



# Targeting ferroptosis in photoaging: mechanisms and therapeutic potential of adipose-derived stem cell exosomes

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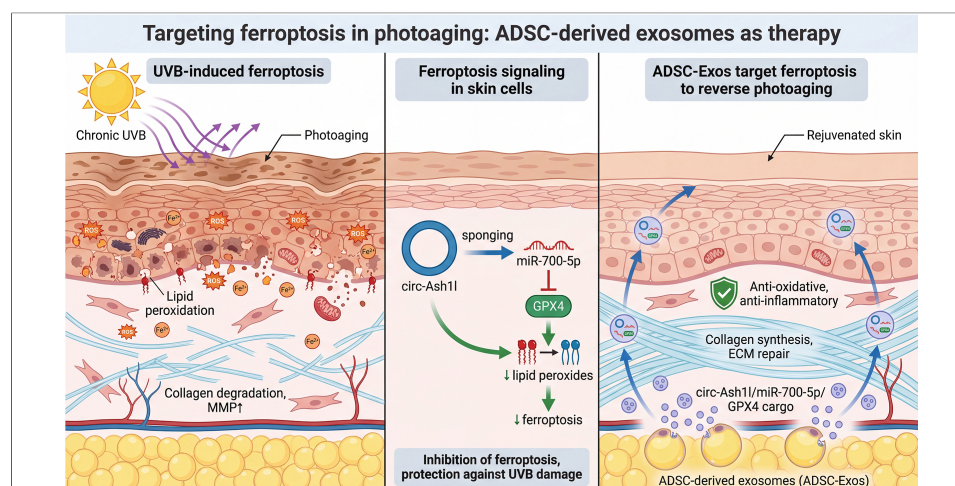
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## Abstract

Skin photoaging is a form of premature cutaneous aging caused by chronic ultraviolet (UV) exposure, manifesting as wrinkling, laxity, and pigmentary disturbances. UV radiation generates reactive oxygen species and upregulates matrix metalloproteinases, leading to extracellular matrix degradation. Emerging evidence implicates ferroptosis - an iron-dependent form of regulated cell death characterized by lipid peroxidation - in ultraviolet B (UVB)-induced photodamage. Studies show that glutathione peroxidase 4 (GPX4)-dependent antioxidant defenses are compromised in UV-exposed skin cells, and ferroptosis inhibitors can partially attenuate UV-induced cellular damage. Exosomes derived from adipose-derived stem cells (ADSC-Exos) have emerged as a promising cell-free regenerative strategy for skin rejuvenation. These 30-150 nm extracellular vesicles offer advantages over whole-cell therapy, including low immunogenicity, reduced tumorigenic concerns compared with replicating cells, and easier standardization. Through paracrine signaling, ADSC-Exos deliver bioactive proteins and non-coding RNAs that promote collagen synthesis, angiogenesis, and anti-inflammatory effects. Circular RNAs (circRNAs) are highly enriched and stable in exosomes due to their covalently closed structure. Notably, hypoxic-preconditioned ADSC-Exos deliver circ-Ash1l into UVB-damaged skin cells, where it sequesters miR-700-5p and upregulates GPX4. This

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circ-Ash1l/miR-700-5p/GPX4 axis inhibits ferroptotic cell death, reduces oxidative damage, and attenuates UVB-induced photoaging phenotypes *in vitro* and *in vivo*. This review summarizes the mechanisms of UVB-mediated photoaging and ferroptosis, the therapeutic potential of adipose-derived stem cell-derived exosomes, the role of exosomal circRNAs, and engineering strategies to enhance exosome therapy. We also discuss clinical translation challenges, including manufacturing, quality control, and regulatory considerations.

## INTRODUCTION

Human skin aging is classified into intrinsic (chronological) and extrinsic forms; long-term sunlight exposure is the major extrinsic driver of cutaneous aging, termed photoaging<sup>[1,2]</sup>. Chronic ultraviolet (UV) exposure leads to premature aging with wrinkles, pigmentary changes, and loss of elasticity<sup>[3]</sup>. Classical mechanisms of photoaging include oxidative stress and extracellular matrix degradation via upregulated matrix metalloproteinases (MMPs)<sup>[4,5]</sup>. In addition to these established pathways, growing evidence implicates ferroptosis - a lipid peroxidation-driven, iron-dependent form of regulated cell death - in UV-induced cutaneous injury and photoaging contexts<sup>[6,7]</sup>. Ferroptosis is defined as an iron-dependent regulated cell death characterized by lipid peroxidation-mediated membrane damage<sup>[8,9]</sup>.

Among regenerative strategies, exosomes derived from adipose-derived stem cells (ADSC-Exos) have emerged as promising cell-free therapeutics for photoaging, improving cutaneous structure and function in ultraviolet B (UVB) models<sup>[10-12]</sup>. Recent clinical scholarship has further outlined the therapeutic potential of exosomes in plastic surgery for skin rejuvenation and wound healing<sup>[13]</sup>. These nanoscale vesicles carry diverse bioactive cargos, including circular RNAs (circRNAs)<sup>[14]</sup>; notably, hypoxia-preconditioned ADSC-Exos deliver circ-Ash1l to modulate the miR-700-5p/glutathione peroxidase 4 (GPX4) axis and inhibit ferroptosis, thereby attenuating UV-induced skin damage<sup>[15]</sup>. This review is organized around a translational framework that progresses from pathophysiological understanding to therapeutic application. We first delineate the mechanistic intersection between ferroptosis and photoaging, establishing why this cell death pathway represents a rational therapeutic target (see Section “Mechanisms of Photoaging and Ferroptosis”). We then examine how adipose-derived stem cell (ADSC)-derived exosomes modulate these pathways, with particular emphasis on the emerging role of exosomal circRNAs (exo-circRNAs) as functional mediators - using the circ-Ash1l/miR-700-5p/GPX4 axis as a paradigmatic case study (see Section “ADSC Exosomes as Anti-Ferroptosis Therapeutics”). The review subsequently addresses engineering strategies that may enhance therapeutic potential and overcome delivery barriers inherent to topical exosome applications (see Section “Therapeutic Applications of ADSC-Derived Exosomes”), before confronting the regulatory landscape and clinical translation challenges that currently limit the progression of exosome therapeutics from bench to bedside (see Section “Clinical Translation and Regulatory Considerations”). Throughout, we critically evaluate the quality of existing evidence and identify knowledge gaps that must be addressed to advance this field. This framework positions ferroptosis-targeted exosome therapy not as an established treatment modality, but as a promising hypothesis requiring rigorous validation through standardized preclinical studies and well-designed clinical trials.

## MECHANISMS OF PHOTOAGING AND FERROPTOSIS

### UV exposure and photoaging

Photoaged skin is characterized by coarse wrinkles, roughness/dryness, laxity, telangiectasia, and mottled pigmentation including solar lentigines<sup>[2,16,17]</sup>. At the histological level, chronic UV exposure produces dermal connective-tissue degeneration with solar elastosis and abnormal accumulation of elastin and glycosaminoglycans, classically termed dermatoheliosis<sup>[18,19]</sup>. Human skin aging comprises intrinsic and extrinsic components, with UV radiation being the dominant extrinsic driver of premature cutaneous aging<sup>[16]</sup>.

Ultraviolet A (UVA) and UVB both contribute through distinct yet complementary mechanisms: UVA penetrates into the dermis and promotes reactive oxygen species (ROS)-driven signaling and inflammation, whereas UVB - absorbed largely in the epidermis - directly induces cyclobutane pyrimidine dimers (CPDs) and also increases ROS<sup>[16,20-22]</sup>. UVA/UVB exposure upregulates matrix-degrading metalloproteinases - most prominently matrix metalloproteinase 1 (MMP-1) (collagenase-1) and matrix metalloproteinase 3 (MMP-3) (stromelysin-1), with induction of gelatinases matrix metalloproteinase 2 (MMP-2) and matrix metalloproteinase 9 (MMP-9) shown *in vivo* - which degrade type I/III collagen and other extracellular-matrix components underlying dermal elasticity loss and wrinkle formation<sup>[2,23-25]</sup>.

Acute *in vivo* UV irradiation of human skin induces MMP-1 and MMP-3 and concurrently suppresses new collagen synthesis; repeated sub-erythral exposures sustain MMP elevation and cumulatively drive collagen breakdown and wrinkle development<sup>[2,23,26]</sup>. Epidemiologically, photoaging is highly prevalent in sun-exposed populations; in a Queensland community study, 83% of adults aged 20-54 exhibited premature skin aging on clinical assessment and surface microtopography<sup>[27]</sup>. Chronic UV exposure also impairs cutaneous immune function by reducing Langerhans cell density and antigen-presenting capacity, contributing to local immunosuppression<sup>[28-30]</sup>. Although melanocyte numbers decline overall with age, long-term sun-exposed skin shows higher melanocyte density and activity than photoprotected sites, helping explain hyperpigmented lesions such as solar lentigines despite age-related melanocyte loss<sup>[31,32]</sup>.

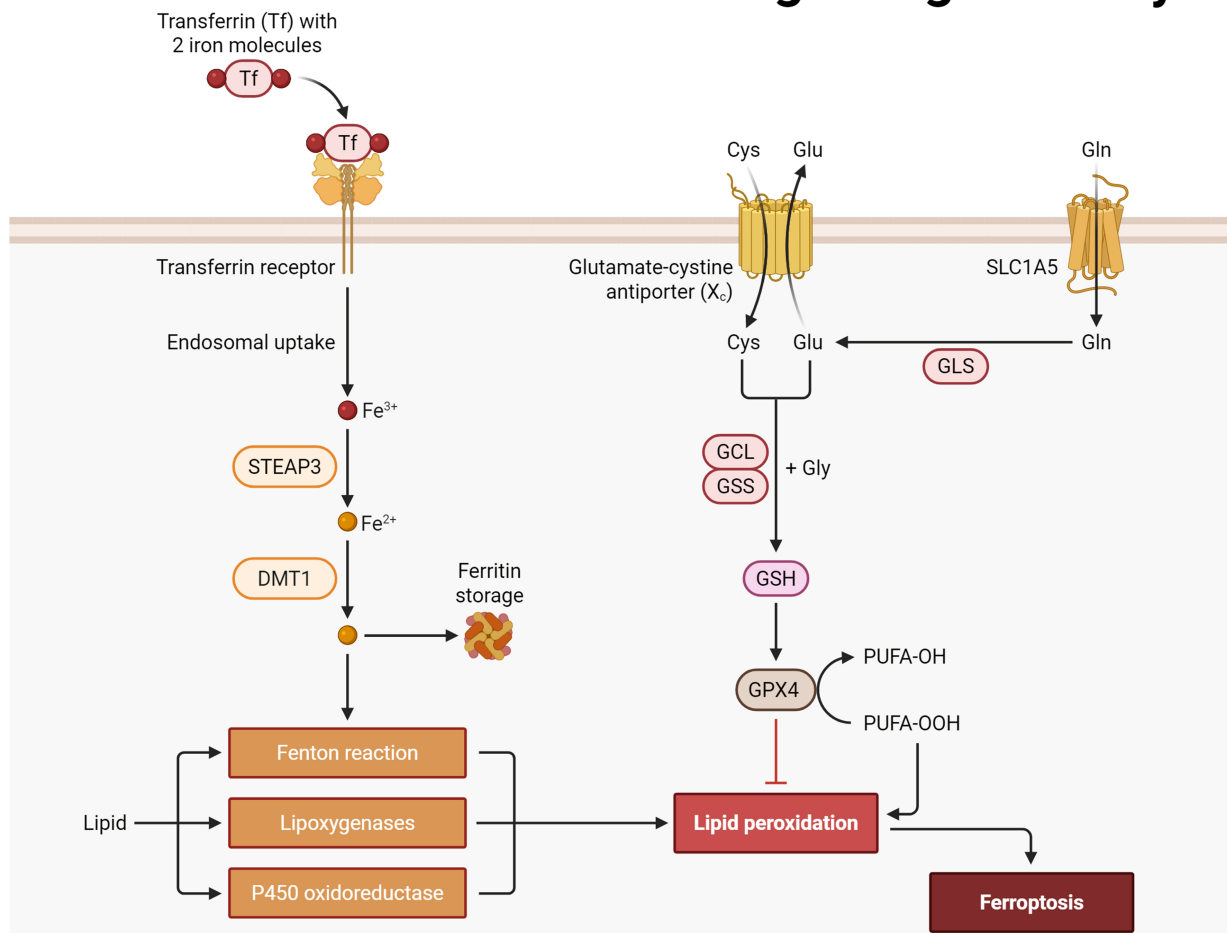
### Ferroptosis in UVB-induced skin damage

Beyond classical oxidative damage and extracellular matrix (ECM) breakdown, recent research has identified ferroptosis as an additional mechanism underlying UVB-induced photoaging<sup>[6,7,33]</sup>. Ferroptosis is a non-apoptotic, iron-dependent form of regulated cell death characterized by excessive lipid peroxidation<sup>[34]</sup>. Unlike apoptosis (which is caspase-driven and involves orderly dismantling of the cell), ferroptosis results from uncontrolled oxidative damage to membrane lipids, particularly polyunsaturated fatty acid (PUFA)-containing phospholipids<sup>[34,35]</sup>. Cells undergoing ferroptosis show distinctive morphological changes including shrunken mitochondria with increased membrane density and loss of mitochondrial cristae, with no chromatin condensation or apoptotic bodies<sup>[35,36]</sup>.

The key molecular players regulating ferroptosis are GPX4 and ferroptosis suppressor protein 1 (FSP1), both of which reduce lipid peroxides to non-toxic lipid alcohols. GPX4 uses glutathione as a cofactor to reduce phospholipid hydroperoxides directly in membranes, whereas FSP1 acts independently via regeneration of coenzyme Q10 to scavenge lipid radicals<sup>[9,37]</sup>. When these protective systems are overwhelmed or suppressed, lipid peroxides accumulate, and lipid membranes become unstable, and cell death ensues<sup>[35]</sup>. UVB radiation impairs these defenses in skin cells. Studies show that human keratinocytes exposed to UVB exhibit glutathione dysregulation with accumulation of ferroptosis-specific oxidized phospholipids and death that is preventable by ferroptosis inhibitors; UVB also promotes autophagy-dependent GPX4 degradation in keratinocytes<sup>[6]</sup>.

The mechanistic link between UVB and ferroptosis includes several pathways. UVB-driven oxidative stress consumes glutathione, limiting GPX4 activity<sup>[6,38]</sup>. In parallel, tumor protein p53 (p53) can suppress the cystine-glutamate antiporter (system Xc<sup>-</sup>) by repressing solute carrier family 7 member 11 (SLC7A11), thereby reducing cysteine uptake needed for glutathione (GSH) synthesis and promoting ferroptosis [Figure 1]<sup>[9]</sup>. UVB exposure is also associated with altered iron handling in skin, including increased transferrin receptor 1 and decreased ferroportin, leading to intracellular iron accumulation<sup>[33]</sup>. Excess intracellular iron catalyzes hydroxyl radical production via the Fenton reaction, exacerbating lipid peroxidation<sup>[39]</sup>. Importantly, inhibiting ferroptosis with chemical inhibitors - Ferrostatin-1 (a lipid radical trap) or deferoxamine (an iron chelator) - can partially protect cultured skin cells from UVB-induced injury and

# Ferroptosis Signaling Pathway



**Figure 1.** UV-induced ferroptosis in skin cells and its link to photoaging. Ultraviolet irradiation increases ROS and p53 activity, which suppresses SLC7A11/SLC3A2 (system Xc<sup>-</sup>) and limits cystine import for GSH synthesis (via GCL/GSS), thereby weakening GPX4-mediated reduction of PUFA-OOH. Meanwhile, iron is imported through Tf/TfR1, reduced by STEAP3, transported by DMT1, mobilized via NCOA4-mediated ferritinophagy, and exported by FPN1/SLC40A1; increased LIP drives Fenton chemistry. Lipid peroxidation is promoted by membrane PUFA-PL remodeling (ACSL4 → LPCAT3) and lipoxygenases (e.g., ALOX15), culminating in ferroptosis. Parallel antioxidant systems such as FSP1-CoQ10 (and mitochondrial DHODH) counteract phospholipid peroxidation independently of GPX4. The downstream consequences in skin include MMP-1/-3/-9 up-regulation, collagen degradation, and loss of elasticity, contributing to photoaging. Created with BioRender.com. ROS: Reactive oxygen species; SLC7A11: solute carrier family 7 member 11; SLC3A2: solute carrier family 3 member 2; GSH: glutathione; GCL: glutamate-cysteine ligase; GSS: glutathione synthetase; GPX4: glutathione peroxidase 4; PUFA-OOH: polyunsaturated fatty acid hydroperoxide; Tf: transferrin; TfR1: transferrin receptor 1; STEAP3: six-transmembrane epithelial antigen of prostate 3; DMT1: divalent metal transporter 1; NCOA4: nuclear receptor coactivator 4; FPN1: ferroportin 1; SLC40A1: solute carrier family 40 member 1; LIP: labile iron pool; PUFA-PL: polyunsaturated fatty acid-phospholipid; ACSL4: acyl-CoA synthetase long-chain family member 4; LPCAT3: lysophosphatidylcholine acyltransferase 3; ALOX15: arachidonate 15-lipoxygenase; FSP1: ferroptosis suppressor protein 1; CoQ10: coenzyme Q10; DHODH: dihydroorotate dehydrogenase; MMP: matrix metalloproteinase.

photoaging-related markers<sup>[6,7,40]</sup>. In mouse models of UVB-induced skin injury, topical Ferrostatin-1 reduced pro-inflammatory cytokine expression and dermal immune-cell infiltration compared with vehicle controls<sup>[33]</sup>. These findings collectively suggest that ferroptosis actively contributes to photoaging pathology. Targeting ferroptosis may thus represent a novel therapeutic avenue for photoprotection and skin rejuvenation, complementing antioxidant strategies and matrix-protective interventions<sup>[33,41]</sup>.

Despite these promising findings, several critical limitations warrant consideration before ferroptosis can be established as a validated therapeutic target in human photoaging. The evidence linking ferroptosis to photoaging derives predominantly from acute, high-dose UVB exposure models in cell culture or short-term animal studies, which may not faithfully recapitulate the pathophysiology of chronic human photoaging that develops over decades of cumulative sub-erythral UV exposure. Whether the ferroptotic signatures observed in acute injury models persist or accumulate in chronically photoaged human skin remains to be systematically investigated. Furthermore, the specificity of ferroptosis markers in photoaging contexts requires careful interpretation. Lipid peroxidation and iron dysregulation also occur in general oxidative stress responses, and distinguishing ferroptosis-specific contributions from broader oxidative damage in the complex milieu of UV-exposed skin presents methodological challenges. The reported efficacy of ferroptosis inhibitors such as Ferrostatin-1 *in vitro* and in mouse models has not yet been validated in human clinical studies. Practical considerations, including percutaneous penetration, metabolic stability, and potential off-target effects on normal iron-dependent processes in the skin, also remain unaddressed. Finally, the relative contribution of ferroptosis vs. other cell death modalities (apoptosis, necroptosis, pyroptosis) to photoaging pathology has not been quantitatively delineated, making it difficult to predict the therapeutic impact of ferroptosis-selective interventions.

## ADSC EXOSOMES AS ANTI-FERROPTOSIS THERAPEUTICS

### The therapeutic potential of ADSC-derived exosomes

ADSCs exert regenerative effects primarily through paracrine secretion of exosomes, 30-150 nm extracellular vesicles (EVs) that deliver bioactive proteins and regulatory RNAs - including circRNAs increasingly implicated in ferroptosis modulation - to recipient cells<sup>[42-46]</sup>.

Compared with live-cell therapies, ADSC-Exos offer key translational advantages: acellular nature, low immunogenicity, reduced tumorigenic concerns, and amenability to lyophilized off-the-shelf manufacturing<sup>[47-51]</sup>. These properties position ADSC-Exos as promising vehicles for delivering anti-ferroptotic cargo to UV-damaged skin. A note on nomenclature: throughout this review, we use “exosome” for consistency with the terminology adopted in the majority of cited studies; however, unless endosomal biogenesis has been experimentally demonstrated, these preparations are more precisely classified as small extracellular vesicles (sEVs) per Minimal Information for Studies of Extracellular Vesicles (MISEV)2023 guidelines. Where cited studies characterized vesicles only at the EV level (e.g., by nanoparticle tracking analysis and tetraspanin markers without confirming endosomal origin), readers should interpret “exosome” as a conventional rather than a strictly biogenesis-defined term.

In photoaging models, ADSC-Exos attenuate UVB-induced oxidative damage, suppress pro-inflammatory cytokines, and limit MMP-mediated matrix degradation, collectively improving skin hydration and reducing wrinkle formation<sup>[48]</sup>. These antioxidant and cytoprotective effects are mechanistically relevant to ferroptosis, given that oxidative stress, glutathione depletion, and lipid peroxidation constitute the core drivers of ferroptotic cell death. A representative selection of recent exosome-based studies in photoaging [Table 1] illustrates that these therapeutic effects have been consistently observed across diverse experimental models. The majority of investigations utilize ADSC- or other mesenchymal stem cell-derived exosomes in both *in vitro* and *in vivo* settings, although ferroptosis-related mechanisms remain underexplored in most current literature.

Critical appraisal of these representative studies reveals several patterns and gaps that should inform future research directions. Regarding experimental models, the majority of investigations employed acute UVB exposure paradigms (single or short-term repeated irradiation) rather than chronic photoaging models, limiting the extrapolation of findings to the clinical reality of cumulative decades-long sun exposure. Sample

**Table 1. Representative studies of exosome-based therapies for photoaging: mechanistic pathways and outcomes**

| Author                              | Year | Primary skin outcomes                                                                                                                                             | Mechanistic pathway                                                    | EV/Exosome source |
|-------------------------------------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|-------------------|
| Liu <i>et al.</i> <sup>[52]</sup>   | 2023 | Vascular injury ↓; collagen degradation ↓; inflammation ↓                                                                                                         | GLRX5 delivery and ferroptosis inhibition                              | hADSCs            |
| Wang <i>et al.</i> <sup>[53]</sup>  | 2025 | -                                                                                                                                                                 | Hypothesis: GSH/ROS pathway                                            | hADSCs            |
| Wang <i>et al.</i> <sup>[11]</sup>  | 2025 | Epidermal thickness ↓; collagen fibers ↑ (Masson); skin damage ↓                                                                                                  | PINK1/Parkin-mediated mitophagy pathway                                | hADSCs            |
| Gao <i>et al.</i> <sup>[54]</sup>   | 2023 | MMPs production ↓; procollagen type I synthesis ↑; epidermal thickening ↓; collagen degradation ↓                                                                 | LncRNA H19/miR-138/SIRT1 axis (gain)                                   | ADSCs             |
| Wang <i>et al.</i> <sup>[55]</sup>  | 2020 | Skin injury ↓ (oxidative stress)                                                                                                                                  | NRF2 defense system                                                    | MSCs              |
| Wu <i>et al.</i> <sup>[56]</sup>    | 2021 | - Skin inflammation ↓<br>- Skin cell regeneration ↑<br>- DNA damage markers (γH2AX, 8-OHdG) ↓<br>- Redness ↓<br>- Scaling ↓<br>- Inflammatory cell infiltration ↓ | 14-3-3ζ/SIRT1 axis (gain)                                              | hucMSCs           |
| Zhang <i>et al.</i> <sup>[57]</sup> | 2022 | SA-β-gal activity ↓; collagen synthesis ↑; elastin synthesis ↑; MMP-1 ↓; MMP-3 ↓; cathepsin K ↓                                                                   | circ_0011129/miR-6732-5p axis (gain); p53 signaling pathway activation | hADSCs            |

This table presents a representative, not exhaustive, selection of studies chosen to illustrate the range of mechanistic pathways, exosome/EV sources, and experimental approaches employed in the field. The term “exosome” is used as reported by the original authors; characterization depth varies across studies, and not all preparations may meet MISEV2023 criteria for exosome-specific identity. ↑ Increased; ↓ decreased. GLRX5: Glutaredoxin 5; hADSCs: human adipose-derived stem cells; GSH: glutathione; ROS: reactive oxygen species; PINK1: PTEN-induced kinase 1; MMP: matrix metalloproteinase; LncRNA: long non-coding RNA; miR: microRNA; SIRT1: sirtuin 1; ADSCs: adipose-derived stem cells; NRF2: nuclear factor erythroid 2-related factor 2; MSCs: mesenchymal stem cells; γH2AX: phosphorylated histone H2AX; 8-OHdG: 8-hydroxy-2'-deoxyguanosine; 14-3-3ζ: 14-3-3 protein, zeta isoform; hucMSCs: human umbilical cord-derived mesenchymal stem cells; SA-β-gal: senescence-associated β-galactosidase; circ\_0011129: circular RNA 0011129; p53: tumor protein p53.

sizes in preclinical studies were generally modest (typically  $n = 3-6$  per group for *in vivo* experiments), and long-term follow-up data beyond 4-8 weeks post-treatment are notably absent, leaving questions about the durability of exosome-mediated effects unanswered. From a mechanistic standpoint, the studies demonstrate considerable heterogeneity in proposed pathways, ranging from canonical transforming growth factor-beta (TGF-β)/Smad and mitogen-activated protein kinase (MAPK)/activator protein 1 (AP-1) signaling to more recently implicated pathways including sirtuin 1 (SIRT1)-mediated deacetylation, nuclear factor erythroid 2-related factor 2 (Nrf2)-dependent antioxidant responses, and mitophagy regulation. Strikingly, ferroptosis-related mechanisms remain underexplored in the exosome-photoaging literature; among the representative studies summarized in Table 1, only entry 1 (Liu *et al.*<sup>[52]</sup>) directly investigated ferroptosis inhibition, while entry 2 (Wang *et al.*<sup>[53]</sup>) examined the related GSH/ROS pathway. This underrepresentation suggests that ferroptosis modulation may be an underexplored aspect of exosome-mediated photoprotection that warrants systematic investigation. The exosome sources also vary substantially - while ADSC-Exos predominate, several studies employed umbilical cord mesenchymal stromal/stem cells (MSCs), bone marrow MSCs, hair follicle MSCs, dermal fibroblasts, and even plant-derived nanovesicles, complicating direct comparisons across studies. Standardization of cell culture conditions, exosome isolation methods [ultracentrifugation *vs.* size exclusion *vs.* tangential flow filtration (TFF)], and characterization protocols according to MISEV guidelines would greatly enhance the reproducibility and comparability of findings in this rapidly evolving field.

Importantly for anti-ferroptosis mechanisms, hypoxia-preconditioned ADSC-Exos can deliver circ-Ash11, which sponges miR-700-5p to upregulate GPX4, a core ferroptosis-suppressing enzyme. Together with established evidence that GPX4 activity prevents ferroptosis by reducing lipid hydroperoxides, these data support a ferroptosis-modulating role for ADSC-Exos under UV stress<sup>[58]</sup>.

### Exo-circRNAs and the circ-Ash1l/miR-700-5p/GPX4 axis

A rapidly emerging area in exosome research is the functional role of circRNAs. These non-coding RNAs are characterized by a covalently closed loop lacking 5' and 3' ends, which contributes to resistance to exonucleolytic decay and confers remarkable stability compared with linear RNAs<sup>[59,60]</sup>. CircRNAs arise via back-splicing, in which a downstream splice donor is joined to an upstream splice acceptor to produce a circular transcript<sup>[61]</sup>. Large-scale transcriptomic surveys established that circRNAs are broadly expressed and conserved in mammals and can be abundant relative to their linear counterparts in specific tissues (notably brain)<sup>[62]</sup>. Functionally, many circRNAs act as competing endogenous RNAs (ceRNAs) or “sponges” for microRNAs - classically exemplified by circular RNA sponge for miR-7/cerebellar degeneration-related protein 1 antisense (ciRS-7/CDR1as) that sequesters miR-7 and derepresses its targets<sup>[63]</sup>. From a kinetic standpoint, endogenous circRNAs show prolonged lifetimes (population averages around ~20-24 h, with several species reaching  $\geq 48$  h), consistent with their general resistance to exonucleases<sup>[60]</sup>.

Exosomes (sEVs, per MISEV terminology) are conspicuously enriched for circRNAs. RNA sequencing (RNA-seq) analyses demonstrated that exo-circRNAs are increased by at least ~2-fold in exosomes relative to producer cells, with circRNA:linear RNA ratios also elevated (reported up to ~6-fold), indicating selective incorporation and/or retention<sup>[64,65]</sup>. Moreover, the lipid bilayer shields exosomal RNAs from RNase degradation, promoting stability in biofluids and efficient cargo delivery to recipient cells<sup>[66,67]</sup>. These properties make exo-circRNAs attractive candidates for intercellular communication and therapeutic delivery, although current guidelines (MISEV2023) recommend precise EV characterization and cautious use of the term “exosome” unless biogenesis is demonstrated<sup>[68]</sup>.

In the context of cutaneous photoaging, hypoxia-preconditioned adipose-derived stem cell exosomes (HExo) mitigate UV-induced skin injury by delivering a specific circRNA, circ-Ash1l<sup>[15]</sup>. *In vitro* and *in vivo*, HExo treatment reversed UVB-provoked oxidative stress and inflammatory readouts and alleviated tissue injury metrics; high-throughput sequencing identified circ-Ash1l as a key effector enriched in HExo; and downregulating circ-Ash1l attenuated these therapeutic benefits<sup>[15]</sup>. Mechanistically, luciferase reporter assays and perturbation studies support a circ-Ash1l/miR-700-5p/GPX4 axis in which circ-Ash1l acts as a molecular sponge for miR-700-5p, thereby sustaining GPX4 expression and constraining ferroptosis-linked lipid peroxidation<sup>[15]</sup>. Notably, miR-700-5p is annotated exclusively in mouse (Mir700; MGI:3629655), with no direct human ortholog identified to date<sup>[69]</sup>. This species restriction has important implications for clinical translation of the circ-Ash1l-mediated anti-ferroptotic mechanism. While the circ-Ash1l/miR-700-5p/GPX4 axis provides compelling proof-of-concept that exo-circRNAs can modulate ferroptosis in photoaged skin, the precise molecular circuitry in human cells likely involves different microRNA (miRNA) intermediaries.

Several human miRNAs have been validated to directly target GPX4 through binding to its 3' untranslated region (3'UTR), including miR-214-3p<sup>[70]</sup>, miR-324-3p<sup>[71]</sup>, and miR-182-5p<sup>[72]</sup>, though their expression patterns in UV-exposed human skin and their amenability to circRNA sponging remain largely unexplored. Future studies should prioritize identifying human-relevant circRNA/miRNA axes that converge on ferroptosis-regulatory nodes. This knowledge gap does not diminish the therapeutic potential of ADSC-Exos for human photoaging. Indeed, the cargo diversity of exosomes suggests that they likely deliver multiple bioactive molecules beyond circ-Ash1l. However, the specific molecular mechanisms validated in murine models require independent verification in human systems before extrapolation to clinical applications.

These mechanistic links are biologically coherent with ferroptosis biochemistry: GPX4 is the principal enzyme that detoxifies phospholipid hydroperoxides in membranes using glutathione, and downregulating GPX4 - or blocking cystine uptake/GSH synthesis upstream - licenses ferroptotic death; conversely, sustaining GPX4 curbs ferroptosis<sup>[73]</sup>. Thus, elevating GPX4 via the circ-Ash1l/miR-700-5p axis offers a plausible route by which HExo blunt UVB-exacerbated lipid peroxidation and tissue damage in skin<sup>[15,73,74]</sup>.

Experimental validation spans gain- and loss-of-function across the axis. Overexpressing circ-Ash1l increases GPX4 and reduces oxidative stress markers under UVB; knockdown of circ-Ash1l diminishes HExo-mediated protection; miR-700-5p elevation impairs, whereas miR-700-5p inhibition rescues, GPX4-linked readouts; and luciferase reporter analysis demonstrates the regulatory relationship between miR-700-5p and GPX4 within the axis<sup>[15]</sup>. Collectively, these lines of evidence implicate the circ-Ash1l/miR-700-5p/GPX4 pathway as a mechanistic contributor to how ADSC-Exos suppress ferroptosis-associated injury in photoexposed skin<sup>[15,73,74]</sup>.

Beyond circ-Ash1l, additional exo-circRNAs are being explored as anti-photoaging payloads. For example, human ADSC-Exos engineered (or enriched via 3D culture) to carry circular RNA hsa\_circ\_0011129 (circ\_0011129) enhanced anti-photoaging efficacy in UV models, reducing senescence markers [senescence-associated  $\beta$ -galactosidase (SA- $\beta$ -gal); p53/cyclin-dependent kinase inhibitor 1A (p21)/cyclin-dependent kinase inhibitor 2A (p16)] and restoring matrix components (collagen I, elastin) more robustly than unloaded exosomes, highlighting how circRNA cargo selection can potentiate sEV-based interventions<sup>[75]</sup>. These and related studies across wound repair and dermatologic indications underscore a broader paradigm wherein exo-circRNAs orchestrate redox balance, extracellular matrix homeostasis, and stress responses in skin biology<sup>[67,75]</sup>.

Consistent with MISEV2018/2023, future work should (i) report EV isolation/characterization in detail; (ii) validate circRNA identity (RNase R resistance, back-splice junction specificity) and functional readouts with appropriate controls [e.g., small interfering RNA (si)/antisense oligonucleotide (ASO) targeting the back-splice junction, rescue with miRNA antagomiR]; and (iii) acknowledge species-specificity (e.g., mmu-miR-700-5p) when extrapolating to human contexts<sup>[68,69]</sup>.

## THERAPEUTIC APPLICATIONS OF ADSC-DERIVED EXOSOMES

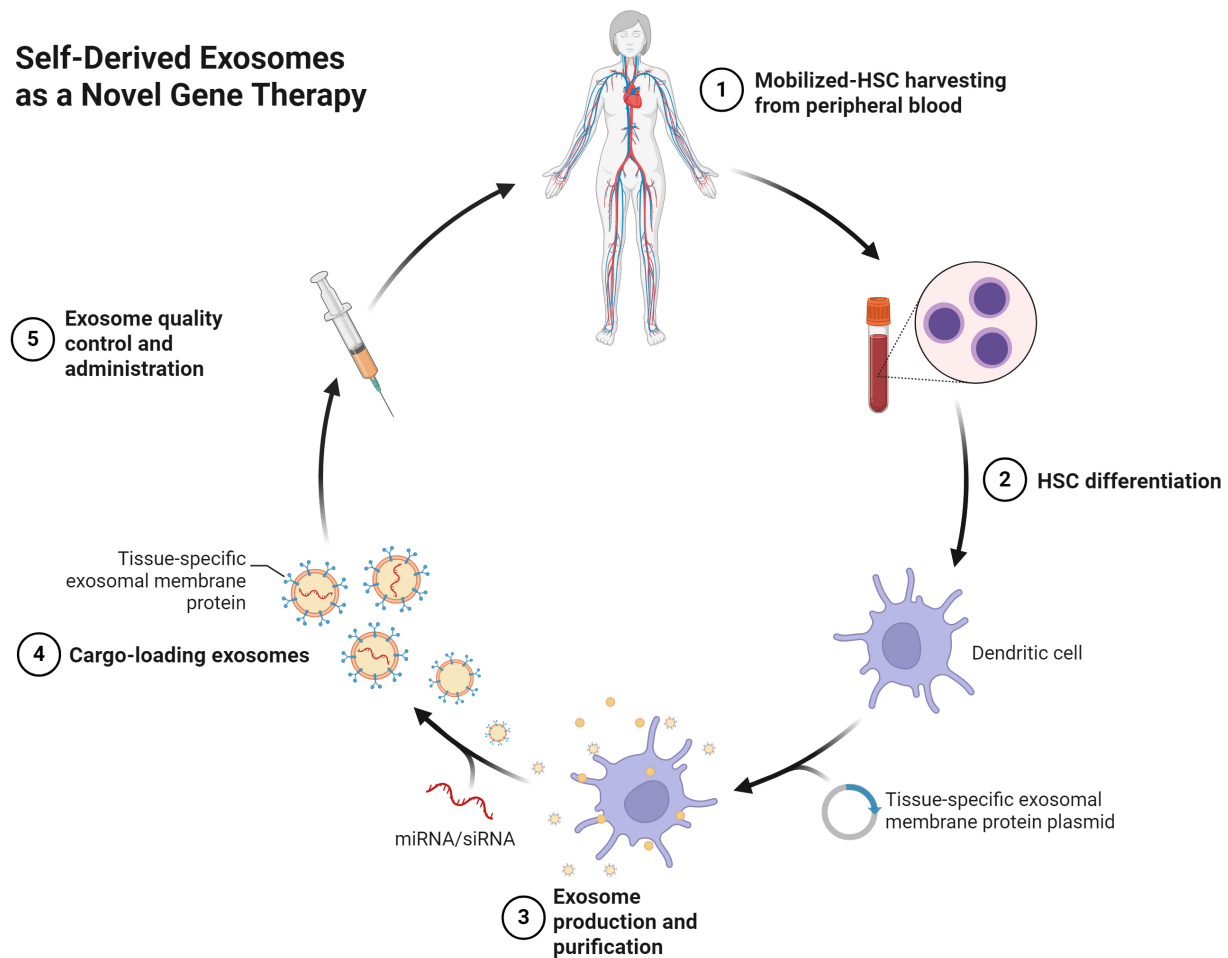
### Engineering strategies to enhance exosome therapy

While native ADSC-Exos show promise, researchers are actively exploring engineering strategies to improve efficacy, targeting, and clinical translatability, typically grouped into parental cell modifications (preconditioning/priming), cargo-loading techniques, and surface engineering [Figure 2]<sup>[76,77]</sup>.

### Preconditioning and priming of parent cells

The composition and potency of exosomes depend on the physiological state of the producer cells; subjecting ADSCs/MSCs to defined cues can remodel exosomal cargo and enhance therapeutic properties<sup>[76]</sup>. Hypoxic preconditioning of human ADSC-Exos upregulates circ-Ash1l and protects UVB-challenged dermal fibroblasts via the circ-Ash1l/miR-700-5p/GPX4 axis<sup>[15]</sup>. Beyond hypoxia, immunological priming with cytokines can imprint immunomodulatory features: interferon-gamma (IFN- $\gamma$ ) increases miR-125a/miR-125b levels in MSC-Exos and augments anti-inflammatory efficacy in colitis models, while combined IFN- $\gamma$ /tumor necrosis factor-alpha (TNF- $\alpha$ )/interleukin-1 beta (IL-1 $\beta$ ) priming elevates programmed cell death protein 1 (PD-1) ligands on EVs and improves outcomes in graft-versus-host disease (GVHD) models<sup>[78,79]</sup>. IL-1 $\beta$ -primed MSC-Exos are enriched in let-7c and suppress p21-activated kinase 1 (PAK1)/nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) to drive macrophage M2 polarization, thereby reducing fibrosis<sup>[80]</sup>. Growth-factor priming can also skew exosomal content toward matrix-supportive effects; EVs released by TGF- $\beta$ -stimulated MSCs modulate dermal fibroblast functions relevant to skin aging and ECM remodeling<sup>[81]</sup>. Small-molecule priming provides further control: curcumin-primed ADSC small EVs show enhanced chondro-protection with reduced oxidative stress and apoptosis, and histone deacetylase (HDAC)-inhibitor (valproate) preconditioning alters the MSC secretome

## Self-Derived Exosomes as a Novel Gene Therapy



**Figure 2.** Workflow for engineering and administration of autologous MSC/ADSC-derived exosomes. (1) Collection of autologous progenitor/stromal cells from the donor; (2) Cell preparation/expansion and optional lineage priming to enable exosome production; (3) Exosome production and purification from conditioned medium; (4) Cargo loading and/or surface engineering of exosomes (e.g., miRNA/siRNA loading; expression or conjugation of tissue-specific membrane ligands); (5) Quality control and administration: vesicles are characterized for size/count and markers, then formulated and delivered according to the intended route. Created with BioRender.com. MSC: Mesenchymal stem cell; ADSC: adipose-derived stem cell; miRNA: microRNA; siRNA: small interfering RNA; HSC: hematopoietic stem cell.

in ways consistent with increased therapeutic activity<sup>[82,83]</sup>. Three-dimensional culture (spheroids/scaffolds) likewise reshapes exosome/secretome profiles; 3D-cultured MSCs secrete EVs enriched for pro-angiogenic factors and angiogenesis-related miRNAs compared with 2D cultures<sup>[84,85]</sup>. Finally, partially differentiating MSCs toward an endothelial-like lineage before harvesting exosomes can yield vesicles enriched in pro-angiogenic miRNAs and ephrin A1 (EFNA1), thereby enhancing endothelial activation and tissue repair<sup>[86]</sup>.

### Direct cargo loading

In addition to modifying the parent cells, exosomes can be directly loaded with therapeutic molecules post-isolation. This approach allows precise control over the delivered cargo, and commonly used post-loading techniques include electroporation, sonication, and membrane-permeabilizing agents such as saponin<sup>[87,88]</sup>.

Electroporation applies brief electric pulses that transiently permeabilize exosome membranes, enabling entry of exogenous nucleic acids or small molecules; it has been widely used to load small interfering RNA

(siRNAs) or miRNA mimics into exosomes for functional gene silencing in recipient cells<sup>[88]</sup>. In oncology models, exosomes electroporated with antitumor or anti-inflammatory miRNAs/siRNAs have shown target gene knockdown and therapeutic effects<sup>[88]</sup>. In dermatologic applications, analogous miRNA-loading strategies are being explored for skin disease models<sup>[88]</sup>. However, electroporation can have limitations: high electric fields may compromise vesicle integrity and can induce aggregation/precipitation of RNA, and loading efficiency can vary across preparations<sup>[87,89]</sup>.

Sonication has been explored as an alternative that transiently pores membranes and can achieve high loading efficiency for certain cargos, though excessive sonication may disrupt vesicle structure or reduce vesicle yield<sup>[90]</sup>. Detergent-based methods (e.g., low concentrations of saponin) create reversible pores by interacting with membrane cholesterol, facilitating cargo entry but requiring careful optimization to balance loading with vesicle integrity and cytotoxicity<sup>[91]</sup>.

Another approach is to use cell-penetrating peptides (CPPs) or hydrophobic anchors conjugated to the therapeutic molecule to promote association with, or insertion into, the exosome membrane or lumen via spontaneous membrane interactions during simple incubation; cholesterol-conjugated siRNAs and cell-penetrating peptide (CPP)-polyethylene glycol (PEG)-lipids are representative strategies that enable EV loading under mild conditions<sup>[92,93]</sup>. These strategies typically require conjugation chemistry and are not universally applicable to all cargos<sup>[92,93]</sup>.

An alternative to post-isolation loading is genetic/producer-cell engineering, in which exosome-producing cells are engineered to enrich specific cargos or display targeting moieties so that they are packaged during biogenesis. For example, fusing therapeutic or targeting peptides to exosome-associated proteins such as lysosome-associated membrane protein 2B (LAMP2B) or to the C1C2 domain of lactadherin can enrich those peptides/proteins in exosomes and direct them to desired targets<sup>[87,94,95]</sup>. Endogenous (cell-based) loading inherently modifies the EV-producing cells to incorporate therapeutic agents during natural EV biogenesis<sup>[87]</sup>.

However, the optimal loading strategy for anti-photoaging applications has not been systematically compared, and whether post-isolation loading alters the intrinsic therapeutic properties of native ADSC-Exos (potentially disrupting endogenous bioactive cargos) remains an open question. Despite the absence of systematic head-to-head comparisons for photoaging applications, general principles can guide strategy selection. Preconditioning approaches (see Section “Preconditioning and Priming of Parent Cells”) offer the advantage of preserving native vesicle integrity and leveraging endogenous sorting mechanisms, but provide limited control over specific cargo enrichment and require optimization for each therapeutic target. Post-isolation loading methods such as electroporation and sonication enable precise cargo selection and higher loading efficiency for exogenous molecules, yet may compromise membrane integrity, induce cargo aggregation, or disrupt endogenous bioactive components. Surface modification strategies (see Section “Surface Modification and Targeting”) can enhance targeting specificity and cellular uptake but add manufacturing complexity and potential immunogenicity concerns. For clinical translation of anti-photoaging exosome therapies, the choice of engineering strategy will likely depend on the specific therapeutic goal, with preconditioning favored for applications leveraging native ADSC-Exo properties and post-isolation loading preferred when delivery of defined molecular payloads is required.

### **Surface modification and targeting**

To improve the specificity and efficiency of exosome uptake by target cells, surface engineering strategies are being developed. One approach is to decorate the exosome surface with targeting ligands that bind receptors enriched on the desired cell type. For instance, engineering exosomes to display an epidermal growth factor

receptor (EGFR)-binding peptide (GE11) or integrin-binding peptides such as internalized Arg-Gly-Asp (iRGD, a tumor-penetrating cyclic peptide) has yielded preferential uptake by the intended cancer cells and greater tumor accumulation *in vivo* compared with unmodified vesicles<sup>[96-98]</sup>. This has been demonstrated in cancer models, where peptide-displaying exosomes showed selective delivery and antitumor effects over non-targeted controls<sup>[96-98]</sup>.

Surface modification can be performed post-isolation via bio-orthogonal coupling (e.g., copper-free click chemistry) or high-affinity biotin-streptavidin bridges, by first functionalizing the exosomal membrane and then conjugating a ligand<sup>[99-101]</sup>. Alternatively, lipophilic anchors - such as cholesterol-modified oligonucleotide/aptamer tethers - can spontaneously insert into the exosome lipid bilayer and display the attached ligand on the surface, enabling modular retargeting without altering parental cells<sup>[102]</sup>.

For topical skin applications, additional modifications and formulations that enhance traversal of the stratum corneum are often required. Chemical penetration enhancers used in dermatologic formulations (e.g., ethanol, propylene glycol) and skin-penetrating peptides have been shown to transiently increase skin permeability, and are commonly leveraged in topical delivery systems<sup>[103-105]</sup>. Current evidence suggests that intact stratum corneum significantly limits the deep penetration of free exosomes; therefore, pairing exosomes with penetration enhancers, microneedles, or hydrogel/exosomal vehicles is typically needed to increase dermal exposure<sup>[106]</sup>.

While these targeting strategies show promise in oncology applications, their utility for topical skin applications is less clear, given that the primary barrier to exosome efficacy in photoaging treatment is likely stratum corneum penetration rather than cell-type selectivity within the dermis.

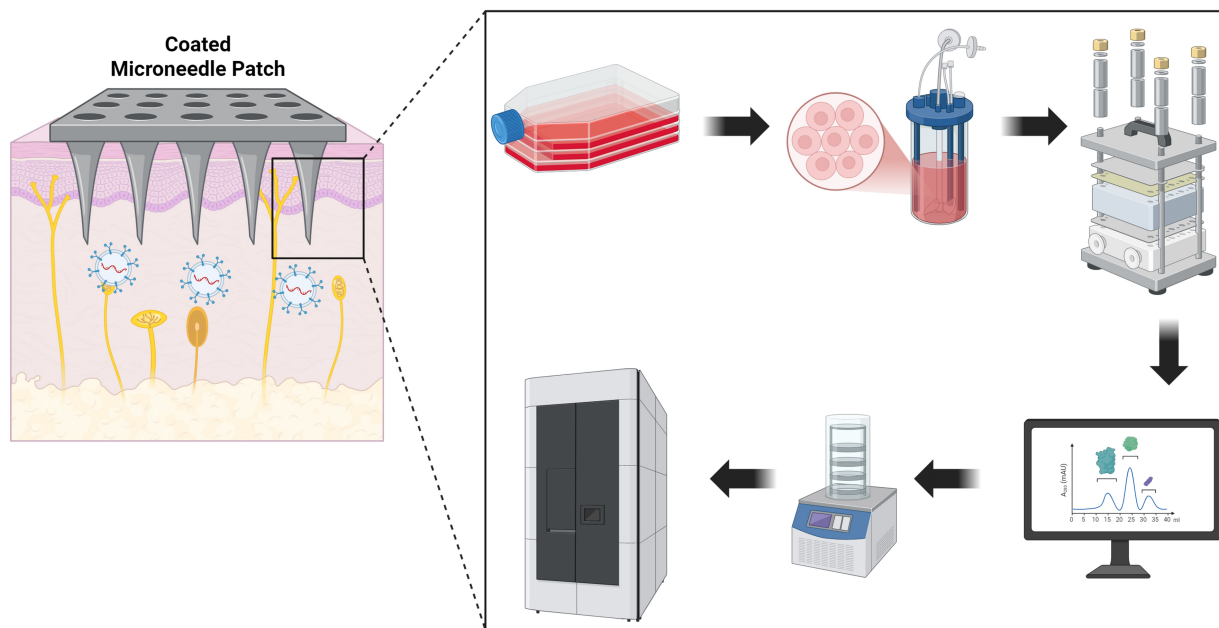
### Lyophilization and formulation

For clinical and commercial viability, exosomes need to be stable during storage and easy to handle. Lyophilization (freeze-drying) with disaccharide cryoprotectants (e.g., trehalose, sucrose) helps preserve vesicle integrity and activity upon reconstitution<sup>[107-109]</sup>. Studies report that appropriately lyophilized EVs retain size/markers and functional activity after storage at room temperature for weeks to months and at refrigerated temperatures, supporting development of off-the-shelf products<sup>[107-109]</sup>.

Formulation into delivery vehicles is another key consideration. For topical use, exosomes can be incorporated into hydrogels or related semisolid bases that protect vesicles and sustain release; for injection-based treatments (e.g., intradermal/subcutaneous), biocompatible depots such as hyaluronic-acid or alginate-based hydrogels can prolong local retention and reduce dosing frequency relative to free exosomes in saline<sup>[110,111]</sup>.

### Scaling up production

For exosome therapies to be practical, especially for topical cosmetic use which could demand large volumes, manufacturing processes must be scalable and cost-effective. Traditional ultracentrifugation, while effective at lab scale, is less suitable for scale-up and often underperforms in yield and time/cost/scalability compared with newer methods. Instead, techniques such as TFF and size-exclusion chromatography (SEC) are being employed for scalable exosome purification [Figure 3]<sup>[112-115]</sup>. These methods can process large volumes of culture supernatant and have been shown to remove abundant soluble protein contaminants (for example, albumin and lipoprotein complexes) while retaining vesicle integrity<sup>[112,113,115,116]</sup>. A combination workflow - using TFF for volume reduction followed by SEC for fine purification - is increasingly adopted in EV manufacturing<sup>[114,117]</sup>.



**Figure 3.** Transdermal delivery and scalable manufacturing/quality control of ADSC-derived exosomes. Left: A coated microneedle patch breaches the stratum corneum and deposits exosomes into the viable epidermis/papillary dermis for uptake by keratinocytes and fibroblasts. Right (workflow): (1) Culture/priming of ADSCs; (2) expansion in a microcarrier or hollow-fiber bioreactor; (3) TFF for clarification and volume reduction (e.g., 300 kDa cassette); (4) size-exclusion chromatography (SEC/qEV or FPLC) for polishing; (5) lyophilization of the exosome-coated microneedle formulation with protectants (e.g., trehalose/sucrose  $\pm$  surfactant); (6) labeled storage (2–8 °C liquid or –80 °C frozen). Quality control is applied across steps, including NTA (size/count), TEM, EV markers (CD63/CD81/CD9, TSG101), and assessment of protein/lipoprotein carryover. Created with BioRender.com. ADSC: Adipose-derived stem cell; TFF: tangential flow filtration; SEC: size-exclusion chromatography; FPLC: fast protein liquid chromatography; NTA: nanoparticle tracking analysis; TEM: transmission electron microscopy; EV: extracellular vesicle; CD: cluster of differentiation; TSG101: tumor susceptibility gene 101.

Upstream, shifting from static 2D cultures to bioreactor systems (such as microcarrier-based stirred-tank or hollow-fiber/perfusion platforms) can substantially increase EV output per run. For MSCs, microcarrier spinner/3D systems and TFF have delivered  $\geq 3$ -fold increases in particle yield (e.g., 7-fold over 3D-UC and  $\sim 20$ -fold over 2D-UC), while maintaining characteristic EV markers and strong bioactivity relative to conventional preparations<sup>[118]</sup>. Bioreactor platforms also offer controlled operation (continuous perfusion/feed and process control) that facilitates consistency across batches<sup>[115]</sup>.

However, scale-up introduces quality considerations such as hydrodynamic/shear stress in bioreactors or during filtration that may affect EV properties; processes should be tuned to minimize shear (e.g., gentle TFF settings and streamlined processing) to help preserve vesicle integrity<sup>[119]</sup>.

## CLINICAL TRANSLATION AND REGULATORY CONSIDERATIONS

### Regulatory and safety considerations

The regulatory landscape for exosome therapeutics is still evolving. As of 2024, no exosome-based therapy has received FDA approval<sup>[120]</sup>. Regulatory agencies such as the Food and Drug Administration (FDA) currently classify human-derived exosomes intended for therapeutic use as drugs/biological products, subject to stringent requirements for safety, purity, and potency testing<sup>[120]</sup>. The lack of a clear, universally adopted categorization creates complexity in determining whether exosomes represent cell therapy, gene therapy, or a novel class altogether, which can complicate the approval pathway<sup>[120]</sup>.

In the European Union (EU), debate continues regarding whether exosome products fall under the definition of an Advanced Therapy Medicinal Product (ATMP) or as a biological medicinal product, depending on their source/engineering status<sup>[120]</sup>. If exosomes are loaded with recombinant nucleic acids or drugs, they may fall under the EU definition of a gene therapy medicinal product, requiring demonstration of safety for all components<sup>[120]</sup>. Regulatory bodies emphasize issues such as immunogenicity, biodistribution, and long-term safety of exosome treatments<sup>[120]</sup>.

While ADSC-Exos are often described as low-immunogenic - e.g., lacking major histocompatibility complex (MHC) class II and with low MHC class I - repeated or systemic administration still necessitates comprehensive toxicity evaluations<sup>[121]</sup>. Key safety questions include risks of unintended coagulation or complement activation, off-target biodistribution, and potential systemic effects even after topical application. Current evidence suggests exosomes are largely cleared by macrophages and accumulate primarily in the liver/spleen after systemic dosing, with generally favorable toxicity profiles in animals; however, rigorous acute/chronic dosing studies remain essential<sup>[122-124]</sup>.

Tumorigenicity is another consideration. Although exosomes cannot divide, they carry nucleic acids and proteins; quality control must ensure they do not transfer oncogenic cargo or promote a pro-tumor microenvironment<sup>[125]</sup>. Studies report both anti-tumor and pro-tumor effects of MSC exosomes depending on context, underscoring the need to characterize RNA/DNA cargo carefully during manufacturing<sup>[125-127]</sup>.

Regulators will require comprehensive Chemistry, Manufacturing, and Controls (CMC) documentation to ensure each batch meets defined criteria (e.g., size distribution, identity/surface markers, sterility, and acceptable endotoxin levels) and that production is reproducible under Good Manufacturing Practice (GMP)<sup>[120,128]</sup>. Given these hurdles, developing standardized production protocols and reference materials is crucial. International initiatives led by International Society for Extracellular Vesicles (ISEV) (e.g., MISEV2023 guidance and EV reference-material efforts) are establishing frameworks that aid regulatory standardization<sup>[68]</sup>.

The absence of approved exosome therapeutics as of 2024 reflects not only regulatory uncertainty but also the inherent challenges of standardizing a biologically complex product; until these issues are resolved, the clinical translation of ADSC-Exos for photoaging will remain constrained regardless of preclinical efficacy.

### Future directions and clinical perspectives

Looking ahead, several perspectives can be outlined for advancing exosome-based photoaging treatment. Well-designed clinical trials are needed to rigorously assess the efficacy of ADSC-Exos treatments in human photoaging<sup>[129]</sup>. Early clinical applications have already appeared in aesthetic dermatology as adjuvants to procedures (e.g., microneedling or fractional laser), where split-face randomized trials reported benefit when exosome formulations were added to standard care<sup>[130,131]</sup>. Beyond these adjuvant applications, Wan *et al.* recently reported a prospective study evaluating exosome therapy combined with microneedling for androgenetic alopecia, demonstrating a mean increase of 35 hairs/cm<sup>2</sup> at 12-month follow-up with high patient satisfaction<sup>[132]</sup>. Although targeting a different indication, this study exemplifies the methodological rigor - objective outcome measures, standardized protocols, and adequate follow-up - needed to advance exosome therapeutics toward clinical validation in photoaging contexts. Initial studies can test an exosome serum or mask aimed at improving visible photoaging signs in adults with moderate facial photoaging<sup>[130]</sup>.

Endpoints should include objective measures - standardized photography/3D imaging and wrinkle grading, biomechanical skin elasticity (e.g., Cutometer), and histologic assessment of dermal collagen from biopsies - together with patient- or investigator-reported outcomes on texture, hydration, and pigmentation<sup>[130,131]</sup>. Such

studies can also explore dosing schedules (e.g., session intervals over 8-12 weeks) and quantify whether exosomes yield tangible cosmetic benefits<sup>[130,131]</sup>. If successful, subsequent trials could evaluate medical outcomes related to chronic photodamage (for example, prevention of precancerous changes such as actinic keratoses)<sup>[47]</sup>.

Customizing exosome formulations for distinct photoaging phenotypes is a logical direction. An anti-wrinkle product could be enriched for factors that stimulate fibroblast collagen synthesis<sup>[133,134]</sup>, whereas an anti-pigmentation product might incorporate miRNAs that suppress melanogenesis pathways in melanocytes<sup>[135,136]</sup>. This framework enables personalized exosome-based regimens targeting wrinkles, laxity, or dyschromia<sup>[133-136]</sup>.

Combining exosome therapy with barrier-disruptive modalities may yield synergistic effects. In practice, fractional lasers and microneedling are used to induce dermal remodeling; applying ADSC-Exos solutions immediately after these procedures, when micro-channels are open and repair programs are activated, has improved outcomes in randomized split-face studies and reduced post-procedure erythema/downtime<sup>[130,131]</sup>. Mechanistically, topical exosomes have limited penetration through an intact stratum corneum and mainly act within that layer; micro-channeling (microneedling) facilitates delivery to viable epidermis/dermis and may thereby enhance efficacy<sup>[137]</sup>.

From a mechanistic research perspective, further work should map how exosome cargo intersects aging pathways and which skin cell types are principal recipients *in vivo* after topical/adjuvant use. Open questions remain regarding relative targeting of keratinocytes, fibroblasts, and immune cells in photodamaged skin; current evidence shows extensive EV-mediated crosstalk among these compartments but requires deeper *in situ* resolution in humans<sup>[138-140]</sup>.

It is also critical to confirm that effects observed in acute/subacute UV models translate to chronic photoaging. Many mechanistic studies - including those on the circ-Ash1l/miR-700-5p/GPX4 axis - have used acute UVB injury models; chronic photoaging instead reflects decades of repetitive low-dose UV exposure with cumulative repair failure<sup>[15,47]</sup>. Exosomal interventions will likely need sustained administration and concomitant photoprotection to impact chronically photoaged skin<sup>[47]</sup>. In acute UV models, hypoxia-primed ADSC-exosomes protect via delivery of circ-Ash1l and downstream ferroptosis control (miR-700-5p/GPX4)<sup>[15]</sup>; whether similar temporal dynamics operate during long-term photoaging requires testing in extended animal or *ex vivo* human-skin models<sup>[15,47]</sup>.

### Limitations of current evidence

Several limitations of the current literature should be acknowledged when interpreting the therapeutic potential of ADSC-Exos for photoaging.

Regarding experimental model fidelity, the overwhelming majority of mechanistic studies employ acute, high-dose UVB exposure paradigms that induce rapid cellular damage within hours to days. This contrasts sharply with human photoaging, which develops insidiously over decades of cumulative sub-erythral UV exposure, allowing for compensatory adaptations and repair processes that may fundamentally alter the pathophysiological landscape. Whether the molecular signatures and therapeutic responses observed in acute injury models translate to chronically photoaged human skin remains an assumption rather than an established fact. Additionally, murine skin differs substantially from human skin in thickness, hair follicle density, and immune cell composition, potentially limiting the predictive validity of mouse photoaging models.

From a mechanistic standpoint, the circ-Ash1l/miR-700-5p/GPX4 axis - while providing elegant proof-of-concept for circRNA-mediated ferroptosis regulation - derives primarily from a single research group and awaits independent replication. The species-specificity of miR-700-5p (present in mouse but absent in humans) necessitates identification of functionally analogous human miRNA targets before this pathway can be therapeutically exploited in clinical settings. More broadly, the relative contribution of ferroptosis *vs.* other cell death modalities (apoptosis, necroptosis, pyroptosis) to photoaging pathology has not been quantitatively established, making it difficult to predict the clinical impact of ferroptosis-selective interventions.

Methodological heterogeneity across studies also complicates evidence synthesis. Exosome isolation techniques (ultracentrifugation, size exclusion chromatography, TFF, precipitation kits) yield preparations of varying purity and bioactivity, yet many studies do not report characterization data consistent with MISEV2023 guidelines. This variability, combined with differences in cell culture conditions, passage numbers, and preconditioning protocols, may account for some of the inconsistencies in reported outcomes and limits the comparability of findings across laboratories.

Finally, clinical evidence remains sparse. The few published human studies are limited to small, short-term, split-face trials evaluating exosomes as adjuncts to microneedling or laser procedures, with follow-up periods typically extending only 8-12 weeks. Long-term efficacy, durability of effects, optimal dosing regimens, and safety profiles with repeated administration have not been systematically evaluated in human subjects.

## CONCLUSION

ADSC-Exos have emerged as a cutting-edge biologic approach for skin rejuvenation, leveraging the naturally packaged toolkit of regenerative molecules from stem cells. They address multiple hallmarks of photoaging including oxidative damage, matrix degradation, inflammation, and ferroptosis in a coordinated manner that single-molecule drugs might struggle to achieve. Challenges remain in production scalability, delivery optimization, and regulatory approval, and while ongoing advancements in bioengineering and standardization are promising, significant hurdles must still be addressed before clinical translation can be realized. Realizing the therapeutic potential of ADSC-Exos will require rigorously validating safety and efficacy through well-designed clinical trials, aligning manufacturing processes with regulatory expectations, and establishing standardized protocols for exosome characterization and quality control<sup>[141]</sup>. If these challenges can be overcome, patients may eventually benefit from non-invasive, cell-free regenerative treatments that ameliorate photodamaged skin, improving both cosmetic appearance and skin health and resilience.

As the field moves forward, interdisciplinary collaboration between cell biologists, bioengineers, dermatologists, and regulatory experts will be essential for translating the promise of exosomal regenerative therapy into widely accessible treatment for photoaging and other degenerative skin conditions.

## DECLARATIONS

### Authors' contributions

Conceptualization, writing - original draft, visualization, project administration: Shi X

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All authors read and approved the final manuscript.

### Availability of data and materials

Not applicable.

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During the preparation of this manuscript, the AI-assisted image generation tool Nanobanana Pro was used solely for generating the Graphical Abstract. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors reviewed and finalized the generated content and take full responsibility for the accuracy, integrity, and originality of the manuscript.

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All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

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### Consent for publication

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