Aging and Disease
www.aginganddisease.org
Early access date: March 4, 2026
http://dx.doi.org/10.14336/AD.2025.1585

Review

The Mitochondrial Blueprint of Skin Aging: From Damage Signals to Dermatologic Interventions

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[Received December 20, 2025; Revised February 24, 2026; Accepted February 25, 2026]

ABSTRACT: Mitochondria are increasingly recognized as central regulators of skin health and aging, providing ATP and coordinating redox signaling, mitophagy, and cell fate decisions. In cutaneous tissues, mitochondrial integrity sustains fibroblast-driven collagen synthesis, keratinocyte proliferation, melanocyte homeostasis, and efficient wound repair. With advancing age and cumulative ultraviolet exposure, mitochondria accumulate hallmark defects. Mitochondrial DNA mutations and deletions, impaired oxidative phosphorylation, excessive reactive oxygen species production, diminished mitophagy and biogenesis, disrupted fission–fusion dynamics, NAD^+ decline, and sirtuin dysregulation all converge to undermine energy metabolism, amplify inflammatory signaling, and accelerate fibroblast senescence, extracellular matrix degradation, pigmentary changes, and delayed wound healing. Recent research also highlights weakened antioxidant defenses and extracellular vesicle–mediated propagation of mitochondrial stress across the cutaneous microenvironment, underscoring the organelle's central role in skin aging. Against this mechanistic backdrop, mitochondria-targeted interventions are emerging as promising therapeutic strategies. Extracellular vesicles loaded with NAD^+ precursors, antioxidant enzymes, or mitophagy stimulators show preclinical efficacy in restoring bioenergetics and accelerating wound closure. Mitochondria-directed antioxidants such as melatonin and coenzyme Q10, NAD^+ boosters and sirtuin activators, red and near-infrared photobiomodulation, and NRF2-based redox reprogramming each enhance mitochondrial homeostasis while improving collagen synthesis, pigmentation balance, and re-epithelialization. Early translational and clinical studies indicate that these approaches protect against UV-induced mitochondrial DNA damage, reduce oxidative stress, and improve cutaneous structure and function. Collectively, these findings position mitochondria as a modifiable hub for cutaneous aging and wound repair, and highlight the potential of integrated metabolic, antioxidant, and vesicle-based approaches to transform dermatologic anti-aging and wound-care interventions.

Keywords: skin aging, mitochondria, oxidative stress, mtDNA deletions

1. Introduction

Mitochondria are central to skin health, functioning as the primary source of ATP while also serving as hubs for redox signaling, apoptosis regulation, and mitophagy. In cutaneous tissues, mitochondrial integrity supports fibroblast-driven collagen synthesis, keratinocyte proliferation, and melanocyte homeostasis [1]. Because these are highly energy-dependent processes, they are acutely sensitive to mitochondrial decline.

Skin aging arises through both intrinsic mechanisms (such as thinning of the dermis, reduced extracellular matrix (ECM) turnover, and impaired epidermal renewal), and extrinsic drivers, most notably chronic ultraviolet (UV) exposure. Notably, intrinsic aging is also driven by well-known hallmarks such as nuclear genomic

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instability, telomere attrition, and loss of proteostasis, which contribute to cellular senescence and tissue degeneration. Photoaging is strongly associated with oxidative stress, with mitochondria acting as both a source and a target of reactive oxygen species (ROS) [1]. Continuous ROS exposure, combined with limited mitochondrial repair capacity, accelerates the accumulation of mitochondrial DNA (mtDNA) damage, including the common 4977-bp deletion [2-5]. Hallmarks of mitochondrial dysfunction in skin include impaired oxidative phosphorylation and ATP synthesis, excessive ROS production, and insufficient mitophagy. These changes promote fibroblast senescence, collagen degradation, altered pigmentation, and visible wrinkling [6-9].

Mitochondrial dysfunction interacts with broader aging pathways, including genomic instability, inflammatory signaling, and impaired skin repair. This positions mitochondria as a key player in cutaneous aging, thus a compelling therapeutic target. Investigational strategies include mitochondria-specific antioxidants (melatonin and coenzyme Q10), NAD^+ boosters, and sirtuin activators (for example, nicotinamide derivatives like NR, resveratrol analogs, and other experimental drugs such as SRT3025, pterostilbene, etc.) [10-14]. Here, we synthesize advances from 2023–2025 spanning basic, translational, and early clinical studies to position mitochondria as a central frontier in dermatologic anti-aging interventions.

2. Mechanisms of Mitochondrial Aging in skin

Mitochondria orchestrate energy production, redox balance, and signaling in the skin, and their progressive dysfunction constitutes a key driver of cellular aging [15]. Accumulated mitochondrial defects are observed in both intrinsic (chronological) and extrinsic (photoinduced) skin aging, characterized by diminished bioenergetic output, increased oxidative damage, and altered communication between mitochondria, the nucleus, and the immune system [16]. Evidence derived from human tissue studies, cultured primary skin cells, and multiple murine models converges to describe a network of pathogenic mechanisms linking mitochondrial decline to dermal thinning, collagen loss, irregular pigmentation, and delayed wound healing [15]. These findings suggest that mitochondrial dysfunction arts as an integrating mechanism that links metabolic decline to structural and regenerative features of skin aging.

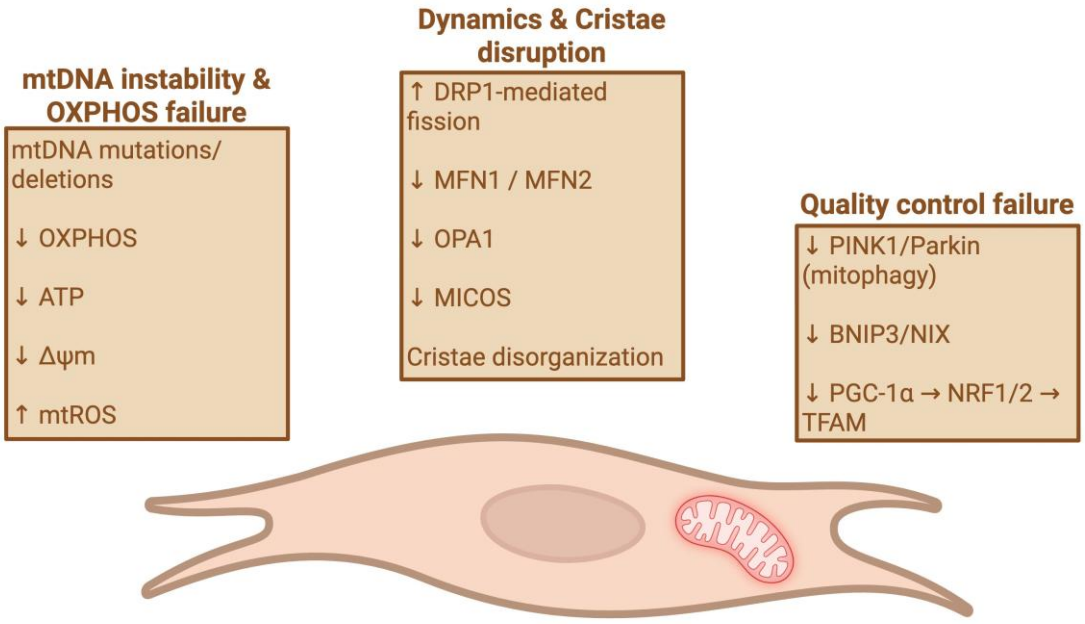

Figure 1. Core mitochondrial defects underlying cutaneous aging. Across keratinocytes, melanocytes, fibroblasts, and endothelial cells, aging is associated with intrinsic mitochondrial structural and functional failure. Accumulation of mitochondrial DNA (mtDNA) mutations and deletions impairs oxidative phosphorylation (OXPHOS), reduces mitochondrial membrane potential (Δψm) and ATP production, and increases mitochondrial reactive oxygen species (mtROS). Concurrent dysregulation of mitochondrial dynamics, characterized by excessive DRP1-mediated fission and loss of MFN1/2, OPA1, and MICOS integrity, fragments mitochondrial networks and disrupts cristae organization. In parallel, mitochondrial quality control declines due to impaired mitophagy (PINK1/Parkin, BNIP3/NIX) and reduced biogenesis driven by suppression of the PGC-1α→NRF1/2→TFAM axis, permitting accumulation of dysfunctional organelles in aging skin cells.

2.1 mtDNA Instability and OXPHOS Failure

The mitochondrial genome, comprising of 16.6kb circular DNA, is highly prone to mutation due to its proximity to the electron transport chain and lack of protective histones. With age, mtDNA accumulates both point mutations and large-scale deletions, most notably the 4,977 bp "*common deletion*," which removes key genes encoding subunits of complexes I, IV, and V. This loss impairs oxidative phosphorylation (OXPHOS), reduces ATP production, and increases ROS generation [17]. Studies of human skin biopsies demonstrate that photoexposed areas exhibit higher mtDNA deletion loads and reduced copy numbers than protected sites, correlating with decreased collagen synthesis and dermal elasticity [2, 8, 18, 19]. Blue-light exposure (405–450 nm) also promotes mtDNA strand breaks and ROS accumulation in dermal fibroblasts [20]. Mouse models such as Twinkle helicase mutants (transgenic mice harboring a proofreading-deficient mitochondrial helicase that promotes accumulation of mtDNA deletions and accelerates skin aging) have been instrumental in elucidating causality. In a strain of mice with fibroblast-specific Twinkle mutation (Twinkle^{FIBRO}), the excess mtDNA damage alters fibroblast differentiation, remodels extracellular matrix gene expression, and induces resistance to fibrotic stimuli, directly linking mitochondrial genome instability to dermal physiology and aging phenotypes. Similarly, POLG mutator mice carry a proofreading-deficient mitochondrial DNA polymerase gamma that drives systemic accumulation of mtDNA point mutations. These animals exhibit striking progeroid features that mirror human cutaneous aging, including alopecia, wrinkled skin, and reduced dermal collagen density [7]. The Twinkle^{FIBRO} mice accumulate high load of mtDNA mutations, resulting in noticeably thinner skin and impaired wound repair, providing strong evidence that mitochondrial genome instability is a driver of skin aging rather than a secondary consequence of oxidative stress [7, 8, 17, 21-23]. Restoration of mtDNA integrity via inducible systems reverses these phenotypes, confirming that mtDNA damage is causal rather than associative (Fig. 1). Collectively, these studies demonstrate that mtDNA damage functions as an upstream regulator connecting oxidative stress to impaired bioenergetics and tissue repair.

2.2 Mitochondria-Nucleus Crosstalk and Epigenetic Reprogramming

Mitochondria modulate nuclear gene expression through retrograde signaling, metabolite flux, and second messenger systems that integrate metabolic and stress responses [24]. A decline in mitochondrial metabolites (such as acetyl-CoA, α-ketoglutarate, FAD, and NAD^+) directly impairs chromatin-modifying enzymes including histone acetyltransferases (HATs), histone deacetylases (HDACs), and DNA/histone demethylases dependent on α-ketoglutarate [25]. This leads to widespread histone hypoacetylation, altered methylation of H3K9 and H3K27, and transcriptional drift associated with fibroblast senescence [26, 27]. Key retrograde signaling pathways involve Ca^{2+}-dependent activation of calcineurin and NFAT, AMPK-mediated phosphorylation of transcription factors such as FOXO1 and PGC-1α, and hypoxia-induced stabilization of HIF-1α. Each of these pathways changes the expression of numerous nuclear genes, driving a shift in cell's metabolic and stress response programs to adapt to mitochondrial dysfunction. In human dermal fibroblasts, suppression of carnitine acetyltransferase reduces cytosolic acetyl-CoA pools, dampening histone acetylation and accelerating senescence with reduced COL1A1, COL3A1, and ELN transcription [28]. Complementary murine studies show that supplementation with NAD^+ precursors or sirtuin activators restores histone acetylation, normalizes AMPK and PGC-1α activity, and rescues youthful extracellular matrix gene expression [11, 29]. Communication between mitochondria and the nucleus also occurs through proteins called sirtuins. At the mitochondrial-nuclear interface, sirtuins coordinate regulation across compartments, where SIRT3 and SIRT4 deacetylate mitochondrial enzymes regulating redox balance, while SIRT1 and SIRT6 coordinate nuclear chromatin remodeling and DNA repair. The interplay between mitochondrial sirtuins and nuclear TET2 demethylase modulates 5-hydroxymethylcytosine turnover and facilitates epigenetic rejuvenation, suggesting that mitochondrial sirtuins can help reset some of the age-associated epigenetic changes in the nucleus, and thus contribute to a more youthful pattern of gene expression [13]. Together, these findings suggest that perturbations in mitochondrial metabolites and signaling cascades (Ca^{2+}, AMPK, HIF-1α, sirtuins) directly remodel nuclear gene programs, linking mitochondrial function to the epigenetic landscape and aging phenotype of skin cells (Fig. 2).

2.3 Mitochondrial-Immune Interface (Inflammaging)

Mitochondrial damage elicits inflammatory signaling through the release of oxidized mtDNA, cardiolipin, and N-formyl peptides collectively known as mitochondrial damage-associated molecular patterns (mtDAMPs). These molecules activate both endosomal and cytosolic pattern-recognition receptors. Oxidized mtDNA binds Toll-like receptor 9 (TLR9) in endolysosomal compartments, triggering MyD88-dependent NF-κB signaling and the transcription of IL-6, IL-1β, and TNF-α

[30, 31]. In parallel, cytosolic mtDNA is recognized by cyclic GMP–AMP synthase (cGAS), leading to production of the second messenger cGAMP that activates stimulator of interferon genes (STING) on the endoplasmic reticulum. STING recruitment of TBK1 and IRF3 leads to the induction of type I interferons such as IFN-β, which contribute to chronic, low-grade inflammation seen in photoaged and intrinsically aged skin.

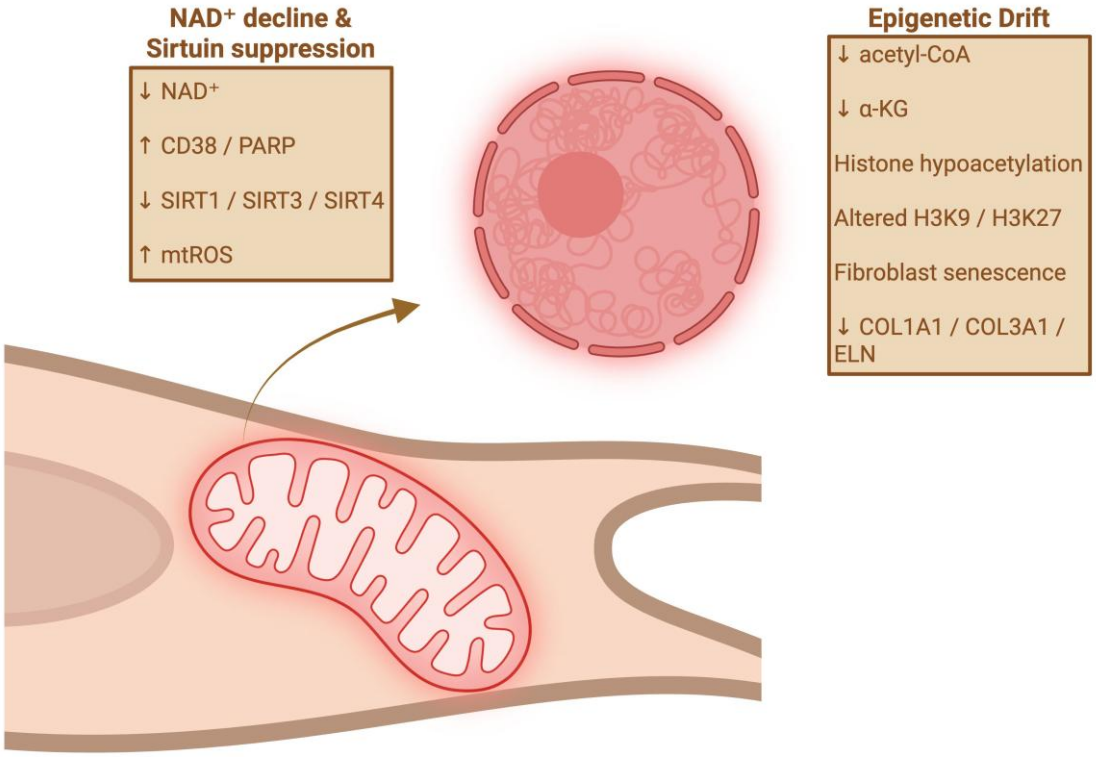

Figure 2. Metabolic and epigenetic reprogramming driven by mitochondrial dysfunction in aging skin. Age-related mitochondrial failure disrupts metabolite availability and retrograde signaling to the nucleus, reshaping the epigenetic landscape of skin cells. Declining NAD^+ pools, driven by reduced synthesis and increased consumption by CD38 and PARPs, suppress sirtuin activity (SIRT1, SIRT3, SIRT4), weakening mitochondrial detoxification, redox balance, and stress resistance while further amplifying mtROS. Reduced availability of mitochondrial metabolites such as acetyl-CoA and α-ketoglutarate impairs chromatin-modifying enzymes, leading to histone hypoacetylation, altered H3K9/H3K27 methylation, transcriptional drift, and fibroblast senescence with reduced expression of extracellular matrix genes (COL1A1, COL3A1, ELN).

In keratinocytes, UVB exposure enhances DRP1-mediated mitochondrial fission and disrupts outer membrane integrity, facilitating mtDNA leakage into the cytosol [32]. This cascade activates both NF-κB and IRF3 pathways, amplifying secretion of IL-1β, IL-6, and IFN-β. Downstream, mitochondrial ROS and cardiolipin externalization further activate the NLRP3 inflammasome, promoting caspase-1 cleavage and maturation of IL-1β and IL-18 [33]. In mouse models of chronic UV exposure, sustained cGAS–STING and NLRP3 activation correlate with dermal infiltration of macrophages and mast cells, ECM degradation, and impaired barrier repair. Pharmacologic interventions that enhance mitophagy (such as urolithin A or spermidine) reduce mtDNA leakage, suppress inflammasome activation, and attenuate cytokine output, confirming the upstream mitochondrial origin of the inflammatory signal [32-41].

These observations are reinforced by experimental data from both 3D human epidermal equivalents and ex vivo skin explants, which demonstrate that ultraviolet (UV) and ozone exposure provoke marked mitochondrial fragmentation, mtDNA release, and downstream pro-inflammatory cytokine induction (most notably IL-6, IL-8, and TNF-α). In these systems, UVB irradiation drives DRP1-dependent mitochondrial fission and outer membrane rupture, promoting cytosolic mtDNA leakage [32], while ozone exposure produces similar damage through excessive ROS generation and mitochondrial membrane depolarization [42]. The resulting oxidized mtDNA acts as a potent inflammatory signal, engaging endosomal TLR9 and cytosolic cGAS-STING pathways that amplify IL-1β and IFN-β expression [30, 31].

Blocking either DRP1 or STING signaling in these models restores mitochondrial network integrity and markedly reduces pro-inflammatory cytokine release, underscoring the mechanistic link between disrupted mitochondrial dynamics and skin inflammaging. Complementary mouse model studies further support this connection, with chronic UV exposure triggering sustained cGAS-STING activation, macrophage infiltration, and extracellular matrix degradation within dermal tissue [32]. In summary, oxidative stress and environmental pollutants start a vicious cycle in the skin, where they damage the mitochondria, which then releases signals (like mtDNA and other distress factors) that activate the immune system and cause inflammation. In turn, this inflammation can further damage mitochondria resulting in a self-perpetuating loop of mitochondrial damage and chronic inflammation that contributes significantly to skin aging (Fig. 3).

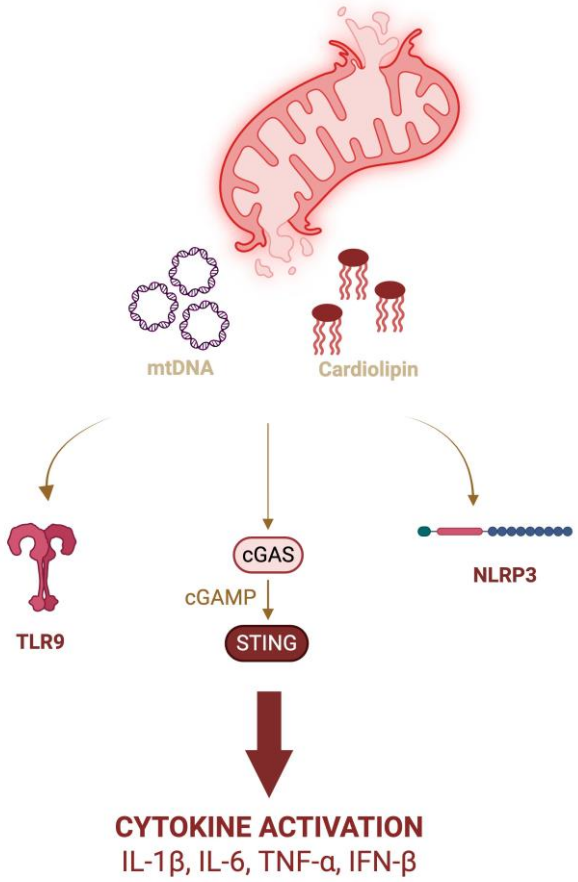

Figure 3. **Mitochondria-driven inflammaging through innate immune activation.** Damaged and dysfunctional mitochondria release mitochondrial damage-associated molecular patterns (mtDAMPs), including oxidized mtDNA and cardiolipin, into endosomal and cytosolic compartments. These signals activate innate immune pathways involving Toll-like receptor 9 (TLR9), the cGAS–STING axis, and the NLRP3 inflammasome, resulting in sustained activation of NF-κB and IRF3 signaling. Downstream cytokine production, which includes IL-1β, IL-6, TNF-α, and IFN-β, drives chronic, low-grade inflammation (inflammaging) that reinforces mitochondrial dysfunction and propagates tissue-level damage in aging skin.

2.4. Mitochondrial Quality Control: Mitophagy and Biogenesis

Mitophagy is the process by which cells remove damaged mitochondria and it operates via two main pathways. The first pathway involved the PINK1/Parkin ubiquitin–proteasome system which flags damaged mitochondria for destruction by tagging them with ubiquitin. The second pathway uses receptor proteins like BNIP3, NIX, and FUNDC1 which are activated under stress conditions (ie low oxygen or energy) and can directly target damaged mitochondria for removal. Both pathways work together to identify and dispose of malfunctioning mitochondria preventing them from harming the cell. Upon mitochondrial depolarization, PINK1 accumulates on the outer mitochondrial membrane and recruits the E3 ubiquitin ligase Parkin, which ubiquitinates outer membrane proteins such as VDAC1 and MFN2 [43, 44].

This ubiquitination signals autophagosome recruitment through LC3 interaction and culminates in lysosomal degradation [43-47]. The receptor-mediated pathways act independently of PINK1/Parkin, with hypoxia-inducible factors upregulating BNIP3 and NIX to promote mitophagy in response to oxidative stress and nutrient deprivation [48-50].

In aged human skin, reduced expression of TFAM and PGC-1α correlates with a marked decline in mitochondrial number, compromised OXPHOS function, and increased ROS production [2]. UV radiation and chronic oxidative exposure impair both mitophagic clearance and mitochondrial biogenesis, leading to accumulation of depolarized mitochondria and elevated oxidative damage. Studies in genetically modified mice underscore how crucial mitophagy is for skin health. Mice lacking PINK1 or Parkin (key mitophagy proteins) demonstrate that their skin cells cannot clear out damaged mitochondria effectively, whereby the resulting dermal fibroblasts accumulate swollen, unhealthy mitochondria that exhibit elevated oxidative damage (e.g., increased lipid peroxidation and subsequent oxidative damage to their membranes). Functionally their skin exhibits delayed wound closure and impaired ECM remodeling [23, 51-54]. Similarly, BNIP3 or NIX knockout mice exhibit defective mitophagy in keratinocytes and sebocytes, resulting in elevated ROS and accelerated epidermal atrophy under UV stress [23, 52-54].

Biogenesis is largely orchestrated by the PGC-1α–SIRT1–NRF1/2–TFAM axis. SIRT1 deacetylates and activates PGC-1α, which in turn induces NRF1/2 transcription of nuclear-encoded mitochondrial genes and TFAM expression, thereby promoting mtDNA replication and mitochondrial mass expansion [55, 56]. Overexpression of PGC-1α in human dermal fibroblasts enhances collagen I synthesis, improves mitochondrial respiration, and confers resistance to UV-induced oxidative injury [11]. Conversely, inhibition of SIRT1 or loss of TFAM reduces mitochondrial transcription and biogenesis, leading to premature senescence and increased MMP-1 expression.

Pharmacologic agents such as urolithin A and spermidine activate mitophagy through PINK1 stabilization and AMPK activation, restoring mitochondrial morphology and reducing senescence markers in aged fibroblasts and keratinocytes [29]. In murine photoaging models, urolithin A treatment rescues mitochondrial function, decreases inflammatory cytokines, and accelerates wound repair. Together, these data from human skin biopsies, primary dermal fibroblast cultures, and murine knockout models establish mitochondrial turnover (via coordinated mitophagy and biogenesis) as a pivotal determinant of skin homeostasis and aging progression.

2.5 Dynamics and Ultrastructure: Fission, Fusion and Cristae Remodeling

Mitochondria continually divide (fission) and merge (fusion), and they restructure their internal folds (cristae) to adapt to energy demands and stress. Interestingly, these mitochondrial dynamics are tightly regulated by specific proteins. Fission is regulated by the large GTPase DRP1, which is recruited to mitochondria by receptors such as MFF, MID49, and MID51; its activity is tuned by phosphorylation at Ser616 (pro-fission; CDK1/CaMKII) and Ser637 (anti-fission; PKA), as well as by calcineurin-mediated dephosphorylation under calcium stress. Fusion requires outer-membrane GTPases MFN1/MFN2 and inner-membrane OPA1; under stress, Parkin-dependent ubiquitination and proteasomal turnover of MFN1/2 tip the balance toward fragmentation (fission) and less fusion [57-59]. OPA1 exists as long (L-OPA1) and short (S-OPA1) isoforms generated by the proteases OMA1 and YME1L; stress-activated OMA1 cleavage diminishes L-OPA1, disrupts inner-membrane fusion, and loosens crista junctions, lowering respiratory supercomplex stability and increasing ROS [59, 60].

Cristae architecture is further organized by the MICOS complex (notably Mic60/mitofilin and Mic19/CHCHD3/CHCHD2), which forms crista junctions that position respiratory chain assemblies and optimize electron flux. Disruption of OPA1 or MICOS components leads to crista dilation and impaired ATP production. In UVA-exposed primary human keratinocytes, excess DRP1 activity and OPA1 processing correlate with mitochondrial fragmentation, membrane-potential loss, and reduced secretion of ECM proteins including type I collagen and fibrillin-1 [61]. In vivo, OPA1-deficient mice display dermal thinning, reduced tensile strength, and delayed wound closure attributable to crista disorganization and bioenergetic failure [62]. At inter-organelle contact sites (MAMs), MFN2 helps tether ER and mitochondria; UV-driven alterations in MAM signaling perturb calcium transfer and further bias networks toward fission, compounding bioenergetic stress.

Therapeutically, stabilizing the inner membrane and cristae mitigates downstream dysfunction. The mitochondria-targeted tetrapeptide elamipretide (SS-31) binds cardiolipin, preserves crista curvature, and enhances respiratory supercomplex assembly; in animal photoaging models this translates to improved mitochondrial coupling, decreased ROS, and better skin elasticity [63]. Collectively, data from human keratinocytes, organotypic skin models, and murine genetics converge on a more unified picture. These data indicate that changes in the proteins controlling mitochondrial fission and fusion (like

DRP1 and MFN1/2/OPA1), as well as proteins that maintain cristae structure (the MICOS complex), can dramatically alter mitochondrial shape and function. When these regulatory proteins push mitochondria toward a fragmented state or disrupt their internal structure, the mitochondria produce energy less efficiently. Over time, less energy and more stress from these fragmented mitochondria means the skin's fibroblasts produce less collagen and other ECM components, and the skin's ability to repair itself diminishes.

2.6 NAD^+ Decline and Sirtuin Dysregulation

With aging, the cutaneous levels of NAD^+ (an essential metabolic cofactor) steadily decreases, in part because the body's production of NAD^+ decreases as well (for example, decreased activity of NAMPT enzyme pathway produces fewer NAD^+ molecules). At the same time, certain enzymes consume more NAD+ in older skin, most notably PART1/2 (which use NAD+ when repairing DNA damage) and CD38 (which breaks down NAD+ as part of cell signaling). The resulting NAD+ reduction has important consequences: a) key mitochondrial enzymes can't function optimally without sufficient NAD^+, and b) proteins called sirtuins (which rely on NAD^+ to function) become less active. For example, when SIRT1 activity drops, it can no longer properly activate PGC-1α, a factor needed to turn on genes for making new mitochondria. As a result, mitochondrial biogenesis is dampened. Likewise, when SIRT3 activity falls, multiple mitochondrial proteins stay overly acetylated (since SIRT3's job is to deacetylate them). Over-acetylation impairs the function of antioxidant enzymes like MnSOD and metabolic enzymes like IDH2. This leads to higher mitochondrial ROS levels and makes cells more susceptible to oxidative damage [11, 29, 51, 64, 65].

Evidence for this axis spans cells, tissues, and animals. Murine skin and wound-healing models show that restoring NAD^+ (e.g., with nicotinamide riboside/NMN or by limiting CD38 activity) improves oxygen consumption and respiratory control, increases SIRT3-dependent deacetylation of MnSOD, lowers mitochondrial ROS, and accelerates re-epithelialization with higher COL3A1 and Ki-67 expression [11, 29, 51, 66-71]. CD38-deficient mice preserve tissue NAD^+ and exhibit delayed onset of dermal aging phenotypes, supporting a causal role for NAD^+ loss in cutaneous mitochondrial decline [29, 72, 73].

In primary human dermal fibroblasts, NAD^+ augmentation enhances basal and maximal respiration, reduces senescence markers, and increases procollagen production, indicating that metabolic rescue translates to extracellular matrix support [11]. Mechanistically, NAD^+ repletion re-engages SIRT1–PGC-1α programs (biogenesis/mitochondrial gene expression) and SIRT3-mediated detoxification (MnSOD activation), while indirectly lowering PARP1 activity by reducing DNA damage burden. Cross-talk with the epigenome likely contributes: sirtuin-dependent regulation of chromatin and the SIRT4–TET2 axis has been linked to maintenance of genomic stability and proliferative capacity in skin cells [13, 64, 66]. Collectively, these data indicate that age-related NAD^+ decline (driven by imbalance between synthesis and consumption) impairs sirtuin-centric control of mitochondrial quality, redox poise, and biogenesis, and that correcting this deficit yields functional benefits across cellular, ex vivo, and in vivo skin models.

2.7 Stem-Cell Niches and Regenerative Decline

Skin regeneration is highly dependent on epithelial stem cells (ESCs) that can adjust their mitochondrial activity as needed. When these ESCs are in a resting state (quiescent), they tend to keep a low level of mitochondrial activity, thus favoring glycolysis and maintaining low ROS levels. Conversely, when ESCs become activated to regenerate or repair tissue, they switch their metabolism increasing OXPHOS and mitochondrial biogenesis, and fatty-acid oxidation. This metabolic flexibility is a hallmark of healthy, functional stem cells during differentiation. Moreover, such a metabolic switch is governed by PDK–PDH control of pyruvate flux into mitochondria, AMPK–mTORC1 energy sensing, and sirtuin-dependent deacetylation of mitochondrial enzymes [74], whereby failure of these circuits raises mtROS above the stem-cell setpoint, triggering p38-MAPK/FOXO stress responses and progressive loss of clonogenic potential. In parallel, aging or stress can impair the removal of damaged mitochondria from these stem cells. If mitophagy pathways (like those controlled by PINK1/Parkin, or BNIP3/NIX) slow down, old and depolarized mitochondria (with low membrane potential ($\Delta\psi m$) start to accumulate. Moreover, stress often causes and increases in mitochondrial fission (mediated by DRP1), leading to more mitochondrial fragmentation, together leading to a scenario where there are more mitochondria that are inefficient at producing ATP, which in ESCs translates to slower migration and diminished wound re-epithelialization [23, 51, 75].

Genetic evidence supports causality. Keratinocyte-specific TFAM knockout mice exhibit reduced basal keratinocyte proliferation, delayed wound closure, and abnormal differentiation consistent with impaired mtDNA transcription/replication[76]. $Twinkle^{FIBRO}$ mice accumulate mtDNA deletions within dermal fibroblasts, show defective extracellular-matrix

deposition and attenuated TGF-β responsiveness, and heal wounds more slowly, thus demonstrating that mtDNA instability in stromal cells alone is sufficient to compromise tissue repair [23]. Complementary mtDNA-depleter models with reversible mitochondrial dysfunction reproduce alopecia and impaired re-epithelialization, and regain normal skin architecture when mtDNA copy number is restored [8], arguing that mitochondrial genome integrity lies upstream of the regenerative phenotype.

In human organotypic skin and primary keratinocyte/fibroblast cultures, replenishing NAD^+ (e.g., nicotinamide riboside or NMN) re-engages SIRT1/SIRT3 programs, improves Δψm and oxygen consumption, increases Ki-67 and COL3A1, and accelerates barrier re-formation after scratch injury [11]. Together, cell-, tissue-, and mouse-model data converge on a mechanistic framework in which coordinated control of biogenesis, mitophagy, dynamics, and redox setpoints preserves stem-cell function; age-related drift in these pathways depletes the regenerative reserve of the skin.

2.8 Lipid Metabolism and Barrier Integrity

Keratinocyte mitochondria supply citrate/acetyl-CoA and reducing equivalents to power the epidermal lipid factory that builds the stratum corneum (outermost layer of skin). Citrate (molecule mitochondria export out to the cytoplasm via the mitochondrial citrate carrier (SLC25A1)) is cleaved by the cytoplasmic enzyme called ATP-citrate lyase (ACLY) to create acetyl-CoA, which then acts as the basic building block for creating new fatty acids (via FASN) and for elongating them into the very-long chain fatty acids required for skin lipids (with enzymes such as ELOVL1/4/7). Mitochondria also help generate NADPH, a molecule necessary for both lipid synthesis and prevention of oxidation of these lipids. This mitochondrial NADPH supply is maintained by NADK2 and produced by malic and isocitrate dehydrogenases (ME2/ME3, IDH2) inside the mitochondria. These inputs feed ceramide/ω-O-acylceramide synthesis: serine palmitoyltransferase (SPTLC1/2) and CERS3 build ultra-long-chain ceramides; peroxisomal/ER enzymes (ELOVLs, CYP4F22) generate ω-hydroxy very-long-chain fatty acids; and the epidermal lipase PNPLA1 esterifies linoleic acid to form ω-O-acylceramide destined for the cornified lipid envelope. Lamellar-body lipid transport depends on ABCA12, and the lipoxygenases ALOX12B/ALOXE3 oxidize the linoleate moiety to enable covalent attachment to structural proteins. When mitochondrial reducing power falls with aging or oxidative stress, several of these steps become rate-limiting: NADPH insufficiency and mtROS-mediated peroxidation of linoleate disrupt acylceramide assembly, lamellar organization, and tight-junction integrity, thereby causing the skin to lose more moisture through impaired barrier (increasing transepidermal water loss) [77].

In murine UV-irradiation models, mitochondrial NADPH homeostasis declines in parallel with barrier dysfunction, reflected by decreased NADK2 and malic-enzyme activity; interventions that restore mitochondrial redox normalize lipid composition and stratum-corneum hydration [11, 51, 78]. Consistent patterns are observed in primary human keratinocytes and organotypic human epidermis exposed to particulate ozone or UV, where mitochondrial damage precedes lipid disorganization and increased TEWL; NRF2 activation helps preserve mitochondrial function and barrier-gene expression in these systems [42, 79]. Together, cell-, tissue-, and mouse-model data indicate that mitochondrial control of acetyl-CoA/NADPH supply, ROS tone, and MAM-linked lipid trafficking is an upstream governor of epidermal lipid synthesis and barrier homeostasis.

2.9 Environmental Pollutants and Combined Stressors

Environmental pollutants amplify mitochondrial injury through convergent mechanisms that elevate reactive oxygen species (ROS), disrupt membrane potential, and trigger pro-inflammatory signaling. Studies using human keratinocytes in culture and 3D skin models show that common air pollutants (such as fine particles like $PM_{2.5}$ and the gas ozone) cause skin cells to produce excessive ROS. These pollutants activate enzymes (e.g., NADPH oxidases) and put extra stress on mitochondria's electron transport chain, leading to a surge in free radicals. The resulting high ROS levels attack mitochondrial membranes (damaging a key lipid called cardiolipin) and make the mitochondria swell and start to break down. One sign of this breakdown is the release of cytochrome c, a mitochondrial protein that, once outside the mitochondria, triggers cells to undergo apoptosis [42]. These insults also oxidize mtDNA, which can leak into the cytosol and engage TLR9 and cGAS–STING pathways, amplifying IL-1β/IFN-β production and linking pollution exposure to inflammaging in skin [30, 31].

High-energy visible (blue) light additionally compromises mitochondria by exciting endogenous chromophores and increasing electron-transport leak; at doses ≥50 J/cm² in human dermal fibroblasts, blue light induces mtDNA strand breaks, depresses oxygen consumption, and elevates ROS [20]. Infrared (IR-A) radiation penetrates the dermis and augments mitochondrial ROS, reduces coupling efficiency, and synergizes with UV/blue light to impair respiration and collagen homeostasis in cell and animal photoaging models [9, 80]. When multiple environmental factors

combine, the damage to skin mitochondria worsens. For example, mice exposed to both UV radiation and air pollutants at the same time show more severe mitochondrial harm than exposure to either stress alone. These "co-exposed" mice have more mtDNA deletions and a greater reduction in their cells' ability to make new mitochondria (indicated by lower PGC-1α and TFAM activity). On a hopeful note, treatments that boost the cells' antioxidant response (like those activating NRF2) or that specifically protect mitochondria can partially counteract this combined damage in these models. Population studies in humans mirror these findings, where it has been demonstrated that people living in chronically polluted urban areas tend to have more mtDNA damage and signs of reduced mitochondrial renewal in their sun-exposed skin, compared to those in cleaner environments[4, 79-81]. [2]. Together, evidence from primary human cells, reconstructed/ex vivo human skin, murine co-exposure models, and epidemiology converges on a model in which mitochondria act as integrators of environmental stress (and as actionable targets to mitigate extrinsic skin aging).

Collectively, the mechanisms spanning mtDNA instability, retrograde signaling, defective quality control, disrupted dynamics, NAD^+ decline, and environmental stress together outline the mitochondrial blueprint of cutaneous aging. They are supported by cross-validation among human tissues, cell cultures, and diverse murine genetic models, establishing mitochondria as both biomarkers and drivers of skin aging. At the same time, it should be recognized that other factors (e.g., UV-driven mutations in nuclear DNA, telomere shortening, and protein homeostasis defects) also contribute to skin aging, interacting with mitochondrial pathways.

Although mechanistic studies in genetically engineered and murine models have been instrumental in establishing causal relationships between mitochondrial dysfunction and cellular aging phenotypes, extrapolating these findings directly to human skin requires caution. Human data, derived primarily from ex vivo tissue, observational cohorts, and in vitro systems, largely demonstrate strong correlations rather than definitive causation. While these converging lines of evidence strongly implicate mitochondrial decline as a central contributor to cutaneous aging, the degree to which specific molecular lesions drive versus accompany human aging remains an active area of investigation. Explicitly distinguishing where mechanistic certainty is model-derived versus human-derived will be essential for refining translational relevance

Table 1. Mitochondria-targeted strategies to reverse cutaneous aging and enhance repair.

Therapeutic Category	Representative Agents/Modalities	Primary Mitochondrial Targets and Pathways	Functional Outcomes in Skin	Key References (PMID)
Bioenergetic Restoration	Nicotinamide riboside (NR), Nicotinamide mononucleotide (NMN), Sirtuin activators (SRT3025, pterostilbene, resveratrol analogs)	↑NAD^+ → activates SIRT1→PGC-1α→NRF1/2→TFAM (biogenesis) and SIRT3 (antioxidant enzyme deacetylation)	↑Δψm, ↑ATP production, ↑collagen I/III, ↓senescence markers, accelerated wound closure	39513906, 40005371, 37512568
Redox Reprogramming	Melatonin, Coenzyme Q10, NRF2 activators (baicalein, salvianolic acids), Estrogen/NRF2 crosstalk	↓mtROS, ↑NADPH *via* NADK2, activation of NRF2–HO1/NQO1/SOD2, suppression of MAPK→AP-1/MMP-1	Preserves mtDNA integrity and Δψm, ↓oxidative stress, ↑procollagen synthesis, improved dermal elasticity	40147561, 37512568, 37107277, 37958946, 39199263
Photo-biomodulation (PBM)	Red (620–660 nm) and Near-Infrared (780–850 nm) light	Photostimulation of cytochrome-c oxidase (Complex IV) → ↑respiration, ↑Δψm, activation of NRF1/2–TFAM	↑ATP and procollagen, ↓UV-induced ROS and DNA damage, ↑barrier gene expression. High-fluence blue light (405–450 nm) is deleterious.	40751922, 40599721, 40421626
Engineering Extracellular Vesicles (EVs)	MSC-EVs or fibroblast-EVs carrying NMN, metformin, Gstm2 mRNA, antioxidant enzymes	Delivery of NAD^+ boosters and mitophagy activators (PINK1/Parkin, SIRT3, PGC-1α–TFAM)	Restores Δψm and OXPHOS, ↓mtROS, ↑mitophagy flux, accelerates dermal repair and re-epithelialization	40598314, 38825668, 38608014
Hormonal and Circadian Alignment	Estradiol, timed PBM or NAD^+/NRF2/melatonin topicals	E2→PGC-1α→NRF1/2→TFAM, ↑OPA1/MFN2, ↓DRP1; Circadian coupling of BMAL1–SIRT1/SIRT3→PGC-1α/TFAM	↑Biogenesis, ↓mtROS, ↑collagen synthesis, optimized antioxidant and repair timing	37237866, 39199263, 40599721

Bioenergetics restoration (NR/NMN; sirtuin activation) rebuilds NAD^+ and re-engages SIRT1→PGC-1α→NRF1/2→TFAM and SIRT3 detoxification to raise Δψm/ATP and support collagen synthesis. Redox reprogramming (melatonin, CoQ10, NRF2 activators, red/NIR photobiomodulation targeting

cytochrome-c oxidase) lowers mtROS, preserves mtDNA and membrane potential, and boosts procollagen while suppressing MAPK→AP-1/MMP-1; high-fluence blue light is counterproductive. Engineered extracellular vesicles provide cell-free delivery of NAD^+ boosters, antioxidant enzymes, and mitophagy activators, restoring mitochondrial quality control and hastening repair. Aligning interventions with circadian programs and hormonal status, and deploying them under realistic environmental exposure, maximizes efficacy. Convergent improvements in respiration, redox balance, ECM integrity, barrier function, and wound closure position mitochondria as a central therapeutic target in dermatologic rejuvenation.

3. Therapeutic Frontiers: Converging on Mitochondrial Homeostasis

Advances in understanding mitochondrial dysfunction have opened a wide spectrum of therapeutic opportunities to counteract skin aging. The unifying goal of these interventions is to restore mitochondrial homeostasis by rebalancing bioenergetics, reducing oxidative stress, and stimulating regenerative signaling. Current preclinical and early clinical evidence supports several complementary strategies: a) extracellular vesicle–based delivery systems, b) mitochondria-directed antioxidants and redox modulators, c) NAD^+ boosters and sirtuin activators, d) photobiomodulation, and e) hormone- or circadian-aligned interventions (Table 1).

Among the most innovative approaches are *cell-free delivery systems using extracellular vesicles (EVs).* EVs are tiny membrane-bound particles that cells release to communicate with each other[82, 83]. In skin, mesenchymal stem cells, fibroblasts, and keratinocytes naturally release EVs filled with beneficial molecules for example, antioxidants (enzymes that combat ROS), growth factors that promote repair, and even mitochondrial components such as pieces of mtDNA or proteins from the respiratory chain. When target skin cells take up these vesicles (through normal cellular intake processes like endocytosis), the cargo can directly affect the cell's machinery. For instance, molecules delivered by EVs have been shown to activate SIRT3 and the PGC-1α–TFAM pathway inside cells (which boosts the creation of new mitochondria), as well as stimulate PINK1–Parkin (promoting mitophagy) and turn on NRF2 (enhancing the cell's antioxidant defenses). Through these actions, EV-delivered therapies helped to restore the mitochondrial membrane potential ($\Delta\Psi m$), increase energy production (OXPHOS), and reduce inflammatory signals (such as the SASP) in aging skin cells.

Mechanistic and model-based evidence now supports these effects. When engineered to carry nicotinamide mononucleotide (NMN), MSC-sEVs increase intracellular NAD^+, augment SIRT3 expression, and rescue senescence-repressed mitophagy in replicative/senescent human dermal fibroblasts; in a mouse skin-aging model, NMN-sEVs improve dermal thickness and accelerate wound closure [84, 85]. Fibroblast-derived EVs enriched with Gstm2 mRNA reprogram redox metabolism (enhancing mitochondrial respiration and lowering ROS) in primary skin cells and aged-mouse wound models, thereby restoring dermal–epidermal crosstalk and speeding re-epithelialization [85]. Drug-loaded EVs extend this platform's versatility: metformin-engineered EVs preserve mitochondrial ultrastructure, reactivate mitophagy, shift ATP metabolism toward efficient OXPHOS, and improve repair in aged murine wounds with supportive analyses from human aging-skin samples [86, 87].

Collectively, these data bridge in vitro human fibroblasts/keratinocytes, 3D/organotypic skin systems, aged-mouse wound models, and human tissue profiling, and collectively point to EV-based therapies as modulators of mitochondrial quality control and bioenergetics in the skin. Still, successful translation of EV therapies will require addressing potential immunogenicity, optimizing delivery methods, and establishing regulatory pathways for clinical use. Continued adherence to EV standards[83, 88] and control of biogenesis/uptake pathways (RAB27A/B, clathrin/caveolin) will be critical for reproducible clinical translation in dermatology [82, 83].

Redox reprogramming with targeted antioxidants remains another cornerstone of mitochondrial therapy. Melatonin is particularly potent due to its amphiphilicity and ability to concentrate within mitochondria, where uptake involves MT1 signaling and peptide transporter PEPT1, and metabolic effects include upregulation of mitochondrial NADK2 to sustain the $NADP^+$/NADPH pool [78]. In primary human keratinocytes and dermal fibroblasts, melatonin preserves membrane potential ($\Delta\psi m$) and ATP production, increases antioxidant enzymes (SOD2/MnSOD, catalase, GPx), promotes PINK1/Parkin-dependent mitophagy, and reduces UVB-induced caspase activation and apoptosis [51]. In aged human skin (ex vivo/clinical samples), topical melatonin decreases MMP-1 and mTORC1 activity while enhancing mitochondrial markers (TFAM, MTCO-1, VDAC), translating to improved collagen organization and dermal resilience [81]. Melatonin also supports collagen biosynthesis indirectly by restoring mitochondrial proline metabolism via NADK2 [78].

Coenzyme Q10 (CoQ10) functions as a lipid-soluble electron carrier shuttling electrons from complexes I/II to complex III, while its reduced form (ubiquinol) scavenges lipid peroxyl radicals and regenerates α-tocopherol. In clinical and ex vivo human studies, CoQ10 supplementation/topical application reduces lipid peroxidation, dampens MAPK→AP-1 signaling and MMP-1 induction, and improves wrinkles and elasticity, reflecting enhanced mitochondrial coupling and redox

buffering [12]. These antioxidant and redox-modulating strategies, though generally well-tolerated, may require long-term, consistent application and further clinical studies to fully validate their anti-aging efficacy.

NRF2-directed antioxidants (e.g., baicalein and salvianolic compounds) act by modifying KEAP1 cysteines, stabilizing NRF2, and inducing phase-II/antioxidant genes (HMOX1/HO-1, NQO1, GCLC/GCLM) while cross-activating PGC-1α to support mitochondrial biogenesis. In human keratinocytes and murine photoaging models, these agents preserve Δψm and ATP, suppress MAPK/NF-κB pathways, reduce MMP-1, and improve dermal architecture with favorable tolerability profiles [79]. Estrogenic signaling can converge on this axis: estradiol reduces rotenone-induced mtROS and senescence in fibroblasts via NRF2-dependent mechanisms [89-91]. Collectively, evidence across cell, ex vivo human tissue, and clinical studies indicates that antioxidant-centered redox reprogramming restores mitochondrial homeostasis and counters structural hallmarks of skin aging while minimizing irritation relative to retinoids.

Augmenting NAD^+ metabolism and sirtuin activity offers a complementary approach. Mechanistically, nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) replenish the NAMPT/NRK→NMNAT1–3 salvage pathway to rebuild intracellular NAD^+, thereby restoring the activity of NAD^+-dependent enzymes that govern mitochondrial homeostasis—most prominently SIRT1/3/4/6 and DNA-repairing PARP1/2. Re-engaging SIRT1/TFAM programs promotes mitochondrial biogenesis and transcription, while SIRT3 deacetylation of matrix enzymes (e.g., SOD2/MnSOD, IDH2) lowers mtROS and improves coupling; SIRT4 crosstalk with TET2 supports genome maintenance and proliferative capacity in skin cells [11, 13, 29, 63, 65, 92].

In primary human dermal fibroblasts and organotypic/ex vivo human skin, NR or NMN improves basal and maximal respiration, increases Δψm, enhances autophagy/mitophagy readouts, up-regulates procollagen (COL1A1/COL3A1), and reduces senescence markers, consistent with metabolic rescue [11]. In murine wound-healing models, NAD^+ restoration (via NR/NMN or CD38 inhibition) accelerates closure and re-epithelialization and increases COL3A1 and Ki-67 expression, indicating enhanced proliferation and matrix remodeling [11, 29]. Selective sirtuin activation further augments these effects: SIRT3 activation reduces UVB-induced mtROS and cell death in skin cells, while SIRT4–TET2 signaling sustains genomic stability and proliferation, together preserving the mitochondrial network and repair capacity of aging skin [13, 92].

Another non-invasive therapy showing promise is *Photobiomodulation* (PBM) using specific wavelengths of light in the red (about 620–660 nm) or near-infrared (about 780–850 nm) range. PBM works by delivering light that penetrates into the skin and is absorbed by cytochrome c oxidase (also known as complex IV of the mitochondrial respiratory chain). Absorbing this light boosts the activity of mitochondria, leading to increased energy production and improved metabolic function in the skin cells Photon absorption at CCO relieves nitric-oxide–mediated inhibition of respiration, increases oxygen binding/turnover, elevates Δψm and oxygen consumption rate, and triggers low-amplitude redox/Ca^{2+} signals that activate retrograde programs and TGF-β/Smad pathways to boost procollagen while dampening MAPK→AP-1/MMP-1 [93]. In primary human fibroblasts/keratinocytes and organotypic/ex vivo human skin, appropriately dosed PBM increases ATP and procollagen, reduces UV-induced ROS and DNA damage, and improves barrier-gene expression; in murine wound and photoaging models, PBM enhances re-epithelialization and angiogenesis with concomitant mitochondrial biogenesis [93]. PBM has also been linked to higher cutaneous NAD^+ and downstream sirtuin activation, providing a mechanistic bridge to biogenesis and stress resistance [94]. By contrast, blue light at high fluences fragments mitochondria and induces mtDNA breaks, underscoring a biphasic dose response in which excessive irradiance or off-target wavelengths are detrimental [20, 80]. For translational use, key parameters include wavelength, irradiance, fluence, and duty cycle; therapeutic windows used in preclinical skin models generally employ low irradiance and modest fluences to harness mitochondrial activation while avoiding photostress [93, 94].

Hormonal influences further modulate mitochondrial performance. Following menopause, diminished ovarian estrogen weakens estrogen-receptor signaling in skin cells and contributes to reduced mitochondrial biogenesis and antioxidant capacity. Mechanistically, estradiol (E2) engages nuclear ERα/ERβ and membrane GPER1 to trigger both genomic (ERE-dependent) and rapid kinase pathways that converge on mitochondrial programs: E2 promotes TFAM-driven biogenesis, enhances OPA1/MFN1-2 expression and processing while restraining DRP1-mediated fission, and activates the NRF2–KEAP1 antioxidant axis to bolster SOD2 and catalase, thereby lowering mtROS [79, 89, 95, 96]. In primary human dermal fibroblasts, E2 reduces rotenone-induced mitochondrial and cytosolic ROS and preserves Δψm via NRF2-dependent signaling, with downstream improvements in procollagen output [89]. In murine models of estrogen deficiency (ovariectomy) and related preclinical systems, loss of estrogen signaling is

associated with impaired mitochondrial dynamics and antioxidant defenses, whereas E2 replacement or NRF2 activation restores these readouts and improves collagen synthesis [79, 95]. Collectively, these data support life-stage–tailored hormonal or mitochondrial co-therapies to sustain cutaneous mitochondrial homeostasis and matrix integrity.

Circadian programs coordinate mitochondrial metabolism in skin by coupling the core clock (BMAL1:CLOCK) to metabolic effectors. BMAL1: CLOCK drives NAMPT expression to impose NAD^+ rhythms that activate SIRT1/SIRT3; in turn, SIRT1 deacetylates BMAL1 and PER2, closing a feedback loop that times TFAM-mediated biogenesis, DRP1 phosphorylation (fission), and PINK1–Parkin mitophagy cycles. Energy sensors such as AMPK (via CRY1 phosphorylation) and nuclear receptors REV-ERBα/β integrate nutrient status with clock output, further shaping mitochondrial redox and turnover. In primary human keratinocytes and organotypic skin, time-of-day differences are observed in oxygen consumption, Δψm, and ROS; in mouse models, global or epidermal Bmal1 disruption elevates mtROS, suppresses biogenesis markers, and heightens UV/photoaging susceptibility [10, 94]. These insights motivate chronotherapy, timing interventions to phases of peak mitochondrial repair and antioxidant capacity. For example, scheduling red/near-infrared PBM or NAD^+/sirtuin-targeted and NRF2-directed topicals to favorable circadian windows can enhance Δψm, boost biogenesis, and blunt UV-induced ROS [10, 94]. Such temporal targeting may improve treatment efficacy while reducing off-target stress.

Translational and early clinical evidence increasingly validates mitochondria-centered interventions in human skin. In a randomized, controlled trial of photoexposed forearm skin, topical cannabidiol (CBD) nanoparticles reduced UV-induced mtDNA *"common deletion"* burden and oxidative DNA damage markers relative to vehicle, consistent with CBD-driven suppression of mitochondrial ROS and preservation of respiratory function [97]. An open-label regimen combining allyl pyrroloquinoline quinone (PQQ) with a retinoid and sunscreen improved tone, texture, and dyschromia with favorable tolerability; mechanistically, PQQ functions as a redox-cycling cofactor that supports mitochondrial dehydrogenases and antioxidant defenses [98]. Beyond small molecules, proof-of-concept mitochondrial transplantation studies demonstrate causality at the organelle level: transfer of healthy mitochondria into UVA-damaged skin models restores membrane potential (Δψm), lowers mtROS, and increases collagen fiber density [99]. Nevertheless, direct mitochondrial transplantation faces substantial obstacles, including immunologic rejection of donor organelles, challenges in efficient delivery to target cells, and complex safety and regulatory issues, which must be overcome before this strategy can be clinically feasible. Complementary preclinical programs align with these findings, topical melatonin improves mitochondrial markers and dermal matrix organization in aged human skin [78, 81], CoQ10-based treatments enhance elasticity and reduce wrinkles [12, 100], red/near-infrared photobiomodulation increases ATP and procollagen and diminishes UV-induced ROS [93], NAD^+ boosters reduce senescence and accelerate wound closure [11, 29], and engineered extracellular vesicles restore NAD^+/SIRT3 signaling and mitophagy while improving repair in aged mice [84-86]. Collectively, across human in vivo/ex vivo, organotypic, and murine systems, pharmacologic, biophysical, and biologic strategies converge on mitochondrial quality control, redox balance, and biogenesis to rejuvenate aged or photo-damaged skin.

The emerging view is that most effective rejuvenation strategies will require *personalized-multimodal* strategies that stack mechanistically complementary levers. Pairing bioenergetic restoration (NAD^+ precursors such as NR/NMN to re-engage SIRT1/3 programs) with redox reprogramming (melatonin; NRF2-directed polyphenols) and a delivery or stimulation modality (engineered EVs; red/near-infrared PBM) addresses distinct failure nodes (biogenesis/mitophagy, antioxidant defense, and collagen anabolism) and produces additive benefits across human primary cells, organotypic/ex vivo skin, and murine models [11, 29, 79, 81, 84, 89, 93]. Mechanistically, NR/NMN restore NAD^+ to activate TFAM and SIRT3-dependent detoxification; melatonin augments NADK2-supported NADPH and PINK1–Parkin mitophagy; NRF2 activators stabilize redox setpoints and suppress MAPK→AP-1/MMP-1; EVs deliver NMN or redox/mitophagy cargo to fibroblasts/keratinocytes; and PBM targets cytochrome-c oxidase to raise Δψm/ATP and procollagen [51, 78, 79, 84, 93].

Combinations can be rationally sequenced and timed: e.g., circadian-aligned PBM or NAD^+/NRF2 topicals during phases of peak mitochondrial repair, with evening melatonin to reinforce antioxidant and mitophagy programs; in pollution- or blue-light–rich settings, include NRF2/melatonin alongside sunscreen to buffer mtDNA damage and inflammaging [10, 20, 42, 94]. Patient stratification may leverage biomarkers including mtDNA deletion burden/TFAM in photoexposed skin, tissue NAD^+/CD38 status, cGAS–STING/inflammasome signatures, and multiphoton redox imaging [2, 29, 97, 101]. Designed this way, multimodal regimens can enhance mitochondrial turnover, antioxidant capacity, and collagen renewal while minimizing irritation; incorporating environmental exposure, circadian timing, and hormonal status (e.g., postmenopausal estrogen

decline) should improve durability and translatability, moving mitochondrial targeting from preclinical promise to a mainstream dermatologic reality [10, 89].

Despite growing enthusiasm for mitochondria-targeted interventions in dermatology, the current body of human clinical evidence remains limited. Most available studies rely on small sample sizes, short treatment durations, or uncontrolled designs, making it difficult to draw firm conclusions about long-term efficacy or safety. Randomized, adequately powered trials with standardized dermatologic endpoints are still uncommon, and regulatory pathways for emerging modalities, including mitochondrial-targeted peptides, extracellular-vesicle–based products, and NAD^+-modulating agents, are not yet fully defined. Consequently, while preclinical data are compelling and early human findings are encouraging, the translational maturity of these interventions is still in its early stages (Table 2).

Table 2. Key Mitochondria-Targeted Strategies for Skin Aging and Wound Repair.

Intervention	Mechanistic Target	Documented Effects	Translational Status
NAD^+ boosters (NR, NMN, CD38 inhibitors, sirtuin activators).	Elevate cellular NAD^+ levels; activate sirtuins (SIRT1/3/6) and PARPs. Enhance mitochondrial biogenesis & function	Significantly increase cellular/tissue NAD^+ levels (e.g., ~50% in aged mice and humans). Accelerate wound closure (~30–60% faster re-epithelialization in aged models Increase collagen types I/III synthesis in fibroblasts	Early clinical trials underway (oral NR safely raises NAD^+ in humans. Combining NAD^+-boosting with CD38 inhibition (to reduce NAD^+ consumption) shows enhanced efficacy in preclinical studies
Mitochondria-targeted antioxidants (e.g., melatonin, CoQ10) and NRF2 activators (e.g., baicalein).	Neutralize mtROS. Boost antioxidant defenses (↑SOD2, catalase). Stabilize mitochondrial membranes & redox homeostasis	Preserve or restore ΔΨm and ATP production in UV-exposed cells. Reduce oxidative damage (e.g., melatonin ↓ UV-induced ROS, ↓ MMP1 by ~50%). CoQ10 improves skin elasticity and reduces wrinkle depth by ~10–15% in vivo. Support collagen production via improved mitochondrial metabolism.	Widely available topical antioxidants (e.g., CoQ10, melatonin) show good safety profiles. Consistent long-term use and optimized formulation are needed for clinical anti-aging benefits. Larger controlled trials are needed to confirm efficacy
Extracellular vesicles (EV-based therapies) (e.g., MSC-sEVs loaded with NMN). **Fibroblast-EVs with GSTM2 mRNA.** **MSC-EVs with metformin).**	Deliver bioactive cargos (NAD^+ precursors, mRNAs, proteins) directly to target cells. Stimulate mitophagy and biogenesis pathways	Increase intracellular NAD^+ and SIRT3 in senescent cells, restoring mitophagy. Improve ΔΨm and OXPHOS in aged fibroblasts. Accelerate wound closure in aged mice (EV–NMN: ~1.5× faster healing vs. control). Enhance dermal thickness and collagen remodeling in photoaged skin	Preclinical (animal studies) stage. Key challenges: potential immunogenic reactions, delivery to target skin layers, manufacturing and storage (stability), and regulatory considerations. Ongoing research is optimizing EV cargo loading and targeting; clinical translation will require adherence to evolving standardization guidelines (e.g., MISEV)
Red/NIR Photobiomodulation (PBM) (low-level light therapy)	Stimulate cytochrome c oxidase (ETC complex IV) to boost O_2 consumption and mitochondrial signaling pathways	Increases cellular respiration and ΔΨm. Boosts procollagen production and dermal collagen density in aging	Approved for certain dermatologic indications (e.g., LED treatments for wrinkles and wound healing).

		skin (red/NIR light ↑ type I collagen, fibrillin-1 in fibroblasts). Reduces UV-induced mtDNA damage and ROS levels. Improves wound healing and angiogenesis in mice by promoting mitochondrial biogenesis	Noninvasive with minimal side effects. Optimal parameters (wavelength, dose, frequency) are still being refined to maximize efficacy while avoiding off-target photodamage (excess blue light can be harmful.
Mitochondrial transplantation	Direct transfer of healthy mitochondria into compromised cells/tissues to replace or supplement dysfunctional organelles	Proof-of-concept studies show uptake of exogenous mitochondria by skin cells. Improves bioenergetics (restored ΔΨm, ↑ ATP) and lowers oxidative stress in UV-damaged skin explants. Increases dermal collagen fiber content and thickness.	Experimental stage. Major obstacles: immune rejection of foreign mitochondria, short-lived engraftment, efficient delivery to target cells, and regulatory approval. Further research is needed to assess safety, dosing, and long-term benefits in human skin.

Summary of major therapeutic approaches aimed at restoring mitochondrial homeostasis in aged or photodamaged skin. Listed strategies include NAD^+ boosters and sirtuin activators, mitochondria-directed antioxidants and NRF2 modulators, extracellular vesicle–based therapies, red/near-infrared photobiomodulation, and mitochondrial transplantation. For each intervention, the primary mechanistic targets, documented bioenergetic and structural effects (e.g., restoration of ΔΨm, reduction of ROS, stimulation of collagen synthesis, and acceleration of wound closure), and current translational status are outlined.

4. Conclusion and Future Directions

In conclusion, this review underscores that mitochondria lie at the heart of skin aging and are a modifiable factor in this process. A wide range of evidence, from studies on human skin (both in living people and in lab-grown skin samples), to experiments in skin cells and genetically modified mice, all tell a consistent story whereby when mitochondrial health declines, it sets off a cascade of problems in the skin. Damage to mitochondrial DNA (mutations and deletions) reduces the mitochondria's ability to produce energy, causing a drop in membrane potential and a spike in ROS levels. At the same time, shortages of vital mitochondrial metabolites and stress signals from the faulty mitochondria can alter how the cell's nucleus controls gene expression. Together, these changes push skin cells into a state of senescence (biological aging) where they break down more matrix (like collagen) and function less effectively (Fig. 4). Defects in mitophagy and biogenesis, together with an imbalance in fission–fusion and cristae integrity, entrench dysfunction and prime cells for chronic inflammation. In parallel, mitochondrial danger signals (oxidized mtDNA, cardiolipin, formyl peptides) engage TLR9 and cGAS–STING, amplifying NLRP3-linked inflammaging; age-related declines in NAD^+/sirtuin activity erode antioxidant defenses and extracellular-matrix anabolism; stem-cell mitochondrial inflexibility blunts regeneration; and environmental stressors (including UV, blue/IR light, and airborne pollutants) compound these liabilities. Causality is supported by gain- and loss-of-function models (Twinkle and POLG mutants; TFAM, OPA1, PINK1/Parkin manipulations) and by reversibility in mtDNA-depleter systems and interventional studies. Importantly, the various mitochondria-targeted therapies discussed in this review show consistent benefits across many types of models. Whether it's NAD^+ boosters and sirtuin activators, mitochondrial-targeted antioxidants like melatonin or CoQ10 (or drugs that activate the NRF2 pathway), red/near-infrared light therapy, or engineered EV treatments, all have demonstrated positive effects on aging skin markers in research studies. These approaches have been shown to increase mitochondrial membrane potential (ΔΨm) and improve cellular respiration (energy production). They also lower chronic inflammation in aging or damaged skin (reducing the "inflammatory tone") and help skin cells produce more collagen and heal wounds faster. In short, across cell culture experiments, skin tissue models, and animal studies, targeting mitochondrial health has yielded improvements in the hallmarks of skin aging and better wound repair. We note, however, that these emerging therapies should be carefully evaluated for long-term safety and real-world efficacy, and they should be combined with traditional modalities (such as UV protection and DNA repair boosters) to comprehensively address the multifactorial causes of skin aging. An additional consideration relates to the theoretical safety implications of chronically enhancing mitochondrial metabolism, NAD^+ availability, sirtuin activity, or NRF2-mediated stress responses. Persistent activation of these pathways could, in principle, influence proliferation, survival signaling, or redox

balance in ways that may be context-dependent, particularly in UV-damaged or genomically unstable skin. Although no concerning dermatologic safety signals have been observed to date, long-term studies capable of detecting rare or delayed effects remain lacking. Accordingly, the potential intersection between mitochondrial activation and tumorigenesis warrants continued investigation as these therapeutic strategies advance toward broader clinical use.

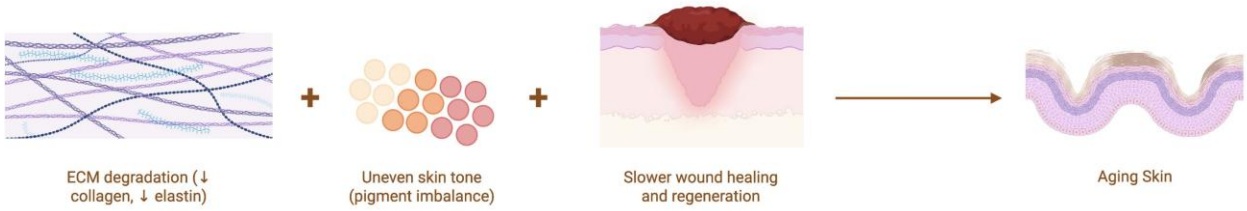

Figure 4. Tissue-level consequences of mitochondrial dysfunction in skin aging. The convergence of mitochondrial bioenergetic failure, metabolic and epigenetic reprogramming, and chronic inflammaging manifests as hallmark features of cutaneous aging. Persistent mitochondrial dysfunction promotes extracellular matrix degradation with loss of collagen and elastin, pigmentary imbalance leading to uneven skin tone, and impaired wound healing and regeneration. Together, these processes culminate in structural and functional decline of the skin, establishing mitochondrial health as a central determinant of aging skin phenotypes.

To translate mitochondrial insights into durable dermatologic benefit, the next phase should couple a) precision genetics, b) mitochondrial structure–function, c) turnover therapeutics, and d) patient-stratified trials under a single, harmonized framework. Tissue-specific, inducible keratinocyte, fibroblast, and melanocyte models equipped with mitoTALENs or DdCBE editors can define lesion types and thresholds for mtDNA point mutations/deletions and (when paired with reversible mtDNA-depleter systems) establish rescue windows for restoring $\Delta\psi m$, respiration, extracellular-matrix output, and wound repair. In parallel, skin-focused cristae biology should clarify how OPA1 processing (OMA1/YME1L) and MICOS integrity govern respiratory supercomplex assembly, and test whether cardiolipin-stabilizing peptides outperform classical biogenesis inducers on biomechanical and healing endpoints. Head-to-head evaluation of mitophagy/biogenesis pathways (PINK1–Parkin vs. BNIP3/NIX/FUNDC1) should proceed with human-ready flux biomarkers (e.g., Keima reporters in skin explants, longitudinal mtDNA deletion/copy-number assays) embedded alongside OCR, $\Delta\psi m$, and ECM readouts. Because NAD^+ is compartmentalized, real-time biosensors mapping nuclear and mitochondrial pools (combined with CD38/PARP activity) can enable patient stratification and rational testing of combinations (NR/NMN ± CD38 modulation ± PBM) with pharmacodynamic panels (tissue NAD^+, sirtuin activity, respiration).

Equally important is resolving mitochondria–innate immunity crosstalk and barrier metabolism in contexts that mirror real life. Studies should distinguish EV-mediated versus cytosolic mtDAMP trafficking and define when TLR9 or cGAS–STING modulation aids repair without compromising antimicrobial defense, with NLRP3 activity and barrier metrics (e.g., TEWL, tight-junction proteins) built into designs. Regenerative programs ought to determine how PDK–PDH, AMPK–mTORC1, and SIRT1/3 control quiescence-to-activation transitions in epidermal/follicular stem cells, and whether restoring mitochondrial flexibility rejuvenates re-epithelialization in aged human skin grafts and $Twinkle^{FIBRO}$/TFAM models. On the barrier front, quantitative lipidomics linked to MFN2-dependent ER–mitochondria contacts (MAMs) should connect mitochondrial acetyl-CoA/NADPH supply (SLC25A1→ ACLY; NADK2/ME/IDH2) to acylceramide synthesis under aging and pollution. Finally, chronobiology-aware trials should time PBM and NAD^+/NRF2/melatonin topicals to NAMPT/NAD^+ and PGC-1α/TFAM rhythms, while co-exposure paradigms (UV + blue/IR + PM/ozone) and rigorously engineered EV platforms (per MISEV; cargo, dose, RAB27/clathrin/caveolin targeting) ensure ecological validity. Harmonized clinical and mitochondrial biomarkers (mtDNA deletion burden/copy number, TFAM/PGC-1α, SOD2/NRF2, cGAS–STING/NLRP3, FLIM redox imaging, biomechanics) and explicit life-stage/skin-of-color stratification will be essential for generalizable, equitable efficacy—charting a clear path from mechanistic clarity to patient-tailored, chronobiology-aware interventions in cutaneous aging and wound care.

Author Contributions

Conceptualization: (I.J., S.A., K.M.M., C.T.M., S.H.); Literature review: (S.A., K.M.M); Writing original draft: (S.A., K.M.M., M.R.S.); Writing review & editing: (S.A., I.J., K.M.M, M.R.S., C.T.M., S.H.).

Acknowledgements

Stanley J. Glaser Foundation and University of Miami Team Science Award in Aging.

Conflict of Interest

The authors declare no conflicts of interest.

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