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MITOCHONDRIAL DYSFUNCTION OXIDATIVE STRESS AND THE NAD/SIRTUIN AXIS IN ANDROGENETIC ALOPECIA: EMERGING MECHANISMS AND THERAPEUTIC IMPLICATIONS

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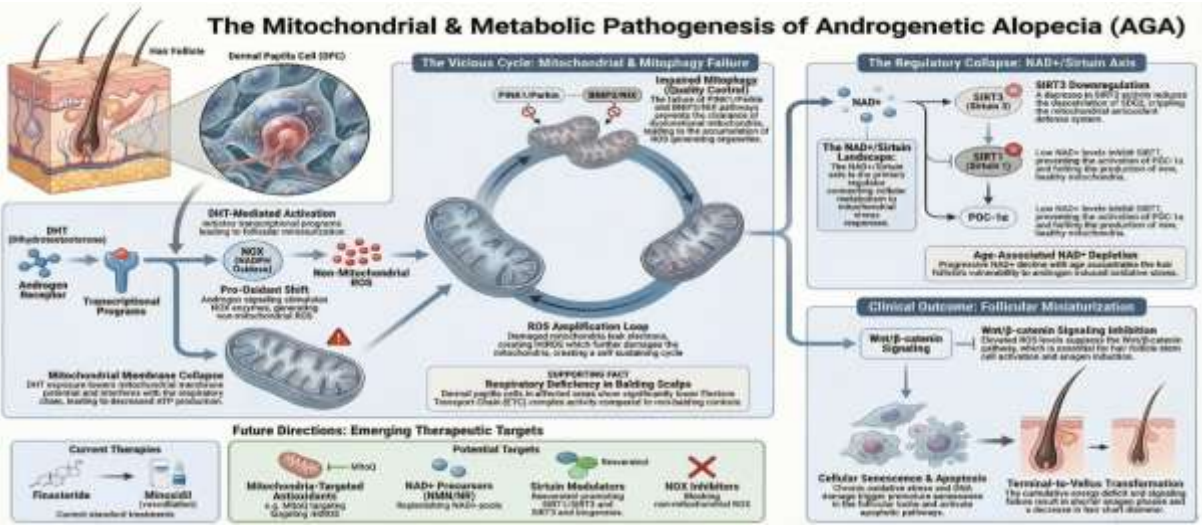
ABSTRACT
Androgenetic Alopecia (AGA) is a widespread type of progressive non-scarring hair loss that has always been theorized to be caused by the mediation of follicular miniaturization by androgens. Nevertheless, failure to respond fully to androgen-targeted therapies and age-related AGA development indicates that other processes are involved in disease pathogenesis. Considering this, new evidence shows that mitochondrial dysfunction, oxidative stress, and defective quality control in the cell can also contribute significantly to follicular degeneration. This review utilizes a recent development (2020-2026) and analyzes the interconnection between oxidative stress, mitophagy, and the nicotinamide adenine dinucleotide (NAD+)/sirtuin axis in AGA. The evidence of experimental research proves that dermal papilla cells of the affected scalp have reduced respiratory activity of mitochondria, enhanced reactive oxygen species, and changes in the expression of mitochondrial regulators. One of them is SIRT3, which is altered and can damage follicular function and regenerative capacity. The therapeutic approaches that mitigate mitochondrial homeostasis, such as mitochondria-targeted antioxidants and NAD + precursor and sirtuin-regulating agents, have shown positive outcomes in preclinical models. Nevertheless, direct records of a connection between canonical mitophagy pathways and AGA in the human tissue, as well as the causal role of NAD+ depletion and sirtuin dysregulation, are not fully demonstrated. Taken together, such results indicate that mitochondrial dysfunction could be an element of AGA pathophysiology, which has been under-recognized previously, and that could be a therapeutic option. A better study of mitochondrial control in human hair follicles can be used to inform the further development of mechanism-based therapies and to understand intra-clinical discrepancies in predicting response to existing therapies.

KEYWORDS: Androgenetic alopecia, Mitochondrial dysfunction, NAD^+/sirtuin axis, Oxidative stress, SIRT3



INTRODUCTION

Androgenetic alopecia (AGA) is the most widespread progressive, non-scarring loss of hair, which occurs in up to 50 percent of men by age 50 and a high percentage of women, and in which prevalence rises with age [1]. AGA is also clinically marked by follicular miniaturization (patterned), where terminal hair follicles become increasingly vellus-like, leading to a drop in hair shaft diameter, a decrease in anagen period, and progressive hair thinning [2]. This is seen mostly in the form of frontotemporal recession and vertex blading in men, whereas in women, there is diffuse thinning of the crown, with the frontal hairline retained[3]. In addition to physical manifestations, AGA has been linked to serious psychosocial burden, such as decreased self-esteem and low quality of life [4]. AGA has long been pathogenized using androgen-dependent pathways, especially the expression of testosterone to dihydrotestosterone (DHT) by 5α-reductase and the subsequent activation of the androgen receptor on the dermal papilla cells [5]. DHT signaling influences reduced duration of anagen phase, early catagen, and increased expression of inhibitory growth factors, including transforming growth factor- beta (TGF- B) and dickkopf-1 (DKK1), eventually resulting in follicular miniaturization [6]. This androgen-based model forms the basis of the contemporary standard therapies, such as finasteride and minoxidil, that are the principal pillars of clinical management [7].

Nonetheless, this paradigm fails to explain several clinically relevant observations. The percentage of non-response to androgen-targeted therapies among patients is relatively high, the progression of the disease tends to continue with stable androgen levels, and partial correction of follicular miniaturization is hardly ever attained [8]. Additionally, AGA exhibits characteristics that are in line with an age-related degenerative disorder that is progressive as one ages [9]. These constraints emphasize the necessity of investigating further possibilities of such mechanisms that can provoke such diseases and resistance to treatment. There is growing evidence that mitochondrial dysfunction and oxidative stress could play a major role in hair follicle aging and degeneration [10]. The hair follicles are mini organs that are of high metabolic activity and demand enormous resources to support an intensive multiplication and differentiation of cells during their anagen phase [11].

Mitophagy, actively autophagic elimination of damaged mitochondria, is a vital element of mitochondrial quality control that avoids the buildup of dysfunctional, ROS-generating organelles [12]. Simultaneously, the nicotinamide adenine dinucleotide (NAD+)-dependent sirtuin family has appeared as one of the most important regulators of mitochondrial homeostasis, oxidative stress responses, and cellular metabolism [13]. SIRT1/SIRT3 affect mitochondrial development, antioxidant defense, and metabolism, which correlates with the balance of energy in the cells, with adaptation to stress [14]. Interestingly, the levels of NAD + decrease as a person gets older, and thus the activity of sirtuins decreases, deteriorating the mitochondrial functioning and making one more vulnerable to oxidative stress [15]. Since AGA occurs with age, disruption of the NAD + / sirtuin axis can also be an upstream agitator of mitochondrial dysfunction and follicular degeneration. In line with this hypothesis, recent observations have shown that there was a decrease in mitochondrial respiratory activity, an increase in oxidative stress, and an increase or decrease in sirtuin expression, depending on the cell of the AGA-affected scalp [16].

Irrespective of these developments, there are a number of gaps in knowledge. There is no direct evidence of a mitophagy pathway to AGA in human follicles; there is no systematic quantification of NAD + levels in affected tissue, and cause-and-effect relationships between sirtuin pathology and follicular miniaturization are yet to be determined. Moreover, the mechanistic interaction of androgen signaling, mitochondrial impairment, and cellular aging processes is yet to be fully comprehended. As such, this literature review summarizes recent findings (2020-2026) on oxidative stress, mitophagy, and the NAD+/sirtuin axis in AGA, and suggests an integrated model of how such mechanisms relate to follicular degeneration. This assumption has been overcome by shifting towards a more translational model centered on androgens rather than solely on it to explain the variation in the response to treatment and help shape mechanism-based therapy regimens.

Oxidative Stress and Mitochondrial Dysfunction in Androgenetic Alopecia

2.1 Reactive Oxygen Species and Dermal Papilla Cell Dysfunction

There has also been an increased incrimination of oxidative stress, an imbalance between the generation of reactive oxygen species (ROS) and antioxidant defense capacity in the pathogenesis of androgenetic alopecia (AGA) [17]. Hair follicle cells, most especially dermal papilla cells (DPCs) and the matrix keratinocytes, have very high metabolic activity and hence are highly prone to oxidative damage [18]In physiological conditions, low concentrations of ROS act as signal molecules that control cellular proliferation and differentiation, but high levels may lead to cellular injury, senescence, and apoptosis [19]. Clinical and research findings have shown that in AGA areas of the scalp, there is apparent oxidative stress as evidenced by activity of primary lipid peroxidation products and lowered antioxidant enzyme functions, such as superoxide dismutase and catalase [20], which are related to oxidative stress. These results indicate that dysfunctional redox homeostasis can be one of the factors of follicular dysfunction. Oxidative stress at the cellular level was also found to lead to impairment in the DPC functions, such as lessening the release of growth-promoting factors, thus adding to the premature follicular regression and the regenerative capacity.

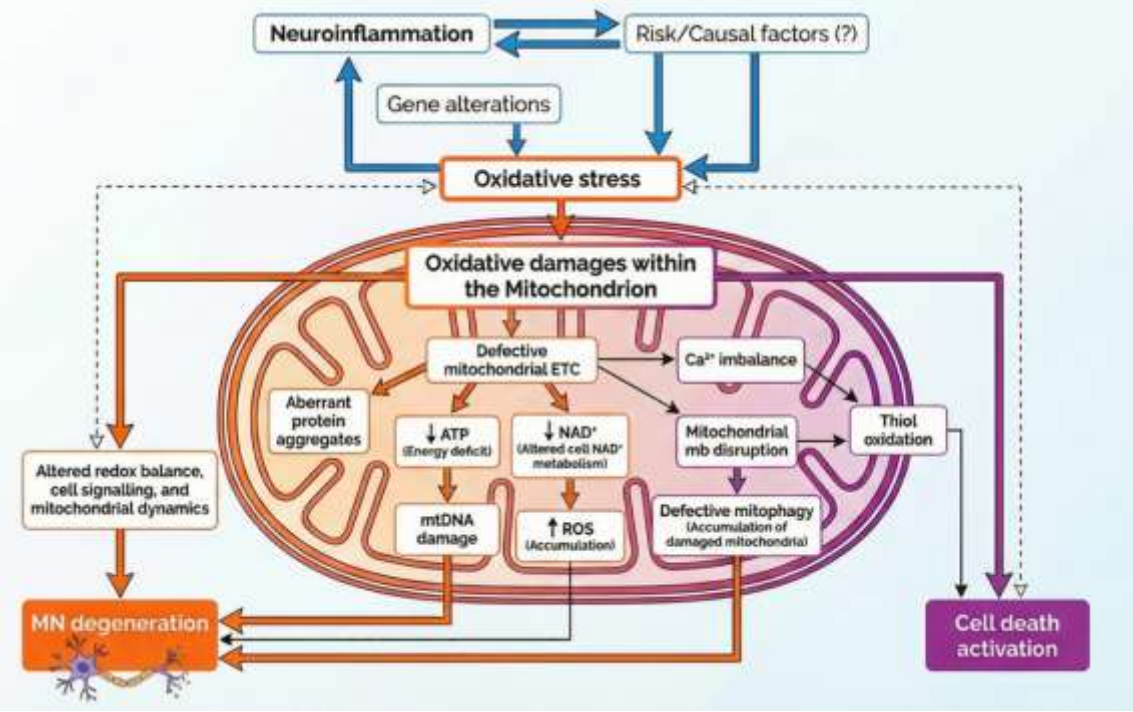


Figure 1: Schematic illustration of oxidative stress–mediated mitochondrial dysfunction in cellular degeneration.

There is new evidence that suggests that oxidative stress may be further heightened by androgen signaling. It has been demonstrated that testosterone and dihydrotestosterone (DHT) stimulate the NADPH oxidase (NOx) enzymes, which results in the typical passage of hydrogen peroxide and triggers the apoptotic process in keratinocytes [21]. NOX inhibition reduces ROS production and follicular injury in preclinical models, indicating that non-mitochondrial sources of ROS cause further damage in androgen-induced injury. The results give a possible mechanistic interconnection between androgen signaling and oxidative stress through pathways other than conventional transcriptional pathways. Besides the direct cytotoxic effects, Oxidative stress interferes with essential hair follicle regeneration mechanism signaling pathways. High levels of ROS have been linked to the Wnt/ -catenin signaling inhibition, a pathway that is critical to activating hair follicle stem cells and triggering the onset of anagenesis [22]. Moreover, oxidative stress encourages the injury of DNA and telomere degeneration, leading to earlier cell senescence in the follicular niche [23]. Such a follicular senescence build-up can also lead to a further destabilization of the follicular microenvironment through the release of pro-inflammatory mediators.

Clinically, these findings indicate that oxidative stress can also play a role in treatment response variability besides disease progression, particularly in non-responders to androgen-targeted treatment. Nevertheless, the relative role of oxidative stress in disease onset versus disease progression has not yet been fully determined, and direct validation in the human scalp tissue is sparse. More research is necessary to identify whether oxidative stress is a therapeutic target that can be altered in AGA.

2.2 Mitochondrial Dysfunction in Balding Follicles

Mitochondria are both critical and important locations of ROS and are the hub of cellular injury due to oxidative stress. In normal oxidative phosphorylation, a minor role of electrons is lost as superoxide radicals through the electron transport chain (ETC) [24]. This leakage of electrons augments under the conditions of mitochondrial dysfunction and causes the overproduction and amplification of oxidative damage excessively by the mitochondrial ROS (mtROS) [25]. This forms a vicious circular process whereby the impairment of mitochondria encourages the production of more ROS and cellular impairment. Recent experimental literature supports the existence of mitochondrial impairment in AGA. Balding scalp dermal papilla cells were found to have lower levels of ETC complex activity, lower levels of ATP, and higher levels of oxidative stress than non-balding controls [26]. These modifications imply that the disruptive nature of the mitochondrial bioenergetics can limit the ability of the follicular cells to maintain normal growth and regeneration. It is interesting to note that there has been a compensatory upregulation of genes that are mitochondrial-related, although this does not seem to be a good response in restoring functional cover of mitochondria.

Mitochondrial dysfunction may also be worsened by exposure to androgens. DHT has been demonstrated to lower the membrane potential in the mitochondria, interfere with the respiratory capacity, and cause apoptosis of DPCs [27]. Notably, mitochondria-targeted antioxidant therapy, including MitoQ, also restores the functionality of mitochondria, lowers the levels of mtROS, and enhances the viability of the cells in preclinical models [28]. The results indicate that

there is a functional interdependence between androgen signaling and mitochondrial dysfunction and follicular degeneration. Further evidence also indicates that mitochondrial stress could be associated with other types of regulated cell death, such as ferroptosis. Ferroptotic cell death, mitochondrial dysfunction, and hair growth have been linked to lipid peroxidation, acid iron regulation by DHT in experimental systems [29]. Such findings suggest that impairment of mitochondria can modulate various cell death mechanisms involved in relation to AGA pathophysiology.

Translational perspective. Due to its progressive nature, AGA can be explained by mitochondrial dysfunction, and the inefficacy of current treatment options that do not target cellular mechanisms of energy supply and the oxidative stress process directly. However, it is still uncertain whether the abnormalities of the mitochondria are a primary pathogenic factor or a result of the androgen signaling and loss of cellular homeostasis with age. It will be essential to clarify this distinction to find out the therapeutic potential of mitochondrial-targeted interventions. On the whole, existing data indicate that the processes of oxidative stress and mitochondrial dysfunction are inextricably linked and may be involved in dermal papilla cell injury, decreased regenerative ability, and gradual follicular shrinking in AGA. Although interesting mechanistic evidence has been obtained in preclinical studies, little direct evidence has been obtained in human follicles. More research is required to establish causality and to identify whether there is a meaningful clinical benefit in targeting mitochondrial dysfunction, which would be found by integrating molecular, cellular, and clinical studies.

3.0 Mitophagy and Mitochondrial Quality Control

3.1 PINK1/Parkin-Mediated Mitophagy

Selective autophagic elimination of impaired or dysfunctional mitochondria as a form of mitophagy is a fundamental process of mitochondrial quality control that ensures cellular homeostasis and prevents excessive production of reactive oxygen species (ROS) [30]. Mitochondrial dysfunction potentiation is mitigated by removing damaged mitochondria, preventing mitochondrial accumulation of ROS-producing organelles, and maintaining mitochondrial activity, especially in metabolically active tissues, by mitophagy. Mitophagy is best defined as a mitotic pathway conducted by the kinase 1 (PINK1) and E3 ubiquitin ligase parkin. In physiological conditions, PINK1 is constantly imported into healthy mitochondria and quickly degraded. Loss of mitochondrial membrane potential -a marker of mitochondrial damage- however, inhibits PINK1 import, resulting in accumulation on the outer mitochondrial membrane. Stabilized PINK1 in turn causes the recruitment and activation of parkin, which ubiquitinates proteins on the surface of the mitochondrion and mediates its recognition by autophagy receptors, leading to mitochondrion degradation through the autophagosome-lysosome pathway [31]. This route is highly investigated in neurodegenerative and metabolic diseases, where deregulated mitophagy adds to the mobilization of dysfunctional mitochondria and higher proportions of oxidative stress [32]. Nevertheless, although it plays the central role in mitochondrial quality control, direct studies on the relevance of PINK1/Parkin-mediated mitophagy in hair follicle biology and AGA are scarce. To this end, no reports have so far shown direct evidence of PINK1 stabilization, Parkin translocation, or mitophagy flux in human AGA follicles.

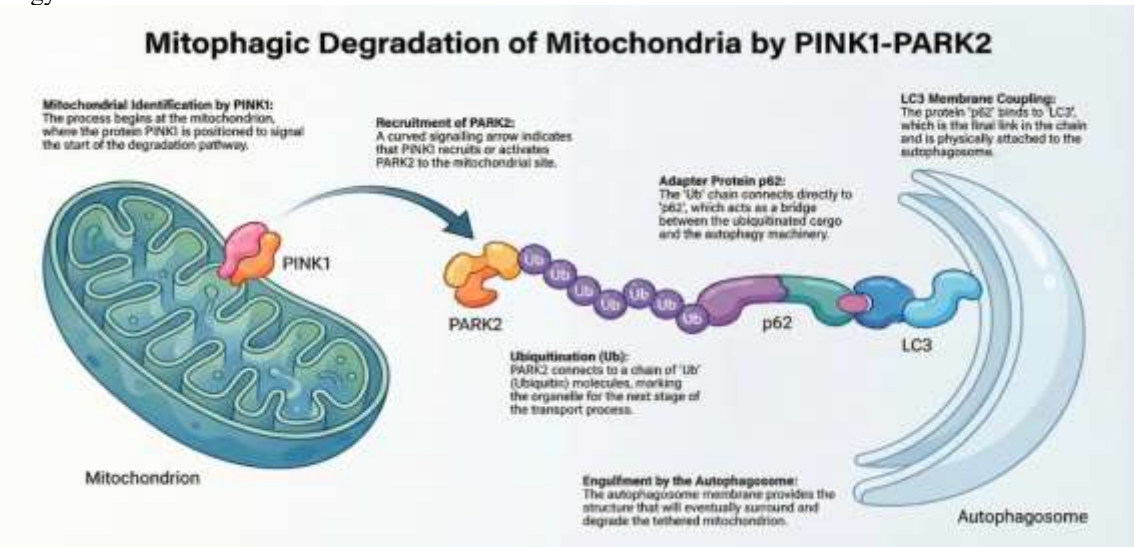


Figure 2: Mechanism of PINK1/Parkin-mediated mitophagy

3.2 Receptor-Mediated Mitophagy: BNIP3 and NIX

Besides the PINK1/Parkin pathway, there are receptor-dependent mechanisms of mitophagy, which include proteins like BNIP3 and NIX situated on the outer mitochondrial membrane, that directly interact with the autophagic mechanism [33]. These receptors are normally stimulated during cell stress, such as hypoxia, nutrient deprivation, and

mitochondrial clearance in the absence of ubiquitination. Finally, it has been demonstrated that BNIP3 and NIX are involved in development and mitochondrial adaptation to stress, such as via mitochondrial sequestration by erythrocytes during maturation and mitochondrial sequestration by hypoxia [34]. Moreover, they are also involved in mitophagy and may also regulate apoptosis as well; this suggests that there is a complex interplay between mitochondrial quality control and cell death pathways.

Although receptor-mediated mitophagy has biological implications, its contribution to hair follicle biology has yet to be fully discovered. To what remains of BNIP3 or NIX expression and activity in dermal papilla cells or hair follicle stem cells under AGA exists no direct evidence of either. Since hair follicles undergo changing metabolism and hypoxic conditions throughout the hair cycle, the systems' mitophagy pathways mediated by receptors have not been systematically studied.

3.3 Mitophagy Dysregulation in AGA

Even though there is no direct evidence that mitophagy causes AGA, there are several indirect observations that quality control mechanisms of mitochondria may be dysfunctional. The electron transport chain activity, as well as the levels of oxidative stress and dysfunctional mitochondria, are found to be increased in the dermal papilla cells of the balding scalp, [35] results, which are in line with the impaired mitochondrial turnover. In the normal condition, mitochondria in the damaged state are eliminated through mitophagy; thus, their presence could be an indication that there is a lack of clearance. Moreover, it has also been reported that age leads to impairment of age-related autophagosome and mitophagosome activities in a variety of tissues and can be regarded as one of the manifestations of cell aging [36]. Since AGA is an age-related disorder, it can be considered possible that a decreased mitophagic capacity leads to a gradual mitochondrial dysfunction and degeneration of follicles. Nevertheless, this has not been directly investigated in human hair follicles.

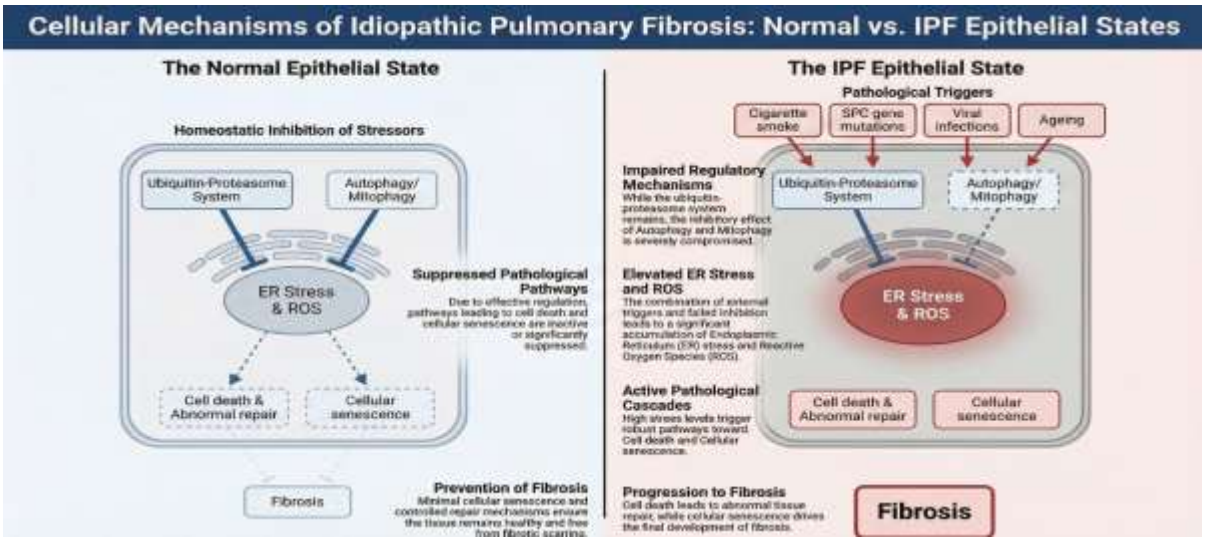


Figure 3: Mitophagy impairment in pathological conditions

A possible connection between mitophagy and the NAD + / sirtuin axis is also a developing fact. SIRT3, a deacetylase in the mitochondrial adult respiratory chain that regulates mitochondrial maintenance and redox state, has been reported to be downregulated in AGA-affected mesenchymal stem cells [37]. Though the association of SIRT3 and mitophagy is not well-determined, the decrease of SIRT3 activity may indirectly cause mitochondrial quality control through the facilitation of oxidative stress and mitochondrial damage. It is not clear that sirtuin dysregulation has a direct impact on mitophagy pathways in AGA. Notably, several therapeutic interventions that enhance the function of mitochondria, including mitochondria-targeted antioxidants and polyphenolic compounds, have shown positive outcomes with respect to preclinical AGA models [38]. Although these studies did not quantitatively measure mitophagy, there may be a risk of these studies that restoring mitochondrial homeostasis is associated with higher mitochondrial turnover. This interdependence of both processes will require further research that involves direct measurements of mitophagy flux in the future.

Mitophagy is a vital but under-studied aspect of mitochondrial quality control in AGA. Though there is indirect evidence to indicate that mitochondrial turnover impediment could be a cause of the formation of dysfunctional mitochondria and oxidative stress, direct experimental proof in the human hair follicles has not been obtained. Among the questions that remain unanswered, it is interesting whether mitophagy is functionally compromised in AGA, if it is affected by androgen signaling and aging, and whether it can be trafficked to offer therapeutic benefit. These gaps should also be considered in the process of determining mitophagy as a mechanistic and translational target of AGA.

4.0 The NAD+/Sirtuin Axis in Mitochondrial Regulation

4.1 SIRT1 and Regulation of Mitochondrial Biogenesis

Nicotinamide adenine dinucleotide (NAD+)/sirtuin is the key regulatory pathway connecting cellular metabolism, mitochondrial functions, and stress [39]. Sirtuins are NAD-dependent deacetylases that regulate a large set of biological activities, such as mitochondrial biogenesis, oxidative stress responses, or autophagy [40]. One of these, SIRT1, is instrumental in the organization of mitochondrial biogenesis through the activation of peroxisome proliferator-activated receptor gamma coactivator-1 (PGC)-1 in terms of mitochondrial gene expression. [41]. This process ensures that SIRT1 upregulates nuclear-encoded mitochondrial genes and oxidative capacity through this pathway. Meanwhile, SIRT1 controls antioxidant defense via deacetylation of forkhead box O (FOXO) transcription factors, which raise the levels of enzymes like ultraviolet dismutases and catalases [42].

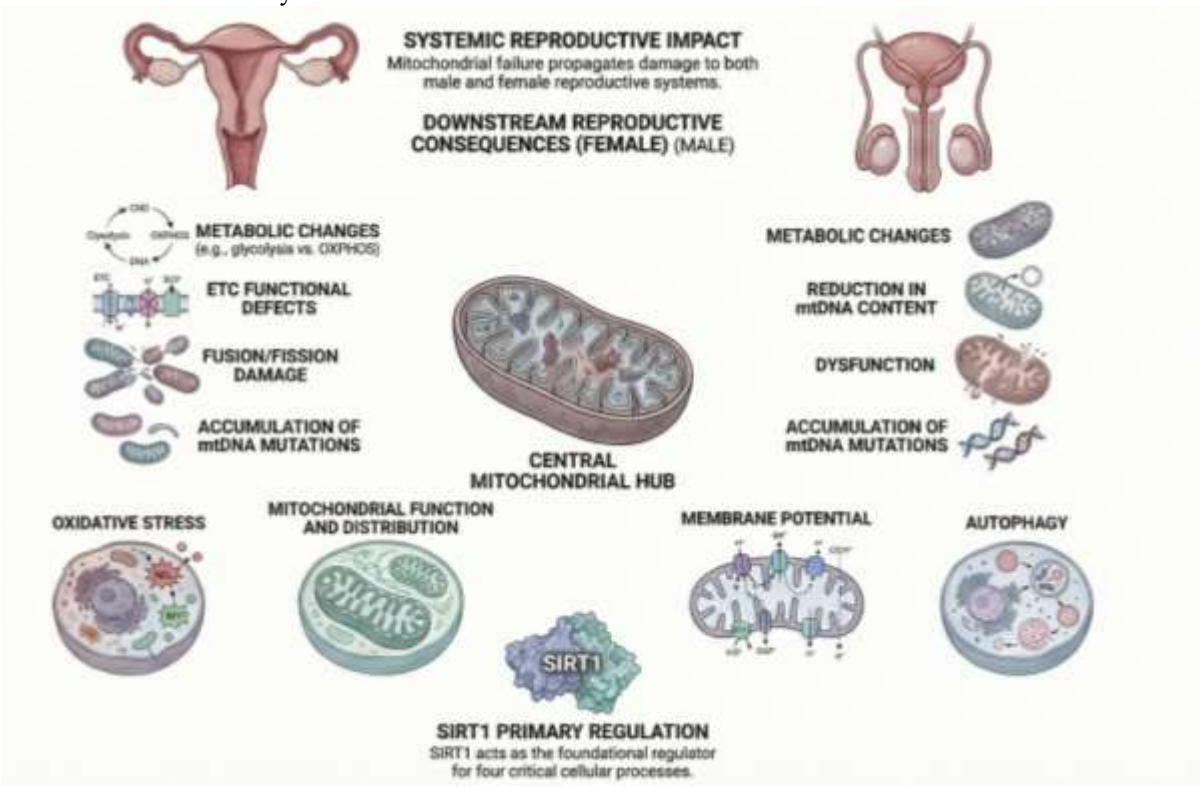


Figure 4: SIRT1-mediated regulation of mitochondrial function

SIRT1 also plays a role in autophagy regulation, regulating major autophagy-related proteins and transcriptional programs [43]. Using these concerted efforts, SIRT1 incorporates the system of mitochondrial biogenesis, antioxidant defense, and cellular quality control in a dermatological framework. Such functions propose that the operation of the SIRT1 may disrupt the resilience of follicles to oxidative stress and reduce the capacity of regeneration. Nevertheless, there is also little direct data on altered SIRT1 expression or activity in AGA, and its role in hair follicle biology is subject to further research.

4.2 SIRT3 and Mitochondrial Redox Homeostasis

SIRT3 is the lead sirtuin located in the mitochondrion and it is the centre of control of mitochondrial metabolism and reductive oxidation [44]. SIRT3 also increases the activity of electron transport chain by deacetylating important enzymes in the mitochondrion and promotes ATP production and oxidative stress. Another important role of SIRT3 is to activate antioxidant systems in the mitochondrial level. SIRT3 activates manganese superoxide dismutase (SOD2) and deacetylates it, decreasing the amount of mitochondrial ROS [45]. It also controls enzymes that are used in the production of the NADPH to aid cell oxidative potential [46]. These mechanisms maintain integrity of mitochondria and inhibit oxidative stress, which is caused by SIRT3.

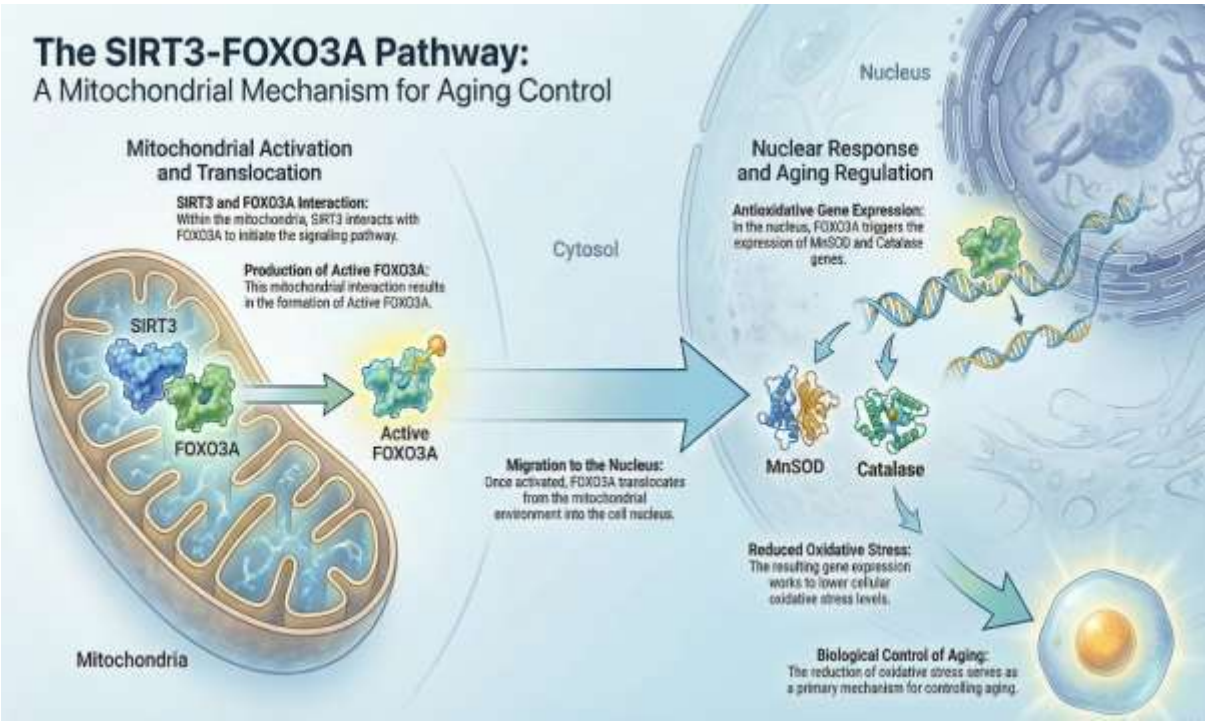


Figure 5: SIRT3-mediated regulation of mitochondrial redox homeostasis

There is also an emergent evidence that SIRT3 can be especially applicable in AGA. SIRT3 has been shown to be down-regulated in mesenchymal stem cells obtained in AGA-afflicted scalp areas [47]. This result correlates with the trends of oxidative stress and mitochondrial impairment of balding dermal papilla cells. The reduction in SIRT3 activity can be seen as a contributor to the deficient antioxidant defense of mitochondria and gradual follicular atrophy. Nonetheless, contemporary findings are still mostly correlational. Functional studies show that the restoration of the activity of SIRT3 enhances mitochondrial activity and hair growth in AGA models lacking this activity. More studies are needed to determine the role of SIRT3 as a causal element or a secondary effect of mitochondrial malfunction.

4.3 NAD+ Metabolism and Age-Associated Decline

NAD+ is a metabolite cofactor that plays important roles in the redox and cellular signaling systems, such as the activity of sirtuins [48]. To balance the cellular levels of NAD +, the salvage pathway is the only one that recycles nicotinamide into nicotinamide phosphoribosyltransferase (NAMPT) [49]. NAD +. Reduction in NAD+ levels has been acknowledged as a hallmark of aging, and has been associated with defects in mitochondrial activity, excessive oxidative stress and diminished repair ability of individual cells [50]. This decrease is believed to be caused not only by the rise of NAD+ consumption caused by the activity of such enzymes as poly (ADP-ribose) polymerase (PARPs) and CD38 but also by the decrease in the biosynthesis of NAD+ as well. NAD+ depletion might be an upstream event which contributes to mitochondrial impairment and sirtuin inactivation, because AGA is age-related. It would be anticipated that the decreased NAD+ concentration would inhibit SIRT1 and SIRT3 activity in the mitochondrial biogenesis, antioxidant defense, and cellular quality control. In spite of this theoretical framework, the NAD+ levels have not been directly measured in human AGA follicles, in the majority of experimental models. This is a large gap in the existing knowledge and obstructs the possibility to define whether NAD+ depletion is a main cause of disease pathogenesis.

4.4 Integration with AGA Pathophysiology

The combination of NAD+/sirtuin axis offers a mechanistic interconnection among the aging, mitochondrial dysfunction, and oxidative stress in AGA. A low amount of NAD+ and sirtuin can possibly lead to mitochondrial biogenesis, antioxidant capacity, and the accumulation of dysfunctional mitochondria. The changes can potentially increase the oxidative damages and decrease hair follicle regenerative ability. Significantly, the interaction between androgen signaling and NAD+/sirtuin axis is not fully identified. It is not clear whether androgen exposure directly affects NAD+ metabolism and sirtuin expression or whether age related NAD+ depletion predisposes follicles to damage due to androgen. This interaction will be important in elucidating how diseases develop.

The NAD+/sirtuin axis is a potential therapeutic target based on a translational viewpoint. Diagnostic interventions to replenish NAD+ levels or improve the activity of sirtuinals, including NAD+ precursors or sirtuin-proliferating antidotes have shown positive responses in mitochondrial performance in other organism systems [51]. Their

effectiveness in AGA, however, has not been proven yet, and clinical results are still not developed. The NAD + / sirtuin axis is a key but not fully defined mitochondrial function regulator in AGA. Direct mechanistic and clinical data is scarce, although emergent evidence has indicated that the sirtuin dysregulation, specifically, loss of SIRT3 expression, may be a source of oxidative stress and mitochondrial malfunction. More research is needed to ascertain whether NAD+ metabolism and sirtuin-targeted therapy can offer any significant treatment in AGA.

5.0 Integrated Mechanistic Model: From Androgen Signaling to Follicular Miniaturization

5.1 Androgen-Induced Oxidative Stress and Mitochondrial Impairment

Androgen- mediated signalling in genetically susceptible individuals initiates the pathogenesis of androgenetic alopecia (AGA). The strongest androgen, dihydrotestosterone (DHT), interacts with androgen receptors in the dermal papilla cells (DPCs) to activate transcriptional programmes leading to the process of follicular miniaturization [52]. Although they used to be explained by the presence of the changed growth factor signaling, there is a growing evidence that androgen signaling also triggers the presence of oxidative stress and dysfunction of the mitochondrion. According to experimental studies, DHT has the potential to damage mitochondrial activity by lowering mitochondrial membrane potential, impairing the activity of electron transport chains, and elevating mitochondrial production of reactive oxygen species (mtROS) [53]. Concurrently, it has been revealed that androgen signaling prompts the NADPH oxidase (NOX) enzymes, resulting in elevated production of non-mitochondrial ROS [54]. These two sources of ROS could be synergistic and enhance oxidative damage on the hair follicle microenvironment. Such cumulative oxidative stress can be an initial occurrence that connects androgen cues with subsequent dysfunction of cells. Nevertheless, the exact molecular pathways involved in the direct action of DHT on the mitochondrial processes are not fully determined and need to be investigable.

5.2 Impaired Mitochondrial Quality Control and ROS Amplification

The quality of mitochondria is regulated in a state of mitophagy by a balance between mitochondrial-biogenesis and mitochondrial degradation under physiological circumstances. Imbalance of this balance can result in a buildup of dysfunctional mitochondria, which causes overproduction of ROS and additional mitochondrial injury. Over AGA, cells of the dermal papilla obtained using the balding scalp show lower mitochondrial respiratory capacity, a reduction of ATP generation, and an oxidative stress elevation [55]. Such results indicate the inability to control the quality of mitochondria. Even though there are no direct measures of mitophagy in AGA, the fact that damaged mitochondria survive suggests the lack of clearance of mitochondria.

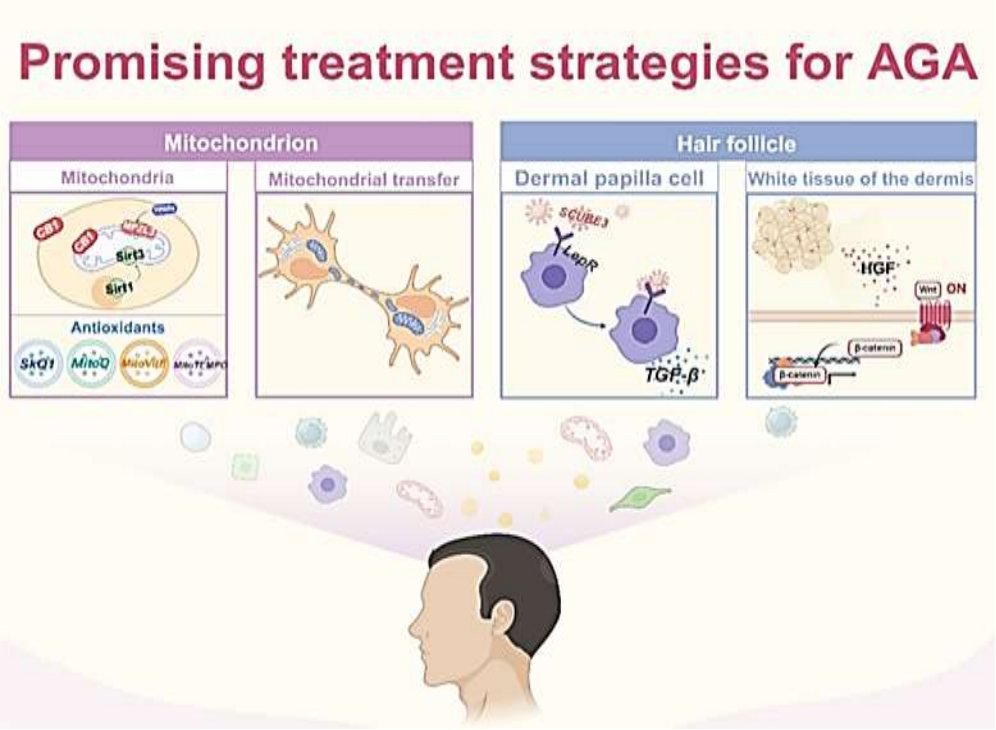


Figure 6: Mitochondrial impairment in AGA

This dysfunction can cause a feedback mechanism: disturbed mitophagy will cause mitochondrial aggregation, which causes high ROS, which then elevates further mitochondrial damage and cellular stress. This cycle will give rise to progressive follicular degeneration with time. This process may be compounded by age-associated deteriorations in autophagy and mitophagy [56], to give a possible basis to the progressive, age-linked character of AGA.

5.3 NAD+/Sirtuin Axis Dysregulation as an Amplifying Factor

NAD+/sirtuin axis is one of the critical metabolism-mitochondrial-stress interface regulation pathways. Aging-associated decreases in NAD+ could cause a decrease in sirtuin activity, specifically SIRT1 and SIRT3, to impair mitochondrial biogenesis, antioxidant defenses and cellular resilience [59]. Regarding AGA, downregulation of SIRT3 has been documented in cell derivatives of regions of the scalp that were affected [57]. This could lead to augmented oxidative pressure in the mitochondrion by decreasing the activation of anti-oxidant enzymes, e.g. superoxide dismutase. Moreover, the dysfunctional activity of sirtuins can potentially inhibit the maintenance and turnover of mitochondria, which further stimulates the formation of dysfunctional organelles. Notably, the interplay of androgen signaling and NAD +/sirtuin regulation is unknown. NAD+ age-associated depletion can make hair follicles more sensitive to the effects of androgens as a source of stress, which results in more rapid disease advancement. Alternatively, androgen signaling in itself can affect metabolic processes that lead to control of NAD+ levels and sirtuin activity. It is a significant area to consider in future studies in order to clarify these relationships.

5.4 Convergence on Follicular Dysfunction and Miniaturization

The synergistic action of androgen signals, oxidative stress, mitochondrial pathopathology, and defective quality control of cells is brought to bear on major downstream activities leading to follicular miniaturization. Overproduction of ROS might cause DNA damage, activate stress-sensitive signaling pathways, and induce apoptosis or other forms of regulated cell death, including ferroptosis [58]. Mitochondrial impairments and ATP loss could affect processes involving energy in the hair follicle development including proliferation and differentiation of keratinocytes [59]. Moreover, oxidative stresses destroy wnt/ -catenin signaling, restricting hair follicle stem cell activation and preventing anagen growth [60]. Moreover, mitochondrial dysfunction and oxidative stress could favour cellular senescence in dermal papilla cells and groups of stem cells, and decrease regenerative potential and change follicular signalling. Androgen stimulates the upregulation of inhibitory factors like TGF-b and DKK1 and inhibitors, which further enhance these changes and provide a microenvironment to support follicular regression [61]. All these processes together offer a mechanistic model of the connections between the upstream molecular events and the clinical picture of the progressive follicular miniaturization in the context of AGA.

According to this integrated model, AGA can result as a manifestation of the meeting of androgen signaling, mitochondrial dysfunction, mitophagy impairment, and NAD+/sirtuin dysregulation. These mutually dependent processes establish a self-amplifying loop of oxidative stress and cell dysfunction leading finally to follicular miniaturization. Although this framework is backed by new experimental data, most mechanistic interactions especially those ones involving mitophagy and NAD+ metabolism are yet to be confirmed in human tissue.

6 Therapeutic Strategies Targeting Mitochondrial Dysfunction and the NAD+/Sirtuin Axis

6.1 Mitochondria-Targeted Antioxidants

The AGA therapy involving special attention to mitochondrial oxidative stress might remain a potentially beneficial treatment due to the critical roles played by the mitochondrion and reactive oxygen species (ROS) involvement in the follicular degeneration process. Antioxidants that target mitochondria can be programmed to localise in mitochondria and neutralises mitochondrial ROS (mtROS) directly, saving mitochondrial form. Conjugated mitochondrial ubiquinone derivative of MitoQ with a lipophilic cation can target mitochondria and decrease oxidative stress specifically [62]. In the preclinical trials, MitoQ has been reported to restore mitochondrial membrane potential, reduce the intra-membrane level of mitochondrial ROS and enhance the viability of the dermal papilla cells upon exposure to dihydrotestosterone (DHT) [63]. In addition, there was a reduced expression of growth factor-0 -3 (TGF- 0) and an increased growth factor-aromatase which suggests that the expression of the follicular microenvironment could have changed. These are clinically encouraging findings, which nonetheless lack evidence to demonstrate other more clinical models. There are no set optional strategies of delivery, and specifically topical formulations that can potentially provide significant access of the hair follicles. Besides, there is no established long-term safety and effectiveness in patients receiving AGA.

6.2 NAD+ Precursors and Metabolic Restoration

The other intervention that can be considered is the restoration of NAD+, which will enhance mitochondrial activity and cellular capacity. It has been demonstrated that nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR) are NAD+ precursors, which raise the intracellular levels of NAD+ and enhance mitochondrial activity in diverse biological contexts [64]. These substances might also elevate the amount of NAD + and consequently enhance sirtuin activity, particularly of SIRT1 and SIRT3 to promote mitochondrial biogenesis, the strength of antioxidant defenses, and cellular quality control. These effects can be especially applicable in AGA, in which age-related NAD+ depletion and sirtuin imbalance are postulated factors of disease development. In spite of this powerful theoretical confirmation, there is as of yet no research reviewed that determines NAD+ precursor supplementation in the AGA models or in clinical groups in particular. The absence of direct evidence is a grievous limitation and further preclinical trials and clinical trials should be done to prove efficacy with dosage and safety of its use in hair loss.

6.3 Sirtuin-Modulating Compounds

Activators of sirtuins, resveratrol and resveratrol analogs are also investigated in terms of alleviation of mitochondrial functions and oxidative stress. Resveratrol has been observed to activate SIRT1 and mitochondrial biogenesis and antioxidant response in various models [65]. Its high bioavailability however negatively affects its clinical applicability. Recently, analogs of resveratrol with better pharmacokinetic characteristics have been discussed. An example of this is oxyresveratrol that has been indicated to reduce oxidative stress, prevent the synthesis of pro-inflammatory cytokines and increase growth of dermal papilla cells in preclinical models [66]. Further, it was connected with preserving wnt/ 2-catenin reaction, which is a fundamental safeguard to restoring the hair follicles. These findings are encouraging but what is not very clear is to what extent these compounds are acting on their activities through direct action of sirtuins. In addition, their application during AGA is not supported on the clinical level, and they are investigative.

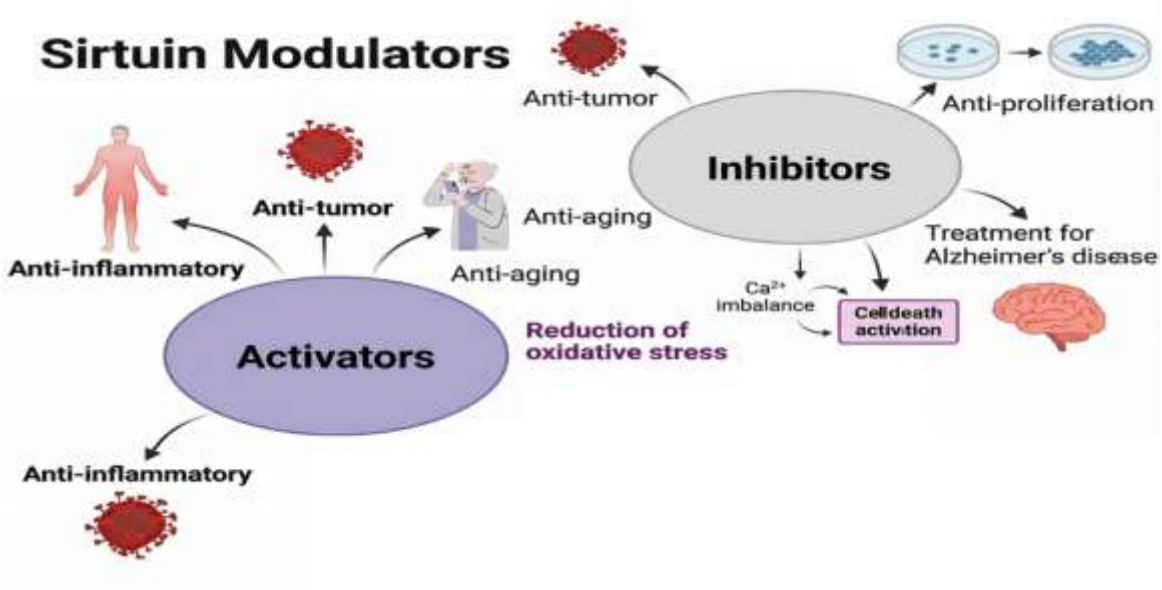


Figure 7: Biological effects of sirtuin modulators

6.4 NADPH Oxidase Inhibitors

Since NOX oxidases play a role in the ROS production that is caused by androgens, the supplementary approach to oxidative stress is NOX inhibition. In preclinical models of androgen-induced hair loss, experimental research has shown that NOX inhibitors reduce the production of hydrogen peroxides, avoid the process of apoptosis in keratinocytes, and induce hair growth [67]. Directing NOX-derived ROS could be of special concern in combating androgen-induced mitochondrial pertinent oxidative stress unopposed by mitochondrial-targeted therapies. Nonetheless, NOX enzymes have also begun to exercise significant physiological functions, such as immune response and cellular regulation [68]. Selective and localized inhibition, therefore, topical delivery, might be required to reduce the possible side effects.

6.5 Comparison with Current Standard Therapies

The existing standard therapies of AGA, such as finasteride and minoxidil, are mostly aimed at androgen signaling and follicular vascularization [69]. Although these treatments have proved useful in most of the patients, they do not directly help in mitochondrial dysfunction or oxidative stress, which could be involved in further propagation of the disease. This drawback can be suggested to be the reason behind the uncertainty in treatment response, but, conversely the existing therapies can be used to target two or more pathogenic mechanisms to treat at the same time, these parameters being oxidative stress, mitochondrial dysfunction, or poor quality-control of cells. Nonetheless, comparisons of mitochondrial-targeted approaches and usual therapies have yet to be made directly. It may have synergetic advantage to combination strategies involving mitochondrial or the metabolic intervention together with androgen suppression, yet yet this has to be examined in clinical trials. Therapeutic approaches to mitochondrial dysfunction and NAD+/sirtuin axis are one of the potential directions that are still in the development of AGA therapy. Although pre-clinical investigations suggest that the nature of the insights is encouraging, clinical data is scarce. Until more research is conducted to clarify whether these approaches can be converted into safe and effective therapy, as a monotherapy or used with current therapies, this research is necessary.

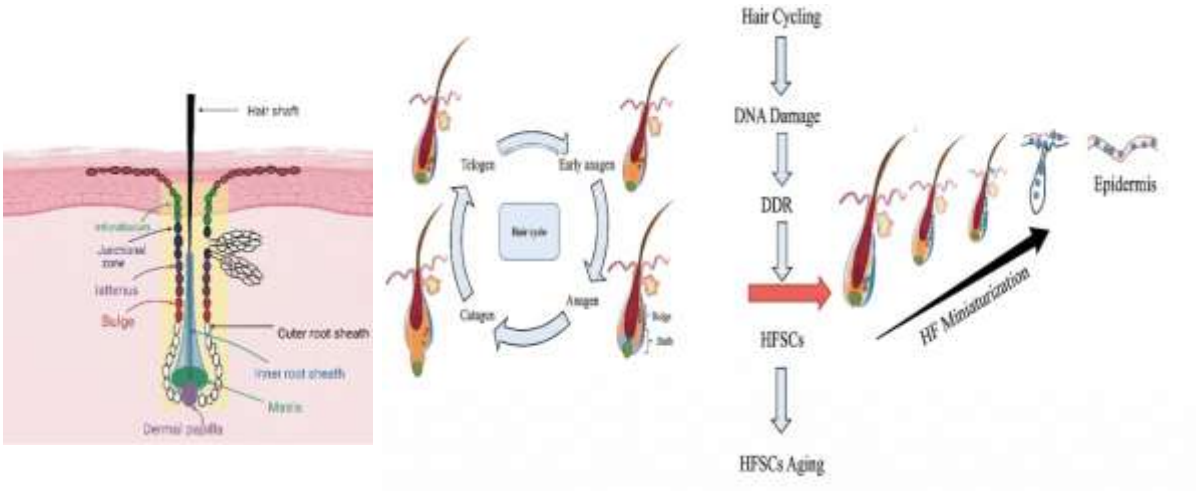


Figure 8: Hair follicle structure and progression to miniaturization

Research Gap

The in vitro study of androgenetic alopecia (AGA) should focus on more biological experimental models in the future. The existing use of two-dimensional cell cultures and animal models restricts the translational usability. Further platforms, such as the three-dimensional hair follicle organoids, ex vivo human scalp systems, and patient-derived cellular models, could be more representative of the complexity of follicular biology and could facilitate a more precise study of the mitochondrial functioning, formation of oxidative stress, and mitophagy. Simultaneously, it is possible that single-cell multi-omics methods could be used to characterize cell-type-specific changes in the follicular niche and enhance the individual cell heterogeneity of the disease. Niche gaps in mechanistic critical investigations should also be made. Mitochondrial dynamics, mitophagy flux, and NAD + metabolism of human AGA tissue have not been directly studied. The clarification of the functional role of the NAD+/sirtuin axis and the interaction between the two in relation to the androgen signal will be necessary to demonstrate causality. Translational-wise, clinical trials should be properly designed to test mitochondrial-targeted therapies, better delivery methods, and biomarkers, which help to stratify patients. Addressing such priorities can help to develop mechanism-based interventions and increase therapeutic outcomes in AGA.

CONCLUSION

Androgenetic alopecia (AGA) has long been considered an androgen-induced disorder, but recently, it is possible to believe that it could also have mitochondrial dysfunction, oxidative stress, and a defect in cell quality control that might play a role in its pathogenesis. This review combines newly obtained evidence suggesting that dermal papilla cells in AGA show a disturbance in mitochondrial activity, elevated levels of reactive oxygen species, and malfunctioning of major metabolic regulators, such as the components of the NAD+/sirtuin axis. These interrelationships have the potential to further enhance follicular injury, compromise regenerative potential, and lead to further miniaturization of androgen signaling itself. Although this developing model offers a more holistic concept of AGA, there are significant gaps in the dark. There is a paucity of direct evidence connecting mitophagy and NAD + metabolism to the pathophysiology of follicles in humans, and cause-and-effect relationships are not established yet. However, the focus on mitochondrial pathways can become an effective addition to existing treatment. Further research incorporating both mechanistic research and clinical research will be needed in order to ascertain whether the modulation of mitochondrial activity can be translated into therapeutic benefit and better patient outcomes with AGA.

REFERENCES

1. Abaci HE, Coffman A, Doucet Y, et al. Tissue engineering of human hair follicles using a biomimetic developmental approach. Nature Communications 2018 9:1 [homepage on the Internet] 2018 [cited 2026 Apr 3];9(1):5301-. Available from: https://www.nature.com/articles/s41467-018-07579-y
2. Abbasian H, Noruzinia M, Garshasbi M. Investigation the role of SIRT3, SIRT7, NFATC1, and PDL-1 genes in androgenetic alopecia. BMC Research Notes 2024 17:1 [homepage on the Internet] 2024 [cited 2026 Apr 3];17(1):343-. Available from: https://link.springer.com/article/10.1186/s13104-024-06980-9
3. Ahn BH, Kim HS, Song S, et al. A role for the mitochondrial deacetylase Sirt3 in regulating energy homeostasis. Proc Natl Acad Sci U S A [homepage on the Internet] 2008 [cited 2026 Apr 3];105(38):14447–14452. Available from: https://pubmed.ncbi.nlm.nih.gov/18794531 /
4. Alfonso M, Richter-Appelt H, Tosti A, Viera MS, García M. The psychosocial impact of hair loss among men: a multinational European study. Curr Med Res Opin [homepage on the Internet] 2005 [cited 2026 Apr 3];21(11):1829–1836. Available from: https://pubmed.ncbi.nlm.nih.gov/16307704/

5. Barber MF, Michishita-Kioi E, Xi Y, et al. SIRT7 links H3K18 deacetylation to maintenance of oncogenic transformation. Nature 2012 487:7405 [homepage on the Internet] 2012 [cited 2026 Apr 3];487(7405):114–118. Available from: https://www.nature.com/articles/nature11043
6. Baur JA, Pearson KJ, Price NL, et al. Resveratrol improves health and survival of mice on a high-calorie diet. Nature 2006 444:7117 [homepage on the Internet] 2006 [cited 2026 Apr 3];444(7117):337–342. Available from: https://www.nature.com/articles/nature05354
7. Bedard K, Krause KH. The NOX family of ROS-generating NADPH oxidases: physiology and pathophysiology. Physiol Rev [homepage on the Internet] 2007 [cited 2026 Apr 3];87(1):245–313. Available from: https://pubmed.ncbi.nlm.nih.gov/17237347 /
8. Birch-Machin MA, Bowman A. Oxidative stress and ageing. British Journal of Dermatology [homepage on the Internet] 2016 [cited 2026 Apr 3];175(S2):26–29. Available from: https://dx.doi.org/10.1111/bjd.14906
9. Brunet A, Sweeney LB, Sturgill JF, et al. Stress-Dependent Regulation of FOXO Transcription Factors by the SIRT1 Deacetylase. Science (1979) [homepage on the Internet] 2004 [cited 2026 Apr 3];303(5666):2011–2015. Available from: /doi/pdf/10.1126/science.1094637?download=true
10. Camacho-Pereira J, Tarragó MG, Chini CCS, et al. CD38 Dictates Age-Related NAD Decline and Mitochondrial Dysfunction through an SIRT3-Dependent Mechanism. Cell Metab [homepage on the Internet] 2016 [cited 2026 Apr 3];23(6):1127–1139. Available from: https://pubmed.ncbi.nlm.nih.gov/27304511/
11. Cantó C, Auwerx J. Targeting sirtuin 1 to improve metabolism: all you need is NAD(+)? Pharmacol Rev [homepage on the Internet] 2012 [cited 2026 Apr 3];64(1):166–187. Available from: https://pubmed.ncbi.nlm.nih.gov/22106091/
12. Cash TF. The psychology of hair loss and its implications for patient care. Clin Dermatol [homepage on the Internet] 2001 [cited 2026 Apr 3];19(2):161–166. Available from: https://pubmed.ncbi.nlm.nih.gov/11397595/
13. Zhang X, Gao Y, zhang S, et al. Mitochondrial dysfunction in the regulation of aging and aging-related diseases. Cell Commun Signal [homepage on the Internet] 2025 [cited 2026 Apr 4];23(1). Available from: https://pubmed.ncbi.nlm.nih.gov/40537801/
14. Chew EGY, Lim TC, Leong MF, et al. Observations that suggest a contribution of altered dermal papilla mitochondrial function to androgenetic alopecia. Exp Dermatol [homepage on the Internet] 2022 [cited 2026 Apr 3];31(6):906–917. Available from: /doi/pdf/10.1111/exd.14536
15. Chini CCS, Tarragó MG, Chini EN. NAD and the aging process: Role in life, death and everything in between. Mol Cell Endocrinol [homepage on the Internet] 2017 [cited 2026 Apr 3];455:62–74. Available from: https://pubmed.ncbi.nlm.nih.gov/27825999 /
16. Coppé JP, Desprez PY, Krtolica A, Campisi J. The senescence-associated secretory phenotype: the dark side of tumor suppression. Annu Rev Pathol [homepage on the Internet] 2010 [cited 2026 Apr 3];5:99–118. Available from: https://pubmed.ncbi.nlm.nih.gov/20078217/
17. Daitoku H, Hatta M, Matsuzaki H, et al. Silent information regulator 2 potentiates Foxo 1-mediated transcription through its deacetylase activity. Proc Natl Acad Sci U S A [homepage on the Internet] 2004 [cited 2026 Apr 3];101(27):10042–10047. Available from: /doi/pdf/10.1073/pnas.0400593101?download=true
18. Dixon SJ, Lemberg KM, Lamprecht MR, et al. Ferroptosis: An Iron-Dependent Form of Non-Apoptotic Cell Death. Cell [homepage on the Internet] 2012 [cited 2026 Apr 3];149(5):1060. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC3367386/
19. Ellis JA, Sinclair R, Harrap SB. Androgenetic alopecia: pathogenesis and potential for therapy. Expert Rev Mol Med [homepage on the Internet] 2002 [cited 2026 Apr 3];4(22):1–11. Available from: https://pubmed.ncbi.nlm.nih.gov/14585162/
20. Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. Nature 2000 408:6809 [homepage on the Internet] 2000 [cited 2026 Apr 3];408(6809):239–247. Available from: https://www.nature.com/articles/35041687
21. Gane EJ, Weilert F, Orr DW, et al. The mitochondria-targeted anti-oxidant mitoquinone decreases liver damage in a phase II study of hepatitis C patients. Liver Int [homepage on the Internet] 2010 [cited 2026 Apr 4];30(7):1019–1026. Available from: https://pubmed.ncbi.nlm.nih.gov/20492507/
22. Gupta AK, Charrette A. The efficacy and safety of 5α-reductase inhibitors in androgenetic alopecia: a network meta-analysis and benefit-risk assessment of finasteride and dutasteride. J Dermatolog Treat [homepage on the Internet] 2014 [cited 2026 Apr 3];25(2):156–161. Available from: https://pubmed.ncbi.nlm.nih.gov/23768246/
23. Haigis MC, Sinclair DA. Mammalian Sirtuins: Biological Insights and Disease Relevance. Annu Rev Pathol [homepage on the Internet] 2010 [cited 2026 Apr 3];5:253. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC2866163/
24. Hanna RA, Quinsay MN, Orogo AM, Giang K, Rikka S, Gustafsson ÅB. Microtubule-associated protein 1 light chain 3 (LC3) interacts with Bnip3 protein to selectively remove endoplasmic reticulum and mitochondria via autophagy. J Biol Chem [homepage on the Internet] 2012 [cited 2026 Apr 3];287(23):19094–19104. Available from: https://pubmed.ncbi.nlm.nih.gov/22505714/

25. Hariharan N, Maejima Y, Nakae J, Paik J, Depinho RA, Sadoshima J. Deacetylation of FoxO by Sirt1 plays an essential role in mediating starvation-induced autophagy in cardiac myocytes. Circ Res [homepage on the Internet] 2010 [cited 2026 Apr 3];107(12):1470. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC3011986/
26. Hebert AS, Dittenhafer-Reed KE, Yu W, et al. Calorie restriction and SIRT3 trigger global reprogramming of the mitochondrial protein acetylome. Mol Cell [homepage on the Internet] 2013 [cited 2026 Apr 3];49(1):186–199. Available from: https://pubmed.ncbi.nlm.nih.gov/23201123/
27. Hirschey MD, Shimazu T, Goetzman E, et al. SIRT3 regulates mitochondrial fatty-acid oxidation by reversible enzyme deacetylation. Nature 2010 464:7285 [homepage on the Internet] 2010 [cited 2026 Apr 4];464(7285):121–125. Available from: https://www.nature.com/articles/nature08778
28. Hirschey MD, Shimazu T, Jing E, et al. SIRT3 deficiency and mitochondrial protein hyperacetylation accelerate the development of the metabolic syndrome. Mol Cell [homepage on the Internet] 2011 [cited 2026 Apr 3];44(2):177–190. Available from: https://www.cell.com/action/showFullText?pii=S1097276511005430
29. Holmström KM, Finkel T. Cellular mechanisms and physiological consequences of redox-dependent signalling. Nature Reviews Molecular Cell Biology 2014 15:6 [homepage on the Internet] 2014 [cited 2026 Apr 3];15(6):411–421. Available from: https://www.nature.com/articles/nrm3801
30. Li Y, Dong T, Wu J, et al. MitoQ upregulates CYP19A1 to protect dermal papilla cells from DHT-induced mitochondrial dysfunction and apoptosis in androgenetic alopecia. Biochem Pharmacol [homepage on the Internet] 2026 [cited 2026 Apr 3];246:117729. Available from: https://www.sciencedirect.com/science/article/pii/S0006295226000602
31. Inui S, Itami S. Androgen actions on the human hair follicle: Perspectives. Exp Dermatol [homepage on the Internet] 2013 [cited 2026 Apr 3];22(3):168–171. Available from: /doi/pdf/10.1111/exd.12024
32. Huang Z, Weng Z, Yuan J, et al. Sinapic acid and glabridin synergistically mitigate androgenetic alopecia by modulating ferroptosis through stabilization of β-catenin against ubiquitin-dependent degradation. Biochem Pharmacol [homepage on the Internet] 2025 [cited 2026 Apr 3];241:117171. Available from: https://www.sciencedirect.com/science/article/pii/S0006295225004368
33. Jin SM, Lazarou M, Wang C, Kane LA, Narendra DP, Youle RJ. Mitochondrial membrane potential regulates PINK1 import and proteolytic destabilization by PARL. J Cell Biol [homepage on the Internet] 2010 [cited 2026 Apr 3];191(5):933–942. Available from: https://pubmed.ncbi.nlm.nih.gov/21115803/
34. Joost S, Annusver K, Jacob T, et al. The Molecular Anatomy of Mouse Skin during Hair Growth and Rest. Cell Stem Cell [homepage on the Internet] 2020 [cited 2026 Apr 3];26(3):441-457.e7. Available from: https://pubmed.ncbi.nlm.nih.gov/32109378/
35. Kane LA, Lazarou M, Fogel AI, et al. PINK1 phosphorylates ubiquitin to activate Parkin E3 ubiquitin ligase activity. J Cell Biol [homepage on the Internet] 2014 [cited 2026 Apr 3];205(2):143–153. Available from: https://pubmed.ncbi.nlm.nih.gov/24751536/
36. Kaufman KD. Androgens and alopecia. Mol Cell Endocrinol [homepage on the Internet] 2002 [cited 2026 Apr 3];198(1–2):89–95. Available from: https://pubmed.ncbi.nlm.nih.gov/12573818/
37. Kaufman KD, Dawber RP. Finasteride, a Type 2 5α-reductase inhibitor, in the treatment of men with androgenetic alopecia. Expert Opin Investig Drugs [homepage on the Internet] 1999 [cited 2026 Apr 3];8(4):403–415. Available from: https://www.tandfonline.com/doi/abs/10.1517/13543784.8.4.403
38. Kaufman KD, Olsen EA, Whiting D, et al. Finasteride in the treatment of men with androgenetic alopecia. J Am Acad Dermatol [homepage on the Internet] 1998 [cited 2026 Apr 3];39(4):578–589. Available from: https://www.sciencedirect.com/science/article/pii/S0190962298700076
39. Khacho M, Clark A, Svoboda DS, et al. Mitochondrial Dynamics Impacts Stem Cell Identity and Fate Decisions by Regulating a Nuclear Transcriptional Program. Cell Stem Cell [homepage on the Internet] 2016 [cited 2026 Apr 3];19(2):232–247. Available from: https://www.sciencedirect.com/science/article/pii/S1934590916300820
40. Kitada T, Asakawa S, Hattori N, et al. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature 1998 392:6676 [homepage on the Internet] 1998 [cited 2026 Apr 3];392(6676):605–608. Available from: https://www.nature.com/articles/33416
41. Lagouge M, Argmann C, Gerhart-Hines Z, et al. Resveratrol Improves Mitochondrial Function and Protects against Metabolic Disease by Activating SIRT1 and PGC-1α. Cell [homepage on the Internet] 2006 [cited 2026 Apr 3];127(6):1109–1122. Available from: https://www.sciencedirect.com/science/article/pii/S0092867406014280
42. Lazarou M, Sliter DA, Kane LA, et al. The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. Nature 2015 524:7565 [homepage on the Internet] 2015 [cited 2026 Apr 3];524(7565):309–314. Available from: https://www.nature.com/articles/nature14893
43. In HL, Cao L, Mostoslavsky R, et al. A role for the NAD-dependent deacetylase Sirt1 in the regulation of autophagy. Proc Natl Acad Sci U S A [homepage on the Internet] 2008 [cited 2026 Apr 3];105(9):3374–3379. Available from: https://pubmed.ncbi.nlm.nih.gov/18296641/
44. Lim X, Tan SH, Yu K Lou, Lim SBH, Nusse R. Axin2 marks quiescent hair follicle bulge stem cells that are maintained by autocrine Wnt/β-catenin signaling. Proc Natl Acad Sci U S A [homepage on the Internet] 2016 [cited 2026 Apr 3];113(11):E1498–E1505. Available from: https://pubmed.ncbi.nlm.nih.gov/26903625/

45. Lombard DB, Alt FW, Cheng H-L, et al. Mammalian Sir2 homolog SIRT3 regulates global mitochondrial lysine acetylation. Mol Cell Biol [homepage on the Internet] 2007 [cited 2026 Apr 3];27(24):8807–8814. Available from: https://pubmed.ncbi.nlm.nih.gov/17923681/
46. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The Hallmarks of Aging. Cell [homepage on the Internet] 2013 [cited 2026 Apr 3];153(6):1194. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC3836174/
47. LUDWIG E. Classification of the types of androgenetic alopecia (common baldness) occurring in the female sex. British Journal of Dermatology [homepage on the Internet] 1977 [cited 2026 Apr 3];97(3):247–254. Available from: /doi/pdf/10.1111/j.1365-2133.1977.tb15179.x
48. Messenger AG, Rundegren J. Minoxidil: mechanisms of action on hair growth. Br J Dermatol [homepage on the Internet] 2004 [cited 2026 Apr 3];150(2):186–194. Available from: https://pubmed.ncbi.nlm.nih.gov/14996087/
49. Milne JC, Lambert PD, Schenk S, et al. Small molecule activators of SIRT1 as therapeutics for the treatment of type 2 diabetes. Nature [homepage on the Internet] 2007 [cited 2026 Apr 4];450(7170):712–716. Available from: https://pubmed.ncbi.nlm.nih.gov/18046409/
50. Minor RK, Baur JA, Gomes AP, et al. SRT1720 improves survival and healthspan of obese mice. Sci Rep [homepage on the Internet] 2011 [cited 2026 Apr 3];1. Available from: https://pubmed.ncbi.nlm.nih.gov/22355589/
51. Murphy MP. How mitochondria produce reactive oxygen species. Biochemical Journal [homepage on the Internet] 2008 [cited 2026 Apr 3];417(Pt 1):1. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC2605959/
52. Murphy MP, Smith RAJ. Targeting antioxidants to mitochondria by conjugation to lipophilic cations. Annu Rev Pharmacol Toxicol [homepage on the Internet] 2007 [cited 2026 Apr 3];47(Volume 47, 2007):629–656. Available from: https://www.annualreviews.org/content/journals/10.1146/annurev.pharmtox.47.120505.105110
53. Narendra DP, Jin SM, Tanaka A, et al. PINK1 Is Selectively Stabilized on Impaired Mitochondria to Activate Parkin. PLoS Biol [homepage on the Internet] 2010 [cited 2026 Apr 3];8(1):e1000298. Available from: https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1000298
54. Naziroglu M, Kökçam I, Şimşek H, Karakilçk AZ. Lipid peroxidation and antioxidants in plasma and red blood cells from patients with pemphigus vulgaris. J Basic Clin Physiol Pharmacol [homepage on the Internet] 2003 [cited 2026 Apr 3];14(1):31–42. Available from: https://www.scilit.com/publications/5d49418107bfda7530c6db4454e5afb4
55. Ney PA. Mitochondrial autophagy: Origins, significance, and role of BNIP3 and NIX. Biochimica et Biophysica Acta (BBA) - Molecular Cell Research [homepage on the Internet] 2015 [cited 2026 Apr 3];1853(10):2775–2783. Available from: https://www.sciencedirect.com/science/article/pii/S0167488915000725
56. Norwood OT. Male pattern baldness: classification and incidence. South Med J [homepage on the Internet] 1975 [cited 2026 Apr 3];68(11):1359–1365. Available from: https://pubmed.ncbi.nlm.nih.gov/1188424/
57. Olsen EA, Dunlap FE, Funicella T, et al. A randomized clinical trial of 5% topical minoxidil versus 2% topical minoxidil and placebo in the treatment of androgenetic alopecia in men. J Am Acad Dermatol [homepage on the Internet] 2002 [cited 2026 Apr 3];47(3):377–385. Available from: https://www.sciencedirect.com/science/article/pii/S019096220200124X
58. Palikaras K, Lionaki E, Tavernarakis N. Mechanisms of mitophagy in cellular homeostasis, physiology and pathology. Nature Cell Biology 2018 20:9 [homepage on the Internet] 2018 [cited 2026 Apr 3];20(9):1013–1022. Available from: https://www.nature.com/articles/s41556-018-0176-2
59. Hur YK, Chae JY, Choi MH, et al. Tanshinone, a Natural NADPH Oxidase Inhibitor, Mitigates Testosterone-Induced Hair Loss. Biomol Ther (Seoul) [homepage on the Internet] 2025 [cited 2026 Apr 3];33(1):210–220. Available from: https://pubmed.ncbi.nlm.nih.gov/39632646/
60. Pickles S, Vigié P, Youle RJ. Mitophagy and Quality Control Mechanisms in Mitochondrial Maintenance. Current Biology [homepage on the Internet] 2018 [cited 2026 Apr 3];28(4):R170–R185. Available from: https://www.sciencedirect.com/science/article/pii/S096098221830006X
61. Pickrell AM, Youle RJ. The Roles of PINK1, Parkin and Mitochondrial Fidelity in Parkinson's Disease. Neuron [homepage on the Internet] 2015 [cited 2026 Apr 3];85(2):257. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC4764997/
62. Qiu X, Brown K, Hirschey MD, Verdin E, Chen D. Calorie Restriction Reduces Oxidative Stress by SIRT3-Mediated SOD2 Activation. Cell Metab [homepage on the Internet] 2010 [cited 2026 Apr 3];12(6):662–667. Available from: https://www.sciencedirect.com/science/article/pii/S1550413110004079
63. Remie CME, Roumans KHM, Moonen MPB, et al. Nicotinamide riboside supplementation alters body composition and skeletal muscle acetylcarnitine concentrations in healthy obese humans. Am J Clin Nutr [homepage on the Internet] 2020 [cited 2026 Apr 3];112(2):413–426. Available from: https://pubmed.ncbi.nlm.nih.gov/32320006/
64. Rodgers JT, Lerin C, Haas W, Gygi SP, Spiegelman BM, Puigserver P. Nutrient control of glucose homeostasis through a complex of PGC-1α and SIRT1. Nature 2005 434:7029 [homepage on the Internet] 2005 [cited 2026 Apr 3];434(7029):113–118. Available from: https://www.nature.com/articles/nature03354

65. Samant SA, Zhang HJ, Hong Z, et al. SIRT3 deacetylates and activates OPA1 to regulate mitochondrial dynamics during stress. Mol Cell Biol [homepage on the Internet] 2014 [cited 2026 Apr 3];34(5):807–819. Available from: https://pubmed.ncbi.nlm.nih.gov/24344202/
66. Sandoval H, Thiagarajan P, Dasgupta SK, et al. Essential role for Nix in autophagic maturation of erythroid cells. Nature 2008 454:7201 [homepage on the Internet] 2008 [cited 2026 Apr 3];454(7201):232–235. Available from: https://www.nature.com/articles/nature07006
67. Scarpulla RC. Metabolic control of mitochondrial biogenesis through the PGC-1 family regulatory network. Biochim Biophys Acta Mol Cell Res [homepage on the Internet] 2011 [cited 2026 Apr 3];1813(7):1269–1278. Available from: https://pubmed.ncbi.nlm.nih.gov/20933024/
68. Schieber M, Chandel NS. ROS function in redox signaling and oxidative stress. Current Biology [homepage on the Internet] 2014 [cited 2026 Apr 3];24(10). Available from: https://pubmed.ncbi.nlm.nih.gov/24845678/
69. Schneider MR, Schmidt-Ullrich R, Paus R. The hair follicle as a dynamic miniorgan. Curr Biol [homepage on the Internet] 2009 [cited 2026 Apr 4];19(3). Available from: https://pubmed.ncbi.nlm.nih.gov/19211055/