotestosterone (DHT). These hormones precipitate the miniaturization of HFs, culminating in a truncated hair growth cycle and progressive hair thinning that inexorably leads to hair loss.[15,16]

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Typically, on an average scalp, between 90–95% of HFs are in the anagen phase.[17] Nevertheless, in individuals afflicted by AGA, a pronounced surge in telogen follicles is observed, accounting for roughly 20% of HFs in the telogen phase, with a mere 80% remaining in the anagen phase. As of now, hair transplantation and pharmacotherapy stand as the principal therapeutic strategies for AGA. The Food and Drug Administration (FDA) has sanctioned exclusively minoxidil and finasteride as efficacious treatments for AGA.[12] Nonetheless, both interventions can induce diverse side effects and necessitate sustained usage, thereby engendering challenges in patient adherence.[18–20]

Alopecia areata (AA) secures the second rank among the non-scarring alopecia, subsequent to MPHL and FPHL.[21] Within China, the estimated prevalence hovers at approximately 0.2%.[22] Though AA can manifest at any age frame, it primarily emerges within the 25 to 36 age bracket. In severe instances, AA may escalate to alopecia totalis (AT) or progress towards alopecia universalis (AU).[21,23] The pathophysiology of AA continues to be enigmatic, with a notable contributing element being the disruption of HF's immune privilege (IP).[24] Predominantly, AA instigates HFs to precipitously transition from the anagen phase to the catagen and telogen stages.[21] T The minimally impacted follicles persist in the anagen phase, yet eventually yield HSs that are undernourished, advancing to the catagen phase.[21] Although AA seldom incites serious physical ailments, its ramifications can considerably impinge upon a patient's self-worth and emotional well-being.[25] Spontaneous recovery may transpire within a year for a cohort of 34%-50% of patients; notwithstanding, recurrences are frequent, with less than 1% attaining full recovery and around 10%-25% advancing to AT or AU.[26,27] At present, treatment modalities remain circumscribed, accentuating the exigency for amplified research efforts and clinical trials to cultivate impactful therapeutic options.[28]

Autophagy, a lysosome-mediated cellular recycling process, is crucial for sustaining cellular metabolism and diverse biological activities. This process plays a pivotal role in the elimination of damaged proteins, organelles, pathogens, and aggregates. A specific form of autophagy, termed mitophagy, oversees the homeostasis of mitochondrial population and function. The role of autophagy in hair loss processes has emerged as a burgeoning field of research. Prior studies have revealed that alopecia and autophagy activation occur concomitantly under stressful conditions, with alopecia attributed to impaired autophagy.[29,30] These observations indicate that autophagy can be a double-edged sword, with excessive autophagy often yielding adverse effects, yet the precise mechanisms of autophagy remain elusive. Effective treatment strategies hinge upon a thorough comprehension of autophagy's involvement, given the varying roles and targets across different forms of alopecia. Contemporary studies have shed light on novel therapeutic avenues by underlining the key role of autophagy in various HF cell types, particularly DPCs and HFSCs.[31–33] This intracellular mechanism has been consistently demonstrated as a vital regulator within the HF developmental cycle and ensuing hair growth. Here we propose a strategic approach for effectively targeting autophagy, grounded in an understanding of autophagy and mitophagy's roles during hair loss, alongside several promising pharmacological candidates.

Autophagy and Mitophagy

Autophagy is an intracellular defense mechanism enabling lysosomes to recycle internal material through the elimination of damaged, senescent, or malfunctioning cellular components. Autophagy can be categorized into three distinct types: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA), each distinguished by the distinct pathway intracellular substrates utilize to access the autolysosome lumen.[34] Microautophagy utilizes membrane invaginations to ensnare and degrade intracellular targets.[35] In contrast, CMA selectively engages proteins adorned with a specific recognition sequence (KFERQ motif). These proteins associate with chaperone molecules like Hsc70 and are conveyed toward lysosomal membrane receptors (LAMP-2A) for subsequent degradation.[36] When referred to singularly, autophagy typically denotes macroautophagy.[37] Autophagy is a multi-faceted process encompassing (1) initiation, (2) phagophore nucleation, (3) phagophore expansion and substrate selection, (4) autophagosome-lysosome fusion, and (5) lysosomal substrate degradation.[38] (Figure 1) Autophagy plays a quintessential role in immunological responses, antiviral defense, cellular energy generation, metabolic regulation, and the removal of senescent or dysfunctional organelles.[39,40]

As a tightly regulated process, autophagy is amenable to modulation by myriad signaling pathways and proteins. Members of the autophagy-related gene(ATG) family, which encode proteins critical to the autophagy process, are among the primary genes involved in autophagy.[41] Autophagy is initiated intracellularly or precipitated by external stressors such as oxidative stress (OS), pathogen infiltration, or nutrient scarcity.[42] T These factors influence autophagy via

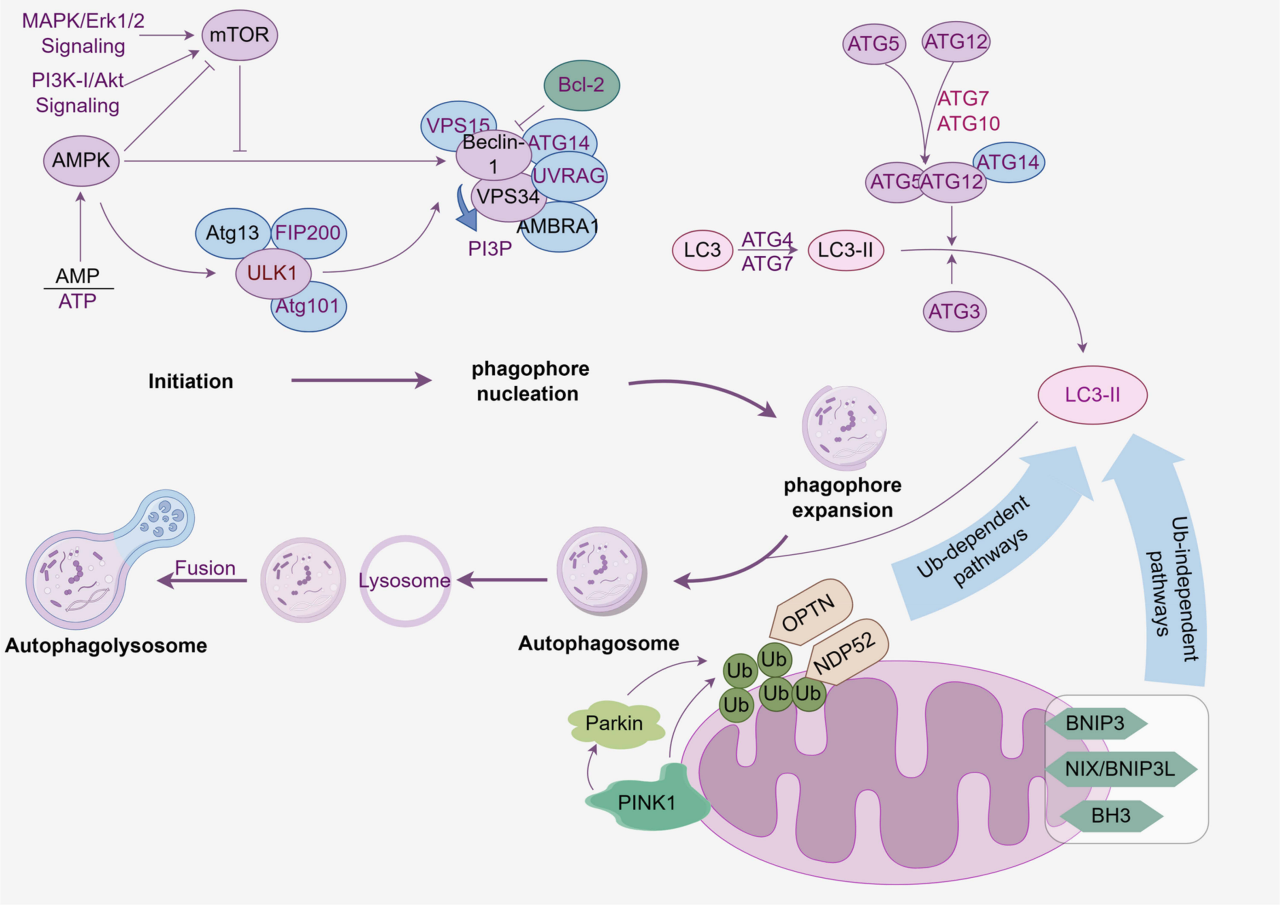

Figure 1 Molecular mechanisms of autophagy and mitophagy (By Figdraw). Autophagy commences in the cytoplasm following the activation of the ULK1 complex. Phosphorylation of the ULK1 complex ensues, leading to the activation of BECN1. The activated BECN1 then complexes with VPS34, a class of PI3K, initiating the production of PI3P, which in turn promotes phagophore nucleation. Subsequently, PI3P attracts additional autophagy-related proteins to form further complexes. During phagophore expansion and substrate selection, ATG5 and ATG12 undergo a conjugation reaction, producing the ATG5-ATG12 complex. This conjugation is facilitated by the proteins ATG7 and ATG10The resulting ATG5-ATG12 complex then associates with ATG16 to form a macromolecular complex, recruiting members of the LC3 protein family to the phagophore membrane. Within this mechanism, LC3-I is converted into LC3-II through the combined action of ATG4, ATG7, and ATG3, and then attaches to the phagophore membrane. This dynamic sequence culminates in the closure of the phagophore and the formation of an autophagosome containing cellular substrates. Mitochondria participate in autophagy via both ubiquitin Ub-dependent and Ub-independent pathways.

Abbreviations: ULK1, unc-51 like kinase 1; ATG, autophagy-related gene; BECN1, beclin 1; PI3K, phosphatidylinositol 3-kinase; PI3P, phosphoinositide-3-phosphate; LC3, light chain 3; Ub, ubiquitin; PINK1, PTEN-induced kinase 1; BNIP3, adenovirus E1B 19 kDa protein-interacting protein 3; NIX NIP3-like protein X; BNIP3L, BNIP3-like; BH3, BCL2 homology 3.

assorted signaling pathways, notably the mammalian target of rapamycin (mTOR) pathway and the 5'adenosine monophosphate-activated protein kinase (AMPK) pathway. Primarily, mTOR impedes autophagy by phosphorylating and regulating proteins involved in autophagy.[43] mTOR, a highly conserved serine/threonine kinase, integrates diverse signaling pathways—like the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinases (ERK) pathway and the phosphatidylinositol 3-kinase(PI3K)/Ak strain transforming (Akt)pathway—with nutrient sensing. In mammals, the mTORC1 complex primarily governs autophagy.[44] Once active, mTORC1 hinders autophagy through several mechanisms, including the inhibition of ULK1 complex activity.[45] Conversely, AMPK, a heterotrimeric serine/threonine kinase, functions as a crucial energy sensor and signaling molecule, its activity modulated by intracellular ATP and AMP concentrations. AMPK facilitates autophagy initiation and progression by mechanisms including ULK1 phosphorylation and mTORC1 inhibition.[45]

Mitochondria, often termed cellular powerhouses, synthesize ATP through oxidative phosphorylation and orchestrate a plethora of cellular functions, including biosynthesis, signaling, proliferation, differentiation, and apoptosis.[46,47] Imbalances in mitochondrial metabolic homeostasis, manifesting as excessive accumulation of reactive oxygen species (ROS), mitochondrial DNA (mtDNA) damage, and alterations in mitochondrial fusion and fission, can jeopardize cellular

viability and functionality.[48] Mitophagy, a specialized form of autophagy, eliminates compromised mitochondria through lysosomal degradation, pivotal for the maintenance of mitochondrial mass and structural integrity.[49] Mitochondrial autophagy is facilitated by two principal mechanisms: ubiquitin(Ub)-dependent and Ub-independent pathways, as depicted in (Figure 1).[50] The PTEN-induced kinase 1 (PINK1)/Parkin pathway represents the most extensively researched Ub-dependent regulatory mechanism. Under baseline conditions, PINK1 is incorporated into and subsequently degraded within mitochondria, a process governed by transmembrane potential.[48] Upon mitochondrial damage, PINK1 accumulates on the outer mitochondrial membrane, thereby attracting and phosphorylating Parkin.[51] Parkin subsequently binds to the impaired mitochondria, facilitating their ubiquitination and sequestration into autophagosomes for eventual autophagic degradation.[51] Additionally, PINK1 can directly recruit autophagy receptors OPTN and NDP52 on compromised mitochondria, thus facilitating mitophagy.[50] Ub-independent pathways characteristically encompass receptors such as BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3), NIP3-like protein X (NIX)/BNIP3-like (BNIP3L), and BCL2 homology 3 (BH3) proteins.[52] Embedded in the outer mitochondrial membrane, these proteins bind directly to LC3, orchestrating the recruitment of mitochondria to autophagosomes for subsequent degradation.[50]

In the realm of disease research, the scrutiny of autophagy has attracted substantial interest, especially with regard to neurodegenerative disorders, cancer, and inflammatory or autoimmune conditions.[53–57] In Alzheimer's disease, dysregulation of autophagy leads to aberrant protein accumulation, whereas an increased autophagic flux could aid in reinstating neuronal equilibrium.[58] In Alcohol-Related Liver Disease (ALD), alcohol-induced mitochondrial dysfunction might be mitigated by augmenting mitophagy, potentially slowing the progression of ALD.[59] Additionally, autophagy acts as a protective mechanism against kidney ischemia-reperfusion injury.[60] In breast cancer cells, elevated cytoplasmic YAP1 levels can initiate autophagy, thereby curtailing the proliferation of the cancer.[61] Recent insights also indicate that within dermatology, enhanced autophagy can attenuate skin photoaging damage and limit the proliferation of cutaneous melanoma cells.[62–64] Furthermore, autophagy is intricately associated with alopecia-related disorders, and continued exploration of its mechanisms could herald novel therapeutic avenues.

Autophagy and Alopecia-Related Diseases

Autophagy is critical in sustaining HF growth, potentially orchestrating a myriad of biological processes throughout the hair cycle. Autophagy emerged as one of the augmented signaling pathways in a Kyoto Encyclopaedia of Genes and Genomes (KEGG) analysis of 105 downregulated mRNAs transitioning from the anagen to the catagen phase.[65] Additionally, a comprehensive evaluation of autophagic activity in the HF cycle on mice's dorsal skin revealed an elevation of autophagy in anagen, a diminution in catagen, and stable low levels during telogen.[66] Active autophagic flux was predominantly observed in hair matrix keratinocytes and dermal adipocytes encircling the HFs.[32,67] The role of autophagy is multifaceted, exerting diverse effects. Suppression of autophagy in keratinocytes notably impacted HFSC activation, precipitating an accelerated switch of HFs from the telogen to the anagen phase.[68] Notably, the upregulation of PTEN to stimulate autophagy in HFSCs supported differentiation, playing a role in HF cycle regulation and hair growth facilitation.[31] Activation of autophagy facilitated HFSC proliferation and was instrumental in scalp regeneration during tissue expansion.[69] Concurrently, autophagy promoted scalp angiogenesis, critical for hair growth. Given that autophagy degrades specific proteins and aids in synthesizing structural proteins, it is significant for HS development and maintenance.[70] This enhanced the mechanical resilience of the HS. Disruptions in autophagy can adversely impact hair health. Premature onset of the catagen phase has been linked to ATG5 knockdown, with observed compromised hair development in Atg7-deficient mice skin grafts.[30,67] Collectively, these outcomes underscore the intimate interplay between autophagy and HFs, alluding to the potential role of autophagy in the pathogenesis of alopecia-related conditions.

Autophagy and Hair Loss

In the field of dermatological research, empirical evidence points to the involvement of autophagy in various hair loss conditions. While the precise mechanisms remain elusive, AGA has genetic and hormonal associations.[71] HFs in the early catagen phase are considered particularly susceptible to external influences.[72] Thus, it is hypothesized that the

pivotal changes in HFs during AGA transpire predominantly in this specific phase. In early-stage AGA-affected individuals, research has confirmed a significant reduction in ATGs and proteins in early catagen phase miniaturized HFs.[73] This deficiency was associated with an upsurge in cellular apoptosis, indicating a role for both apoptosis and autophagy in the HF miniaturization process during AGA. The BCL2 protein, found in substantially higher concentrations during the anagen phase in AGA's alopecia region compared to the non-alopecia region and normal human scalp HFs, impeded autophagy via its interaction with BECN1.[73,74] The co-localization of BCL2 with the autophagy-related protein BECN1 implied that the BCL2-BECN1 interaction might play a role in the pathogenesis of AGA. Furthermore, inhibition of autophagy with 3-methyladenine (3-MA) in organ-cultured HFs arrested hair growth and further hastened the anagen-catagen transition. Parodi et al[67] and Chai et al[66] discovered that autophagy is essential for preserving the anagen phase in HFs and in mice, respectively. DPCs treated with DHT showed decreased levels of the autophagy marker LC3 II.[75] It is noteworthy that Nam et al[76] uncovered that DHT induces dephosphorylation of mTOR, accelerating apoptosis and autophagy in AGA, in contrast to previous experiments suggesting inhibited autophagy.[77,78] This discrepancy could be attributed to the different stages of AGA progression. It seems that while high concentrations of DHT promote DPC autophagy, lower concentrations inhibit it, with both levels influencing HF health.[79] The AC2 peptide, derived from Trapa japonica fruit extract, mitigated the detrimental effects of DHT on DPCs while fostering their growth.[76] By inhibiting mTORC1 activation, AC2 curbed excessive autophagy and apoptosis induced by DHT, underscoring the importance of autophagic equilibrium in DPC protection.[76] In summary, these diverse observations demonstrate that the role of autophagy in AGA may vary according to the disease's stage of progression.

A plethora of studies have elucidated the linkage between autophagy and AA. Genetically, a 2010 genome-wide association study (GWAS) revealed an association between AA susceptibility and two autophagy-related pathways, notably involving the PARK2 and PFKFB3 genes.[80] Additionally, autophagy-regulated genes STX17 and BCL2L1 were linked to AA pathology.[80] Furthermore, a 2020 GWAS underscored the presence of copy number variants entailing deletions of crucial autophagy-associated genes ATG4B and BOK in AA patients.[81] Both ATG4B and BOK reside on chromosome 2.[82,83] A ATG4B, an encoded cysteine protease, serves as a pivotal enzyme in autophagy, whereas BOK, a member of the BCL2 family, likewise facilitates autophagy promotion.[81,84,85] The deletion of either ATG4B or BOK might induce a cumulative effect, thereby impacting other autophagy-related genes and pathways.[81] Furthermore, the gene CLEC16A has been shown to play a significant role in autophagy regulation and is also implicated in AA.[86] From a pathogenic perspective in AA, interferon-γ (IFN-γ) is acknowledged for its role in triggering the collapse of HF IP.[87] Treating anagen HFs with IFNγ unveiled a decrease in autophagy flux and an increase in histocompatibility complex (MHC) class I expression within the anagen HF bulb, suggesting a strong correlation between IP collapse and autophagy.[24,88] Spermidine, identified as an autophagy promoter, was discerned to reinitiate autophagy and reduce MHC expression in HFs when combined with IFNγ.[88] Subsequent observations of AA patients exhibited a notable reduction in autophagic flux within the HFs. Conversely, non-lesional scalp areas manifested significantly elevated levels of Atg5 and LC3B in HFs compared to healthy counterparts. These observations pointed to an initial phase of temporary autophagy upregulation in AA's early stages. Nonetheless, autophagy significantly waned as compensatory mechanisms diminished, indicating dysfunctions in autophagic activity at both the protein and ultrastructural levels in AA patients. In summary, autophagy plays a role in pathogenic processes, genetic predispositions, and physical manifestations. This presents potential opportunities for gene therapy in AA by modifying the expression or activity of specific autophagy-related genes. Given the varied declines of autophagy across different regions in AA patients during the disease's active phase, it is imperative to consider each patient's autophagic status for an individualized and precise treatment approach.

Among young individuals, stress is a prevalent cause of hair loss.[89] Prolonged stress prompts HFs to secrete excess corticotropin-releasing hormone (CRH).[90] In both the chronic social defeat stress and chronic unpredictable stress mouse models, autophagy and hair growth were observed to be impeded within HFs.[91] Subsequent research disclosed that CRH diminishes autophagy through the mTOR-ULK1 pathway, whereas its promotion appeases symptoms of hair loss. CRH may serve as a potential therapeutic target, and adjusting its impact on the autophagy pathway could aid in treating hair loss.

Topical application of dexamethasone (Dex) has been shown to induce follicular degeneration and impede hair growth.[92,93] Human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs), sourced from umbilical cord

tissue, are pluripotent in nature.[94] An array of studies has demonstrated that the transplantation of hUCB-MSCs can address a spectrum of diseases.[95–97] Transplantation of hUCB-MSCs onto the dorsal surface of C57BL mice significantly ameliorated Dex-induced hair loss.[98] Enhanced autophagy in the HFs of the transplanted mice suggested a link between Dex-induced HF damage and decreased autophagy. Furthermore, co-culturing MSCs with HaCaT cells in vitro resulted in elevated expression of autophagy-related mRNA and proteins, implying the activation of numerous autophagic pathways. This indicated that MSCs may shield keratinocytes from Dex damage by enhancing autophagy.

In cases of radiation-induced dermatitis, notable hair loss and a decrement in HFs were observed.[99] These conditions were correlated with the initiation of both apoptosis and autophagy in skin cells due to radiation exposure. The mechanism by which radiation induces autophagy is complex, and such autophagy may exhibit a dual role.[99] Although specific details are yet to be elucidated, there exists potential for developing innovative preventive and therapeutic approaches that mitigate radiation-induced dermatitis and alopecia through the pharmacological regulation of autophagy and subsequent cellular protection.

Prolonged exposure to particulate matter (PM) is recognized as harmful to human skin and capable of exacerbating existing dermatological conditions.[100,101] Its application to outer root sheath (ORS) cells, ex vivo-cultured human HFs, and the dorsal skin of C57BL/6 mice compromised the cell viability within HFs and hastened the catagen phase onset.[102] PPM also amplified autophagic activity in HFs in both in vitro and in vivo contexts. Compared to normal HFs, those deficient in autophagy exhibited significantly increased transitions from anagen to catagen phases, underscoring autophagy's potential as a protective mechanism against PM-induced hair loss. Further investigation into skin damage induced by PM demonstrated a concentration-dependent reduction in human dermal fibroblast (HDF) viability upon exposure to PM10.[103] Such exposure also provoked the expression of pro-inflammatory cytokines in HDFs, aggravating the inflammatory response of the skin.[103] As a compensatory response, HDFs enhanced autophagy, along with alterations in the expression of autophagy-associated genes, including the upregulation of CTSL and the downregulation of DAPK1 and DAPK2. HDFs facilitated the division and proliferation of HFSCs as well as DPC activation by producing growth factors and extracellular matrix molecules throughout the HF cycle.[104] Collectively, these findings suggest that PM's impact on HFs could be associated with its influence on autophagy in HDFs and ORS cells.

The critical role of Gasdermin 3 (Gsdma3) in HF development has been corroborated by extensive research.[105,106] Research by Tamura and Masaru[107] demonstrated that mouse mutants expressing Gsdma3 exhibited a hair loss phenotype. This phenotype was associated with increased autophagy activation, attributable to mutations in the C-terminal domain of Gsdma3. Additional evidence of autophagy was noted in the HFs of these mutant mice, underscoring the pivotal role of autophagy in HF biology regulation.[105]

Beyond numerous common human ailments that lead to alopecia, autophagy has also been observed in dogs suffering from atopic dermatitis (CAD) or pituitary-dependent hyperadrenocorticism (PDH), both culprits of baldness.[108] Scanning electron microscopy revealed reduced damage to the hair surface and hair cuticle layers in dogs diagnosed with CAD or PDH after an eight-week regimen with a synthetic autophagy inducer.[109] Recent studies have suggested that specific mechanisms may involve autophagy mitigating oxidation-based inflammation in the skin of canines, a result of oxidative stress (OS). These lend credence to the notion that targeted activation of autophagy could alleviate hair damage caused by diseases associated with inflammation.[109,110]

Autophagy has been implicated in numerous hair loss-related conditions (Figure 2), yet the precise cells and signaling pathways affected by autophagy remain a key unanswered question. Hence, the broad modulation of autophagy might provoke unintended side effects on hair. Consequently, further studies are essential to therapeutically target the pathway in various alopecia-related disorders.

Mitophagy and Hair Loss

Mitochondria and HF

HF cells perform a multitude of critical functions and physiological processes that necessitate substantial energy expenditure, rendering them among the most energy-intensive organs in the body.[111] Within HFs, mitochondria situated in a paraxial "ring of fire", crucial for the hair cuticle and outer cortex formation, exhibit pronounced hyperpolarization and ROS generation, pivotal for energy production.[112] The Annurca Apple polyphenolic extract reportedly promoted hair

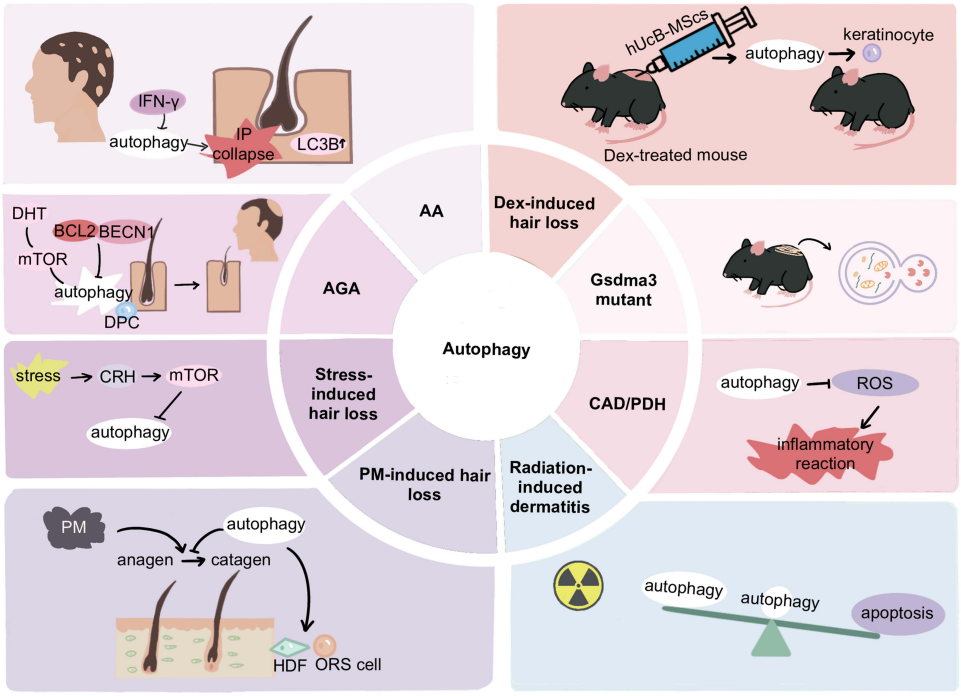

Figure 2 The role of autophagy in different hair loss disorders. → represents promotion, ┤ represents inhibition.
Abbreviations: AA, areata alopecia; AGA, androgenetic alopecia; PM, particle matter; CAD, canine atopic dermatitis; PDH, pituitary-dependent hyperadrenocorticism; Gsdma3, Gasdermin 3; Dex, dexamethasone; IP, immune collapse; BECN1, beclin 1; mTOR, mammalian target of rapamycin; CRH, corticotropin-releasing hormone; HDF, human dermal fibroblast; ROS, reactive oxygen species; hUCB-MSCs, Human umbilical cord blood-derived mesenchymal stem cells; LC3, light chain 3.

growth by energizing mitochondrial respiration and β-oxidation in HFs, culminating in the production of adenosine triphosphate (ATP).[113] This generation of ATP assists in the protection of keratin-synthesizing proteins from oxidative damage.[113] Recent findings suggest that mitochondria play a critical role in both HF growth and the orchestration of the HF cycle. The lack of the mitochondrial protein Myelin Protein Zero-like 3 (MPZL3) led to a postponed entry into the growth phase of HFs in mice following normal birth.[114] Intriguingly, during the second hair cycle, these mouse HFs transitioned into the anagen phase more rapidly. Nonetheless, localization studies of MPZL3 have confirmed its predominant presence in the distal pre-cortex, upper epidermal layers, and HF sebaceous glands during the mid to late anagen phases. The precise regulatory mechanisms that mitochondria employ to engage in the HF cycle remain unclear. Levels of Bcl-2 and Bax, in conjunction with WNT/β-catenin signaling, could serve as important determinants in this process.[115–118] Conversely, Harlequin (Hq) mutant mice harboring the Aifm1 gene exhibited either deletion or functional loss of the apoptosis-inducing factor protein.[119]

The primary manner in which mitochondria impact HF is through their influence on HFSCs and DPCs (Figure 3). Typically, mitochondrial function in HFSCs operates in parallel with the cellular state. Sirtuin-1 (Sirt1) oversees mitochondrial function and biosynthesis and ameliorates damages induced by inflammatory stress through the MAPL-ERK-Mfn2 pathway.[120] The overexpression of Sirt1 accelerates HFSC migration and proliferation while protecting them from the inflammatory response elicited by TNF-α. Diminished mitochondrial function likewise exerts a detrimental impact on HFSC. Melanocytes, HF mesenchymal cells, and immune cells were adversely affected by significant mitochondrial dysfunction following the epithelium-specific deletion of mitochondrial transcription factor A (TFAM) in mice.[121,122] This led to increased apoptosis, reduced proliferation, and premature progression to the catagen phase of the HFs on the mice's dorsal.[121] A mitochondrial-associated protein named Crif1 regulates transcription and translation.[123] In the case of epidermis-specific icKO mice (Crif1 K14icKO), a delay in the HF growth cycle was observed.[123] Correspondingly, a comparable delay was evident in HFSC-specific icKO mice (Crif1 K15icKO), in which the effect on the normal differentiation of HF cells was apparent. Although impaired mitochondrial function is linked to stem cell apoptosis, it was noteworthy that in Crif1 K15icKO mice, the HFSCs retained viability.[120,124] Interestingly,

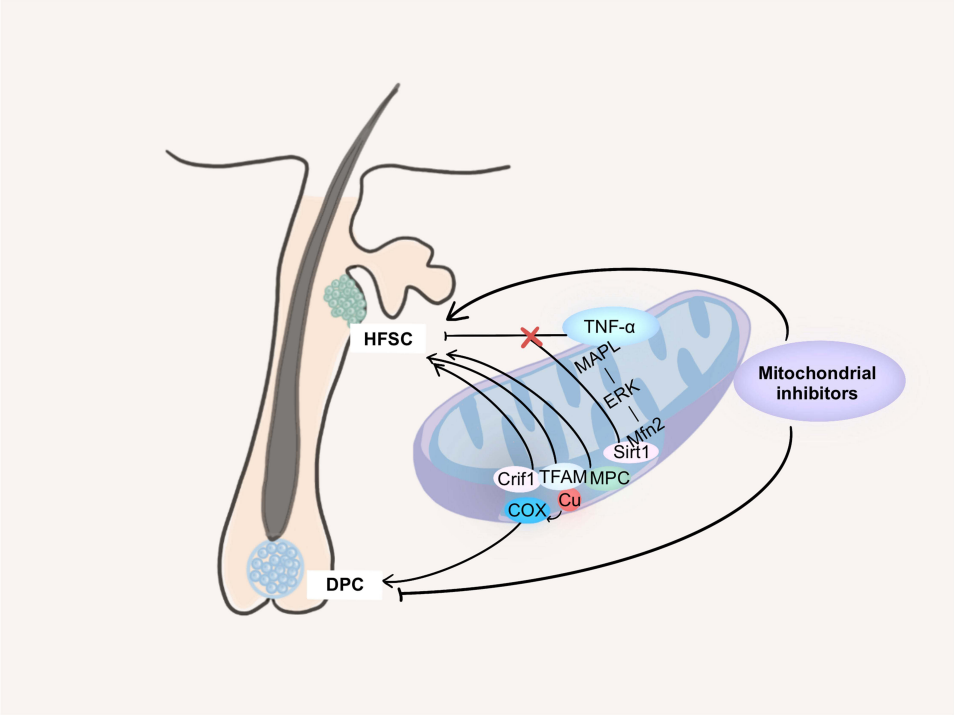

Figure 3 Relationship between mitochondria and HFs →represents promotion, ┤represents inhibition.
Abbreviations: HFSC, hair follicle stem cell; DPC, dermal papilla cell; Sirt-1, sirtuin-1; TFAM, transcription factor A; MPC, mitochondrial pyruvate carrier; ERK, extracellular signal-regulated kinase.

moderate suppression of mitochondrial function has been found to stimulate the induction of HFSCs, enabled by a transition in mitochondrial metabolism.[125] When mitochondrial oxidative phosphorylation was mildly inhibited by mitochondrial inhibitors, an uptick in both glycolysis and lactate synthesis became evident, resulting in an increased population of HFSCs.[126,127] This mechanism is considered to actively promote early-stage HF regeneration.[126,127] The process also implicated the involvement of the Wnt and Shh pathways.[127] Echoing this discovery, it was observed that the inhibition of the mitochondrial pyruvate carrier (MPC) on the inner mitochondrial membrane precludes cytoplasmic pyruvate from entering mitochondria, thereby inducing HFSC activation.[126,128]

As highly differentiated cells within the HF, DPCs require augmented energy from mitochondria.[129] Compounds like Polygonum multiflorum, Houttuynia cordata extracts, and Quercitrin have been shown to foster mitochondrial activity, elevate mitochondrial membrane potential (MMP), boost energy metabolism in DPCs, and stimulate hair growth.[117,130,131] In instances of Tetrathiomolybdate (TM)-mediated copper depletion in DPCs, diminished cytochrome c oxidase activity led to impaired mitochondrial productivity, heightened ROS production, and MMP depolarization.[132] Interestingly, the study revealed that elevated ROS levels, rather than an ATP deficit, influenced DPCs' biological functions. The employment of agents like Tetrathiomolybdate (TM), 2-deoxyglucose, bongkrekic acid, and ibipinabant was noted to affect ATP production while preserving DPC activity intact. These findings point to the presence of potent compensatory mechanisms within DPCs that enable them to maintain their essential functions during ATP scarcity. This also implies that in the treatment of hair loss, medications directly targeting mitochondrial energy metabolism may not immediately yield the desired effects due to complex cellular regulatory mechanisms potentially causing divergent outcomes. In conclusion, a mild mitochondrial inhibitor may prove beneficial in promoting hair growth as it does not drastically alter DPC function, but rather enhances the proliferation of HFSCs. Nevertheless, additional research is required to ascertain the exact manners in which mitochondria and ATP influence DPC activity and the adjustment of DPCs to fluctuations in ATP levels. Concurrently, the use of N-acetyl cysteine, ascorbic acid, and a combination of nanoencapsulated anti-hair loss compounds may serve to reduce mitochondrial ROS (mtROS) and ameliorate hair loss derived from mitochondrial dysfunctions.[115,132]

Hair loss is commonly observed in a variety of diseases associated with mitochondrial dysfunction.[133] Particularly in AGA progression, DHT amplified VDAC1 expression, a pivotal protein regulating mitochondrial calcium influx.[134] This amplification

occurred via the p38 signaling pathway, leading to increased formation of mitochondria-associated membranes (MAM) and subsequent mtROS accumulation.[134] In AGA patients, the compensatory upregulation of twelve mitochondrial-related genes within DPCs was observed.[135] Specifically, male AGA patients displayed elevated mtROS levels in persistently balding scalp regions compared to non-balding areas, alongside an increase in the expression of certain genes associated with antioxidant activities. Subsequent investigations revealed a decline in electron transport chain (ETC) complex activity, alongside reduced mitochondrial ATP synthesis. These factors collectively promote increased apoptosis in DPC cells, thereby expediting AGA progression. It has been hypothesized in frontal fibrosing alopecia that defects in mitochondrial β-oxidation, together with inflammatory responses induced by an accumulation of excess metabolites and oxidized proteins, may initiate the loss of HFSCs.[136] Whole-genome sequencing (WGS) has successfully pinpointed genes related to X-linked alopecia in Pomeranian dogs, featuring a significant number of mtDNA mutations.[137] Recent research has shown the effectiveness of certain ROS scavengers in diminishing mtROS levels and bolstering cellular metabolic activity, indicating their potential therapeutic value in managing alopecia areata. Collectively, these studies underscore the significant roles mitochondria play in AGA, alopecia areata (AA), and numerous prevalent forms of hair loss.

The relationship between mitochondrial function and HF aging is closely intertwined. On the one hand, aging skin exhibits aberrant mitochondrial function. In aging skin, common occurrences such as mtDNA deletions and point mutations are frequently observed.[138] Oxidative stress is believed to play a pivotal role in hair graying, with mitochondria potentially playing a part in this process.[139] Conversely, mitochondrial damage can contribute to the manifestation of aging symptoms. Mice with defective mitochondrial DNA polymerase underscored significant premature aging and reduced hair density.[138,140] Notably, a mouse model with inhibited polymerase gamma (PolG), termed the "tDNA-depleter" mouse, displayed early signs of premature aging.[141] Despite no reduction in the number of HFs and the HF cycle, the majority of HFs became dysfunctional, unable to produce normal HSs. These mice exhibited active senescence-associated inflammation, increased expression of senescence markers such as IGFIR, VEGF, and MRPS5, along with decreased Klotho expression in the skin. However, restoring mtDNA levels significantly ameliorated these symptoms. Mitochondrial dysfunction was also observed in isolated keratinocytes from patients with Cockayne syndrome type A, consequently leading to premature aging.[142,143] In Rothmund-Thomson syndrome, loss of RECQL4 function affected mitochondrial biogenesis and mtDNA stability, resulting in hair thinning observed in both mice and human patients.[143–145] Research indicated that dermal fibroblasts from long-lived dog breeds possessed more uncoupled mitochondria, minimal electron leakage, and enhanced respiratory capacity.[146] Targeting mitochondrial function holds promise in diminishing HF aging effectively. Older mice treated with allogeneic mitochondrial transplantation conjugated with Pep-1 conjugation (P-Mito) exhibited significant hair loss delay and maintained longer and denser hair.[147] Examination of dorsal skin sections revealed that mitochondria-injected mice retained a greater number of HFs and facilitated the entry into the anagen phase. Concurrently, the treatment augmented collagen deposition and stimulated thickening of the subcutaneous fat layer of the skin. Genetically, a pronounced reduction in the expression of aging-related genes IGF1R and MRPS5 was noted, alongside an upregulation of the anti-aging gene Klotho in mitochondria-treated mice.

Mitophagy and Hair Loss

AA is primarily associated with mitochondrial autophagy. The pathophysiology of AA may entail OS arising from the release of copious amounts of ROS from impaired mitochondria, subsequently eliminated by mitophagy.[148,149] When ORS cells were exposed to IFNγ and polyinosinic-polycytidylic acid (poly[I: C]), emulating the inflammatory response typical of AA, concurrent mitochondrial DNA damage and escalated mitochondrial ROS levels were identified.[150] Concurrently, an accumulation of PINK1 within mitochondria was reported to enhance LC3-II expression and diminish p62 expression, indicating mitophagy activation. Moreover, triggering mitochondrial autophagy with carbonyl cyanide chlorophenylhydrazone (CCCP) reduced the activation of the NLRP3 inflammasome within ORS cells. This suggests that compensatory activation of PINK1-mediated mitophagy may help to curtail AA disease progression. Most recently, reductions in autophagic activity were observed in the HFs of C3H/HeJ AA mice.[151] While the induction of autophagy decelerated AA development, conditions that promoted autophagy blockage intensified AA pathogenesis.[151] Therefore, modulating mitophagy to alleviate mitochondrial dysfunction and prevent inflammasome activation presents a promising avenue for forthcoming AA therapies. Copper supplementation was found to inhibit the phosphorylation of AMPK and activate mTORC1, restoring DPC activity in TM-treated DPCs. It was hypothesized that copper insufficiency could instigate mitochondrial damage and excessive mitophagy activation and that fostering autophagy homeostasis

could enhance cellular functionality.[132] Werner Syndrome (WS) likewise presented a notable correlation with mitochondrial dysfunction and heightened ROS, inducing diverse manifestations of skin aging.[143] Further examination showed an accumulation of damaged mitochondria in individuals with WS. Inducing mitochondrial autophagy did improve general health and somewhat increased lifespan.[152] Moreover, alterations in mitochondrial function were observed in hair loss disorders induced by PM,[103] Dex,[98] AGA,[76] radiation-induced dermatitis,[99] and Gsdma3 mutant mice,[105] as previously discussed. These indicate the potential involvement of mitophagy, but further investigation is needed to determine the relationship between mitophagy and hair loss. Specifically targeting mitochondrial autophagy in HFs could present a more targeted treatment approach compared to general autophagy mechanisms.

Autophagy Modulation in Hair Loss Treatment

Currently, in addition to previously mentioned treatments like Trapa japonica fruit extract and hUCB-MSCs, a broad array of therapeutic strategies is under investigation, targeting hair loss treatment through autophagy modulation (Table 1).

Table 1 Some Therapeutic Strategies Targeting Autophagy Modulation to Address Hair Loss and Promote Hair Growth

Targeting Cell	Drugs	Mechanisms to Promote Autophagy	Effects
DPC	HT[153]	/	Alleviate inflammation caused by ROS, increase hair growth factors.
	Myristoleic acid[33]	mTOR pathway Wnt/β-catenin pathway ERK pathway	Promote cell proliferation
	Adipose-derived stem cells nanovesicles[75]	AKT pathway	Restore autophagy and promote Wnt/β-catenin pathways
	Limonin[154]	Wnt/β-catenin pathway PI3K/AKT pathway	Promote cell proliferation
	BDB[155]	/	Promote cell proliferation
	Ginsenoside Re[156]	/	Reverse the decrease in Wnt/β-catenin pathway signaling and the shift from anagen to catagen caused by 3-MA
	AC2 peptide from the Trapa japonica fruit extract[76]	mTOR pathway	Inhibit excessive autophagy and apoptosis induced by DHT
ORS cell	CCCP[150]	Increase PINK1 expression	Reduce NLRP3 inflammasome and rescue IP collapse in AA
HaCaT cell	hUCB-MSCs	/	Protect HaCaT cells against Dex damage
/	Spermidine	/	Rescue IP collapse in AA
/	Red OLEDs[157]	/	Promote the transition of HFs from telogen to anagen and increase the flow of surface blood oxygen
/	Small molecules(rapamycin, metformin, α-KG and α-KB)	mTOR pathway/AMPK pathway	Promote the transition of HFs from telogen to anagen

Abbreviations: HT, hydroxytyrosol; ROS, reactive oxygen species; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; ERK, extracellular signal-regulated kinases; AKT, Ak strain transforming; BDB, 5-bromo-3,4-dihydroxybenzaldehyde; 3-MA, 3-methyladenine; DHT, dihydrotestosterone; CCCP, carbonyl cyanide chlorophenylhydrazone; PINK, PTEN-induced kinase 1; hUCB-MSCs, blood-derived mesenchymal stem cells; AA, areata alopecia; IP, immune collapse; OLEDs, organic light-emitting diodes; HF, hair follicle, α-KG, α-ketoglutarate, α-KB, α-ketobutyrate; AMPK, 5'adenosine monophosphate-activated protein kinase.

Targeting DPCs

OS has been recognized as exerting detrimental effects on DPCs, with subsequent negative impacts on hair health and growth.[158] Hydroxytyrosol (HT), an olive-derived antioxidant compound, has demonstrated potential in mitigating ROS generation in DPCs from OS-induced rat whiskers by promoting autophagy, thus limiting HF damage.[153,159] Additionally, HT has proven effective in enhancing the secretion of hair growth factors including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF).[153] Consequently, this elevates HT to the status of a promising candidate for anti-hair loss treatments.

Myristoleic acid has been found to induce autophagy via the mTOR pathway followed by the upregulation of ATG7 and LC3II.[33] HF development, hair cycle regulation, and hair regeneration are all influenced by the Wnt/β-catenin signaling pathway.[160] Myristoleic acid activated cellular autophagy in DPCs through the Wnt/β-catenin pathway and triggered autophagy via the ERK pathway, which in turn stimulated DPC proliferation. Studies have indicated that Myristoleic acid can inhibit 5α-reductase, functioning similarly to finasteride, potentially offering a treatment for AGA.[20,161] Adipose-derived stem cells nanovesicles also showed treatment potential for AGA, restoring autophagy in DHT-treated DPCs by inhibiting the AKT pathway via the junctional adhesion molecule A protein.[75]

Limonin, a natural compound primarily found in citrus fruits, has exhibited therapeutic effects on skin diseases, according to recent research.[162–164]

Notably, limonin is observed to promote DPC proliferation in rats by stimulating autophagy via the activation of the PI3K/AKT and Wnt/β-catenin pathways.[154]

In an experiment cultivating Rat vibrissa follicles with 5-bromo-3,4-dihydroxybenzaldehyde (BDB) or minoxidil, 1 μM BDB induced greater hair fiber length enhancements than minoxidil.[155] Follow-up research connected the hair growth-promoting effect of BDB to the activation of DPC proliferation. DPCs treated with BDB showed an increase in autophagic vacuoles and higher levels of ATG7, ATG5, ATG16L, and LC3B. These findings indicate that BDB prompts autophagy in DPCs, which subsequently contributes to DPC proliferation and hair growth stimulation. Like MA, BDB is recognized to stimulate the Wnt/β-catenin pathway; yet, it's still uncertain whether BDB prompts autophagy via the identical mechanism used by MA.[33,155]

In human HFs, it was discovered that the autophagy inhibitor 3-MA suppressed DPC autophagy, accelerating the transition from anagen to catagen phase and curtailing HS elongation.[156] Following 3-MA treatment, DPCs demonstrated downregulation of canonical Wnt target genes like LEF1, AXIN2, and MYC, together with diminished nuclear translocation of β-catenin. However, Ginsenoside Re managed to counter the 3-MA-induced downregulation of Wnt/β-catenin signaling by bolstering autophagy in DPCs. It also reversed the transition from anagen to catagen phase and tempered the reduction in hair growth caused by 3-MA. These findings suggest Ginsenoside Re possesses therapeutic potential for treating autophagy-related hair loss. Notably, a complex interplay exists between the Wnt/β-catenin pathway and autophagy, with both capable of influencing each other's mechanisms.[33,156]

Others

Autophagy-associated small molecules like rapamycin, metformin, α-ketoglutarate (α-KG), and α-ketobutyrate (α-KB), were administered to the dorsal skin of mice, thereby eliciting autophagy via either the mTOR or AMPK pathways.[66] These compounds instigated a swift transition of HFs from the telogen to the anagen phase and promoted significant hair growth. Subsequent research indicated that autophagy activation via rapamycin enhanced lactate dehydrogenase expression and its activity, enabling HFSCs to intensify glycolytic processes.[165] Glycolysis activated HFSCs, which subsequently advanced the aforementioned HF cycle. However, inhibiting mTOR appeared to facilitate a faster entrance into the anagen phase compared to AMPK activation, pointing to the necessity of further exploration of the distinct effects these pathways exert on autophagy induction.

In a different realm, photobiomodulation therapy has seen broad application across multiple disciplines, including dermatology for skin disease treatment.[166–168] Experiments with therapeutic exposure of shaved mice to red organic light-emitting diodes (OLEDs) over a determined period showcased marked improvements in hair regrowth by area, rate, length, and diameter, exceeding control group results.[157] Autophagy activation in the dorsal skin of mice was detected.

This outcome suggests that the beneficial effects of red OLEDs are associated with autophagy. Concurrently, increased expression of cytokeratin14 (Ker14) was observed upon HFs entering the anagen phase, a trend that also manifested in the treated group. Collectively, these observations suggest that light irradiation fosters autophagy, subsequently facilitating an efficient transition of HFs from the telogen to anagen phase.

Although numerous autophagy-modulating drugs have been detailed above, a crucial aspect of using autophagy modulators in vivo is their inevitable regulation of autophagy not only in HF cells but also in surrounding and distant stromal cells within the host. In oncology, it has been demonstrated that modulating systemic autophagy could offer a more profound anti-cancer effect compared to targeting individual cells.[169] Investigating whether an autophagic microenvironment can more effectively address hair loss remains essential.

Conclusions

The critical role of autophagy and mitophagy in elucidating and treating alopecia, as well as associated conditions, is presently the subject of intensive research. These cellular processes are fundamental to the growth, regeneration, and upkeep of HFs. Autophagy is crucial for preserving cellular equilibrium and removing dysfunctional organelles and proteins, thereby playing a vital role in maintaining the health of HFs. Similarly, mitophagy, a specialized form of autophagy, is crucial for ensuring cellular health and energy balance. Consequently, this review highlights the roles that autophagy and mitophagy play within the HF cycle, particularly concerning hair loss. We explore the regulatory mechanisms of autophagy and mitophagy, shedding light on their interactions with HFSCs and DPCs, both essential for hair regeneration and growth. A full understanding of the roles of autophagy and mitophagy in this context is paramount to the development of effective treatments for hair loss.

Although valuable, the present study has several limitations. Our comprehension of autophagy and mitophagy's roles is still foundational, requiring additional investigation to grasp their precise mechanisms within the HF. Therapeutic strategies targeting autophagy and mitophagy are in their infancy, and identifying their distinct mechanisms and potential clinical applications poses challenges. The impact of autophagy modulators on individuals of various ages and genders warrants further investigation.[66] Additionally, the precise targets of autophagy modulators may also sway their influence on hair growth. Future studies should aim to clarify the mechanisms of autophagy and mitophagy across different aspects of HFs, particularly their intricate relationship with pathways like the Wnt/β-Catenin pathway. Natural compounds that exhibit the potential in enhancing autophagy represent an intriguing avenue for future applications. Concurrently, focused research efforts should yield autophagy modulators that precisely target cells implicated in hair loss, thus providing a more targeted approach to treating conditions related to hair loss.[170] It is noteworthy that any imbalance in autophagy, be it excessive or insufficient, has the potential to compromise HF health, highlighting the importance of determining an optimal autophagy level conducive to hair regrowth. Achieving this balance will pave the way for sophisticated interventions to regulate autophagy and mitophagy, unlocking new potential for hair regrowth and maintenance. As technological advancements continue to deepen our understanding of these cellular processes, we look forward to future breakthroughs in hair regeneration medicine – offering fresh hope for individuals struggling with hair loss.

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Disclosure

The authors report no conflicts of interest in this work.

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