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Human umbilical cord mesenchymal stem cell-derived exosomes enhance follicular regeneration in androgenetic alopecia via activation of Wnt/ β -catenin pathway

Aiqing Yu^{1,2,3}, Yujun Zhang^{4*}, Saifeng Zhong^{1,2}, Zhizhen Yang⁴ and Mingming Xie⁴

Abstract

Background Exosomes isolated from human umbilical cord mesenchymal stem cells (hUCMSCs) have demonstrated the capacity to alleviate dihydrotestosterone (DHT)-induced disruptions in the hair follicle growth cycle. However, the precise role and underlying mechanisms by which hUCMSC-derived exosomes influence hair shaft regeneration in androgenetic alopecia (AGA) remains unclear.

Methods hUCMSCs were isolated using fluorescence-activated cell sorting following enzymatic digestion with TrypLE™ Express. Exosomes derived from these hUCMSCs were purified through ultracentrifugation and subsequently characterized by transmission electron microscopy and Western blotting to confirm their morphology and protein markers. To model human AGA, mice received daily subcutaneous injections of dihydrotestosterone. The effects of MSC-derived exosomes (MSC-Exo) on hair follicle growth were evaluated through transparent skin visualization, hematoxylin and eosin staining, and immunofluorescence assays. Additionally, EnoGeneCell™ Counting Kit-8 assays and scratch wound healing assays were conducted to assess the proliferative and migratory responses of human dermal papilla cells (hDPCs) following MSC-Exo treatment.

Results In vivo, MSC-Exo significantly promoted hair follicle enlargement and facilitated the transition of follicles into the anagen (growth) phase. These exosomes modulated the proliferation and differentiation of key cellular players in hair follicle biology, particularly dermal papilla cells, while also altering the secretory profile of hDPCs. Notably, high levels of two microRNAs, miR-21-5p and let-7b-5p, were identified within hUCMSC exosomes. Both microRNAs are recognized regulators of genes critical to hair follicle function, including Cyclin D1, c-MET, and LEF1, which collectively activate the Wnt/ β -catenin signaling pathway and thereby enhance the functional differentiation of hDPCs.

Conclusions Exosomes derived from hUCMSCs enrich miR-21-5p and let-7b-5p, which target key genes such as Cyclin D1, c-MET, and LEF1 to activate the Wnt/ β -catenin pathway, promoting hair shaft regrowth in an AGA model. These findings reveal a novel therapeutic target for stem cell-derived exosomes and underscore their potential in activating Wnt/ β -catenin signaling for the treatment of AGA. Our study provides new insights into the mechanistic role of stem cell exosomes in AGA and advances the development of regenerative therapies for this condition.

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Keywords hUCMSCs derived-exosomes, Hair follicle growth cycle, Androgenetic alopecia, Dihydrotestosterone, Human dermal papilla cells

Introduction

The hair growth cycle in healthy individuals progresses through three well-defined phases: anagen (active growth), catagen (regression), and telogen (resting). Disruption of this cycle is a hallmark of androgenetic alopecia (AGA), primarily driven by elevated levels of dihydrotestosterone (DHT). Excess DHT shortens the anagen phase and triggers persistent perifollicular inflammation, which gradually leads to follicular miniaturization, progressive thinning of hair shafts, and ultimately irreversible hair loss due to degeneration of hair follicle structures [1]. Structurally, hair follicles are composed of both epidermal and dermal components, with the dermis functioning as a critical stem cell niche that supports ongoing follicular renewal. Among the dermal cell populations, dermal sheath cells located in the hair bulb can differentiate into human dermal papilla cells (hDPCs)—specialized mesenchymal cells that function as signaling hubs, orchestrating the cyclical progression of the hair follicle through paracrine signaling and molecular cross-talk [2].

Although exosomes secreted by hDPCs have demonstrated the ability to stimulate hair follicle development and cycling, their inductive capacity diminishes significantly in vitro under epithelial-deprived conditions. This presents a major limitation for their translational application in clinical hair regeneration therapies [3–5]. In contrast, human umbilical cord mesenchymal stem cells (hUCMSCs) are pluripotent cells with high self-renewal capacity and the ability to differentiate into multiple cell types. Exosomes released by hUCMSCs have emerged as potent biological carriers capable of modulating a variety of cellular functions, including proliferation, differentiation, apoptosis, extracellular matrix (ECM) remodeling, and inflammation suppression [6, 7]. These exosomes have shown therapeutic promise in a range of regenerative contexts, including skin wound healing and neural tissue repair, owing to their regenerative and immunomodulatory properties [8–10]. However, further research is essential to comprehensively elucidate the therapeutic potential of MSC-derived exosomes (MSC-Exo) in targeting hair follicles and hDPCs in the context of AGA. Building upon recent scientific advancements, the primary therapeutic goals in AGA management include extending the anagen (growth) phase of hair follicles, promoting the transition of follicles from the telogen (resting) to the anagen phase, reversing follicular miniaturization,

and stimulating the formation of new hair follicles. In this regard, MSC-Exo holds promise as a modulator of the hair follicle growth cycle, offering a novel strategy to combat AGA while advancing our understanding of the underlying molecular mechanisms.

Materials and methods

Cell culture

hUCMSCs and hDPCs were obtained from Wanquan Biotechnology (Jinan, Shandong, China). Cells were seeded at a density of 1.05×10^6 cells per T125 flask and maintained in either ncMission hMSC Medium (Nuwa-cell, Hefei, China) or DMEM/F-12 (Gibco, NY, USA), depending on the cell type. Cultures were incubated at 37 °C in a humidified atmosphere containing 5% CO₂ and passaged every 3 days to maintain optimal growth conditions.

The hUCMSCs used in this study were procured from a certified biological sample bank, with preparation and handling conducted in accordance with national regulations for stem cell clinical research. Quality control parameters for this cell line have been previously validated in collaborative studies [11]. Donor tissues were collected following informed consent, under ethical approval from Qilu Hospital of Shandong University (documentation of ethics approval is maintained with this study). hDPCs were isolated using a proprietary technique protected under Chinese Patent No. CN117946961A, which has undergone full substantive examination and approval by the China National Intellectual Property Administration [12]. All biological samples were anonymized and handled in strict compliance with the Ethical Review Measures for Life Science and Medical Research Involving Humans (National Health Commission Order No. 1, 2023).

We would like to clarify that the human umbilical cord mesenchymal stem cells (hUCMSCs) used in this study were purchased from Jinan Wanquan Biotechnology Co., Ltd. However, Wanquan Biotechnology and Shandong Qilu Stem Cell Engineering Co., Ltd. are effectively under the same legal ownership and share the same technical and ethical documentation. While commercial transactions and communications are handled via Wanquan Biotechnology, the technical development, cell isolation procedures, and ethical approvals—including the granted patent (ZL200910260704.1) covering donor consent and ethical review—are managed and documented under the Qilu Stem Cell Engineering framework. Therefore, the ethical approval described in the granted patent applies

fully to the cells we purchased, and we confirm that the donor tissues were collected with informed consent and appropriate ethical review in compliance with relevant guidelines.

Fluorescence-activated cell sorting

hUCMSCs were harvested using TrypLE™ Express Enzyme (Gibco), washed with Dulbecco's Phosphate-Buffered Saline (DPBS), and counted. The cell suspension was adjusted to a concentration of 7×10^6 cells/mL, and the appropriate primary antibodies were added to the cell mixture in Eppendorf tubes. After incubation in the dark for 30–60 min, cells were washed three times with DPBS. Each wash was followed by centrifugation, and cells were resuspended in DPBS. The final suspension was transferred to flow cytometry tubes for analysis. Cells were deemed to meet qualification criteria if the expression of CD73, CD105, and CD90 was $\geq 95\%$, while the expression of hematopoietic and immune markers (CD45, CD34, CD14, HLA-DR, and CD79a) was $\leq 2\%$. Flow cytometry data were analyzed using FlowJo software (Ashland, OR, USA). The primary antibodies used in fluorescence-activated cell sorting were as follows: PE anti-human CD73 (BioLegend, USA; Cat. No. 344003), PE anti-human CD105 (BioLegend; 800503), PE anti-human CD14 (BioLegend; Cat. No. 325605), PE anti-human CD34 (BioLegend; Cat. No. 343605), PE anti-human HLA-DR (BioLegend; Cat. No. 307605), FITC anti-human CD90 (BioLegend; Cat. No. 328107), FITC anti-human CD45 (BioLegend; Cat. No. 368507), and FITC anti-human CD79a (BioLegend, Cat. No. 333511).

Isolation and purification of MSC-exo

Exosomes were isolated from fourth-passage hUCMSCs once cultures reached approximately 90% confluence. The conditioned medium was first collected and processed using a sequential gradient centrifugation protocol: $300 \times g$ for 10 min to remove residual intact cells, followed by $2000 \times g$ for 10 min to eliminate apoptotic or dead cells. Cell debris was cleared by centrifugation at $10,000 \times g$ for 30 min. The supernatant was then filtered through a $0.22 \mu\text{m}$ filter (Millipore) to remove large extracellular vesicles and particles. To isolate the exosomes, ultracentrifugation was conducted at $100,000 \times g$ for 70 min at 4°C . The exosome-containing pellet was washed once with phosphate-buffered saline and subjected to a second round of ultracentrifugation at $100,000 \times g$ for an additional 70 min. The final exosome pellet was re-suspended in DPBS for further analysis.

Transmission electron microscopy

A $10 \mu\text{L}$ suspension of MSC-Exo in phosphate-buffered saline (PBS) was deposited onto a copper grid coated

with a supporting membrane. The grid was rendered hydrophilic by glow discharge and subsequently stained with an aqueous uranyl acetate solution. The prepared sample was imaged using a JEM-1400PLUS transmission electron microscope (JEOL, Showa City, Tokyo, Japan) at an accelerating voltage of 100 kV.

Western blot analysis

Total protein was from the samples and separated using a 10% SDS-PAGE gel (Beyotime, Shanghai, China). Following electrophoresis, proteins were transferred onto polyvinylidene fluoride membranes. Membranes were blocked with 5% bovine serum albumin in Tris-buffered saline containing 0.1% Tween-20 (Beyotime) for 1 h at room temperature under gentle agitation. The membranes were then incubated overnight at 4°C with primary antibodies diluted 1:1000 in blocking buffer. After three washes with 0.1% Tween-20, membranes were incubated with HRP-conjugated secondary antibodies for 1 h at room temperature. Signals were developed using the BeyoECL Star-enhanced chemiluminescence substrate (Beyotime). Primary antibodies used for Western blotting are listed in Table 1.

Particle size detection and counting

A $50 \mu\text{L}$ suspension of MSC-Exo was analyzed for particle size distribution and particle concentration using a NanoFCM instrument (Xiamen, Fujian, China).

Animal studies

Male C57BL/6 mice (42 days old, weighing 18–22 g) were purchased from GemPharmatech (Jiangsu, China) and acclimatized for one week before experimentation. Following baseline body weight measurement, mice were randomly housed. A $2 \times 3 \text{ cm}$ rectangular area on the dorsal skin was depilated using depilatory cream 1 day before treatment initiation. The mice received daily intraperitoneal injections of 2 mg/kg DHT; Solarbio, Beijing, China) dissolved in corn oil. Body weight was recorded daily throughout the experiment.

Photographs of each mouse were taken under standardized conditions using a fixed camera angle in a controlled table-top photo studio. All images underwent blind evaluation by five independent observers and were subjected to grayscale image analysis using ImageJ (NIH, USA). Statistical analyses were performed using Prism 8 (GraphPad Software, San Diego, CA, USA).

Mice were anesthetized using isoflurane delivered through a precision vaporizer system (RWD R540SS), with 5% isoflurane used for induction and 1–2% for maintenance. The anesthetic mixture (30% oxygen with isoflurane) was administered at a flow rate of 0.18–0.22 L/min, confirmed using an FL-201 flowmeter. Terminal

Table 1 Antibodies used in Western Blot and IF

Name	Brand	Item no
smooth muscle actin Polyclonal antibody	Proteintech(CHI,USA)	14395-1-AP
LEF1 Polyclonal antibody	Proteintech(CHI,USA)	14972-1-AP
Exosome panel (Calnexin,CD9,CD63,CD81,Hsp70,TSG101)	Abcam(USA)	ab275018
β-Catenin Rabbit pAb	ABclonal(Wuhan, China)	A0316
Mouse Anti-phospho-AKT(Ser473)antibody	Bioss(USA)	bsm-33281m
Bcl-2 Antibody	MCE(NJ,USA)	HY-P80029
PERK Antibody	MCE(NJ,USA)	HY-P80781
AKT1/AKT2/AKT3 Antibody (YA635)	MCE(NJ,USA)	HY-P80535
ERK1/2 Antibody	MCE(NJ,USA)	HY-P80393
c-Myc Antibody	MCE(NJ,USA)	HY-P80626
Cyclin D1 Antibody (YA485)	MCE(NJ,USA)	HY-P80098
c-Jun Antibody	MCE(NJ,USA)	HY-P80084
PERK Antibody	MCE(NJ,USA)	HY-P80781
c-Met (Cytoplasmic) Polyclonal antibody	Proteintech(CHI,USA)	25869-1-AP
Cytokeratin 15 Polyclonal Antibody	Thermo Fisher(Waltham, MA,USA)	PA5-82854

procedures were conducted under deep anesthesia by cervical dislocation in accordance with the 2020 AVMA Guidelines for the Euthanasia of Animals. Isoflurane concentration was consistently maintained at $1.5 \pm 0.2\%$ using the RWD isoflurane vaporizer (Cat. No. R51022).

Histological assessments

Harvested dorsal skin tissues were immediately fixed in 4% paraformaldehyde or flash-frozen in liquid nitrogen. Tissue clearing was performed using the BeyoCUBIC™ Animal Tissue Optical Clearing Kit (Beyotime) to enable visualization of hair follicle structures.

For histopathological analysis, formalin-fixed tissues were embedded in paraffin and sectioned. Hematoxylin and eosin staining were used to assess general tissue morphology. Frozen sections were immunostained with specific primary antibodies (listed in Table 2) following fixation. Fluorescently labeled secondary antibodies targeting the Fc region of the primary antibodies were used for detection. Fluorescence images were acquired and analyzed using CaseViewer software.

RNA sequencing

hDPCs were treated with 40 µg/mL MSC-Exo for 24 h. RNA was extracted from three biological replicates per group (treated and controlled) and submitted to TIAN-GEN (Beijing, China) for quality control, library preparation, and high-throughput sequencing on an Illumina platform. Transcriptomic data were aligned to a reference genome, and differentially expressed transcripts were identified. Gene Ontology (GO) enrichment analyses were conducted for biological processes and cellular components. Pathway enrichment was evaluated using

the Kyoto Encyclopedia of Genes and Genomes database and Gene Set Enrichment Analysis.

CCK8 analysis

Cell proliferation was assessed using the EnoGene-Cell™ Counting Kit-8 (CCK-8; Shanghai, China) according to the manufacturer's instructions. Each experimental group was tested in triplicate. Following a 24 h incubation period, 10 µL of EnoGeneCell™ Counting Kit-8 reagent was added to each well, and the plates were incubated at 37 °C for an additional 4 h. Absorbance was measured at 450 nm using a microplate reader. The cell proliferation rate was calculated using the following formula: Cell viability (%) = $(OD_{\text{sample}} - OD_{\text{blank}}) / (OD_{\text{control}} - OD_{\text{blank}}) \times 100\%$

Scratch wound assay

Cell migration following MSC-Exo treatment of hDPCs was evaluated using a scratch wound healing assay. hDPCs were seeded into 6-well plates at a density sufficient to reach 100% confluence by the following day. A sterile 200 µL pipette tip was used to create a straight scratch perpendicular to the reference grid lines on the underside of the plate. Images of the wound area were captured at 0 h and 24 h to assess the extent of cell migration.

Enzyme-linked immunosorbent assay (ELISA)

VEGF secretion levels in cell culture supernatants were quantified using the QuantiCyto® Human VEGF ELISA Kit (NeoBioscience, Shanghai, China) according to the manufacturer's instructions.

Table 2 Primer list of real-time PCR and digital PCR

Primer	Sequence(5'–3')
GAPDH	F: ACAACAGCCTCAAGATCATCAGCAAT R: GTCCTTCCACGATACCAAAGTTGTCA
VEGF	F: GGAAACCGACAAACCC R: AATCCCCAAAGCACAGC
IGF-1	F: GATGCTCTTCAGTTCGTGTG R: CAATACATCTCCAGCCTCCT
TGF-β	F: ACCACACCGCCCTGTTC R: CGTCAGCACCAGTAGCCA
LEF-1	F: AATAAGTGCCCGTGGTG R: ATGCCTTGTGTGAGTTGA
c-MET	F: CCCACCTTTGTTCAG R: GCCTTGCCCTCCTTCA
c-JUN	F: CCCACCCAGTTCCTGT R: GAAGCCCTCTGCTCATCT
Cyclin D1	F: AGAGCGGAGGAGAACA R: GAGAGGAAGCGTGTGAGG
c-MYC	F: CAGATCAGCAACAACCGA R: CGCCTCTTGACATTCTCC
β-catenin	F: CTGCCATCTGTGCTCTT R: TCTCTGCTTCTTGGTGTCTG
SMAD2	F: TGAGAAAGCCATCAAGAGA R: GGAGACGACCATCAAGAGA
SMAD3	F: ACGAGCAAACCCAGAGG R: TTAAGCCACCAGAGCAGAC
GSK3A	F: CCCATCTCAAGGCTCTC R: GGTTCACGACATCGCA
GSK3B	F: CCGCTTCCCTTCTTCATT R: TTTCCCTCCCTTCTCT
hsa-let7b-5p	F: CAC GCATGAGGTAGTAGG R:CCA GTG CAG GGT CCG AGG TA
hsa-miR-23a-3p	F: GCGGTCATCATTGCCAG R:TATGCTTGTTACGACACCTTCAC
hsa-miR-25-3p	F: AGCCGCATTGCACCTGTCT R:TATGGTTGTTACGACTCCTTCAC
hsa-miR-1246	F: CAGATGCGTAATGGATTTTGG R:TATGGTTGTTACGACTCCTTCAC
hsa-miR-21	F: TCGCCCGTAGCTTATCAGACT R:CAGAGCAGGGTCCGAGGTA
hsa-miR-130a	F: CGATGCTCTCAGTGCAATGTTA R:TATGGTTGTCTGCTCTCTGTCTC
hsa-let-7b	F: CGTGCTGTGAGGTAGTAGTTGT R:TATGGTTGTTACGACTCCTTCAC
hsa-let-7a	F: GCCGCTGAGGTAGTAGTTGTA R:CAGAGCAGGGTCCGAGGTA

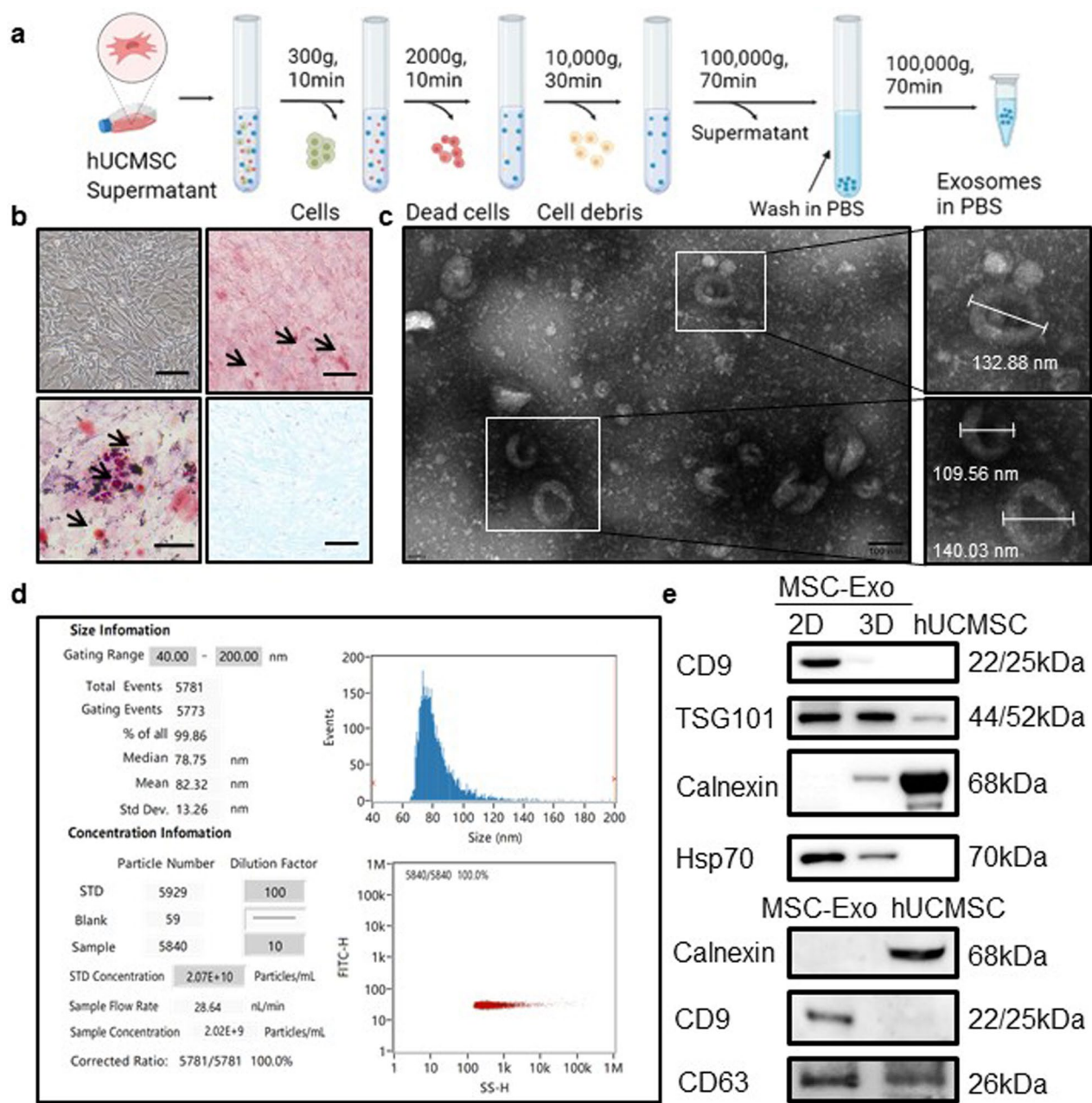
Quantitative real-time polymerase chain reaction (qPCR)
Total RNA was extracted from hDPCs using the EasyPure RNA Kit (TransGen, Beijing, China). First-strand cDNA synthesis was carried out using the ReverTra RT Master Mix (Toyobo, Osaka, Japan). qPCR was performed using Hieff® qPCR SYBR Green Master Mix (Yeasten, Shanghai, China), with cDNA as the template, to determine the relative mRNA expressions of target genes. Each sample was analyzed in triplicate. Gene expression was

quantified using the $2^{-\Delta\Delta CT}$ method. Primer sequences (Rui Biotech, Beijing, China) are listed in Table 2.

Digital polymerase chain reaction (PCR)
To isolate microRNAs, 200 μL of MSC-Exo was processed using the miRNeasy Serum/Plasma Kit (QIAGEN, Shanghai, China) following the manufacturer’s protocol. The extracted RNA was eluted with 20 μL of DEPC-treated water, heated at 95 °C for 5 min, and immediately placed on ice to preserve RNA integrity. Reverse transcription was conducted using M-MLV Reverse Transcriptase (Tagmine Biotech, Beijing, China). Serial dilutions of the cDNA were prepared and analyzed using the QIAcuity Digital PCR System (QIAGEN, model QIAcuity-00683).

Statistical analysis
All statistical analyses were performed using GraphPad Prism software (GraphPad Software, San Diego). Unless otherwise specified, comparisons between groups were conducted using two-tailed unpaired Student’s t-tests. Quantitative data from three independent biological replicates were expressed as mean ± standard deviation (SD). Statistical significance was defined as $p < 0.05$.

Results
hUCMSCs culture and exosome identification
Exosomes were isolated from the conditioned medium of hUCMSCs as outlined in the experimental workflow depicted in Fig. 1a. The morphological assessment confirmed that hUCMSCs retained their characteristic spindle-shaped appearance and exhibited robust trilineage differentiation potential, confirming their multipotency (Fig. 1b) [1, 2]. Transmission electron microscopy revealed abundant exosomes displaying typical biconcave disc shapes with diameters ranging from 100 to 130 nm, averaging 115 ± 15 nm, and a concentration of approximately 20 μg/mL (Fig. 1c). These dimensions fall within the widely accepted size range of 40–160 nm for cellular exosomes[3]. Nanoflow cytometry (Nano FCM) further characterized these vesicles, demonstrating a prominent size distribution peak centered around 80 nm (Fig. 1d). Notably, exosomes derived from hUCMSCs cultured under three-dimensional (3D) conditions exhibited superior yield and growth characteristics than those obtained from conventional two-dimensional cultures [4]. Therefore, exosome isolation and comprehensive characterization were also performed on vesicles derived from 3D-cultured hUCMSCs. Western blot analysis confirmed the absence of Calnexin—a molecular chaperone absent from exosomes—while exosomal markers CD9, CD63, Tsg101, and the conserved chaperone Hsp70 were



consistently expressed, validating the purity and identity of the isolated exosomes (Fig. 1e).

MSC-exo mitigates DHT-induced hair growth inhibition in an AGA mouse model

DHT binds androgen receptors with approximately five-fold greater affinity than testosterone and exhibits tenfold higher potency in receptor activation [5, 6, 9]. Elevated local DHT concentrations on the scalp are implicated as a principal driver of AGA pathogenesis. To investigate the therapeutic potential of MSC-Exo against AGA, we established a murine model by administering daily subcutaneous DHT injections, as illustrated in Fig. 2a. Hair regrowth on the dorsal skin was evaluated using a validated scoring system (Fig. 2b) [7]. Throughout the study period, mice remained in good health with stable body weights, and no significant differences were observed between the DHT-treated and wild-type cohorts (Fig. 2c). By day 7—corresponding to the first postnatal hair growth cycle—DHT-treated mice exhibited clear suppression of hair regrowth compared to controls (Fig. 2d). Moreover, DHT administration significantly delayed the hair cycle progression, with measurable effects evident as early as day 3 post-treatment initiation (Fig. 2e). To ensure consistent monitoring, standardized photographic settings were employed to capture the dorsal region of each mouse throughout the experimental timeline. Strikingly, 7 days after MSC-Exo treatment, the dorsal skin of treated mice displayed pigmentation and hair density resembling wild-type animals, in stark contrast to untreated DHT mice (Fig. 2f). Quantitative hair coverage analysis revealed that MSC-Exo treatment significantly improved hair regrowth compared to the 5% minoxidil group, which served as a positive control. Notably, the hair restoration effect of MSC-Exo approached that of wild-type mice, underscoring its therapeutic potential in mitigating DHT-induced hair growth retardation (Fig. 2g).

MSC-Exo initiates the early behavior of hair follicle growth

AGA is characterized by alterations in the hair cycle, progressive miniaturization of hair follicles, and

localized inflammatory infiltration. As the anagen phase shortens, hair growth becomes insufficient for hairs to emerge above the skin surface [8]. The hair growth cycle is schematically represented in Fig. 3a. In a study utilizing 7-week-old mice, the telogen phase followed the initial hair growth cycle; however, subsequent cycles were delayed under continuous DHT administration, resulting in disrupted hair regeneration. The dorsal skin condition of mice during treatment is shown in Fig. 3b. Wild-type mice exhibited 2–3 robust hairs per follicle, whereas these were largely absent in the AGA model. In contrast, mice receiving MSC-Exo treatment demonstrated well-formed hair follicles with healthy hairs fully penetrating the epidermis.

Histological analysis of skin tissue sections harvested on day 15 post-treatment revealed marked differences among groups (Fig. 3c, d). Hair follicles in the MSC-Exo-treated group retained complete structural integrity, with follicle depths comparable to those observed in wild-type mice. Moreover, hair follicles were open at the epidermal surface, allowing the emergence of healthy hairs, and the previously noted follicular atrophy was notably reversed. Previous studies have shown that β -catenin promotes new hair follicle formation independent of follicular stem cells [13, 14]. However, in our model, MSC-Exo treatment did not increase the total number of hair follicles, as evidenced by hematoxylin and eosin (HE) staining. These findings suggest that MSC-Exo facilitates hair restoration primarily by enhancing the architecture and function of existing follicles rather than by inducing de novo follicle formation.

Cytokeratin 15 (keratin 15) serves as a marker for epithelial stem cells residing in the bulge region of both human and murine hair follicles [13–15]. Throughout the experiment, fluorescence intensity and spatial distribution of keratin 15 remained consistent across all groups, indicating no significant alteration in the stem cell compartment. Additionally, an increase in hair follicle papilla diameter correlates with approximately a two-fold increase in papilla cell numbers. MSC-Exo treatment significantly promoted follicular enlargement, suggesting

(See figure on next page.)

Fig. 2 MSC-Exo treatment effectively restores hair growth in AGA mice. **a** Schematic depiction of the method for establishing an AGA mouse model by DHT injection. **b** The scoring criteria for hair growth level on the back of mice. **c** The trend of mouse body weight changes. **d** An overview of hair growth in the observation area on the back of wild-type and AGA mice. **e** Scores of hair growth in the observation area on the back of wild-type and AGA mice. **f** Representative appearance of hair growth on the back of AGA mice treated with different treatment methods, $n=5$ mice/group. The wild-type group was left untreated, whereas the other three groups were administered daily subcutaneous injections of DHT in the posterior triangle area of the neck. Meanwhile, the exosome treatment group was administered a daily topical application of MSC-Exo. **g** Hair coverage rate. The gray value of the back skin color was statistically analyzed, and day 0 corresponded to the initial value. ImageJ was applied for unified standard gray value analysis of the hairless area on the back of the mice. Each bar represents the mean $\pm$ s.d. for triplicate experiments, $**p \leq 0.005$, $****p \leq 0.0001$

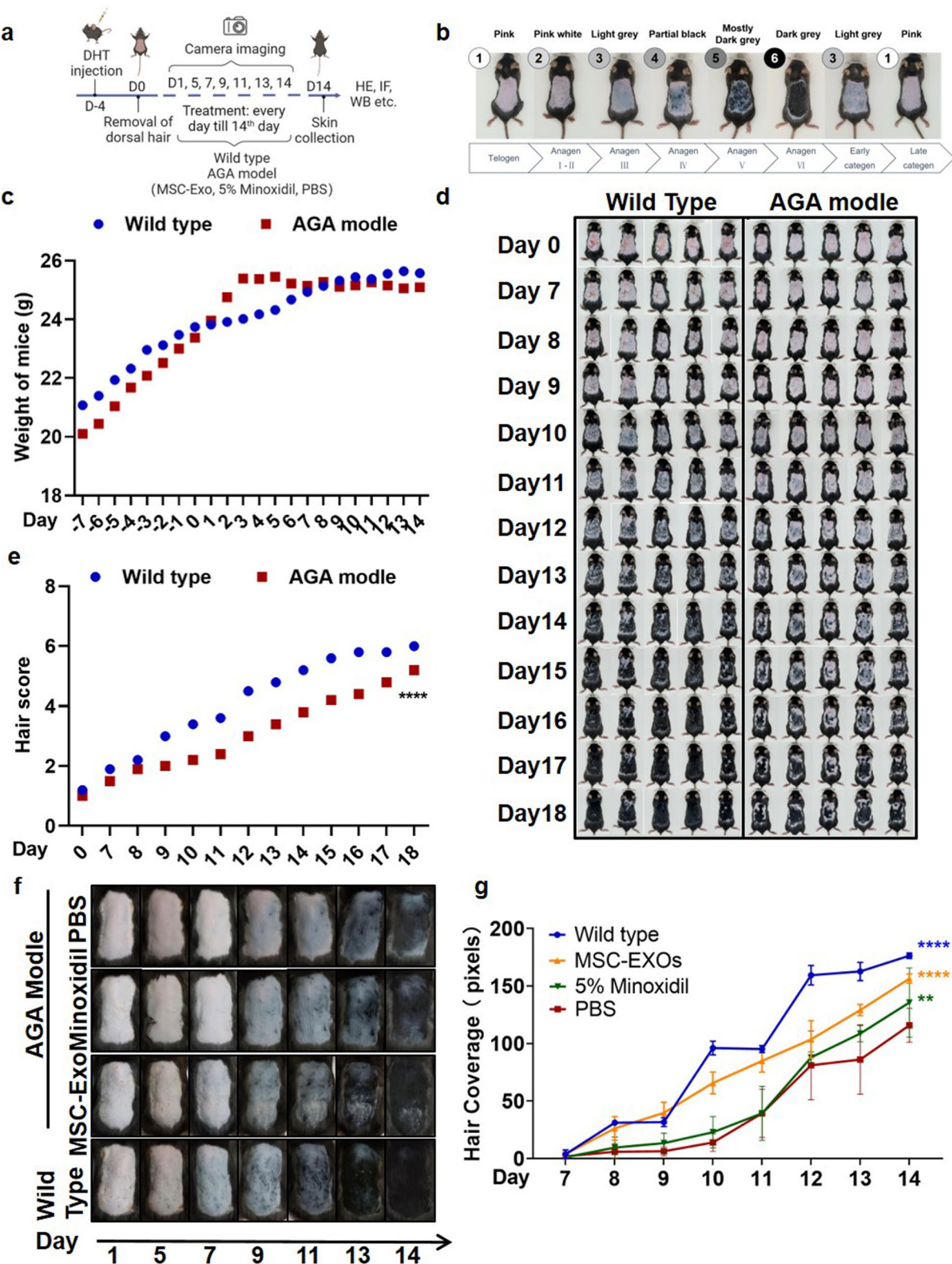


Fig. 2 (See legend on previous page.)

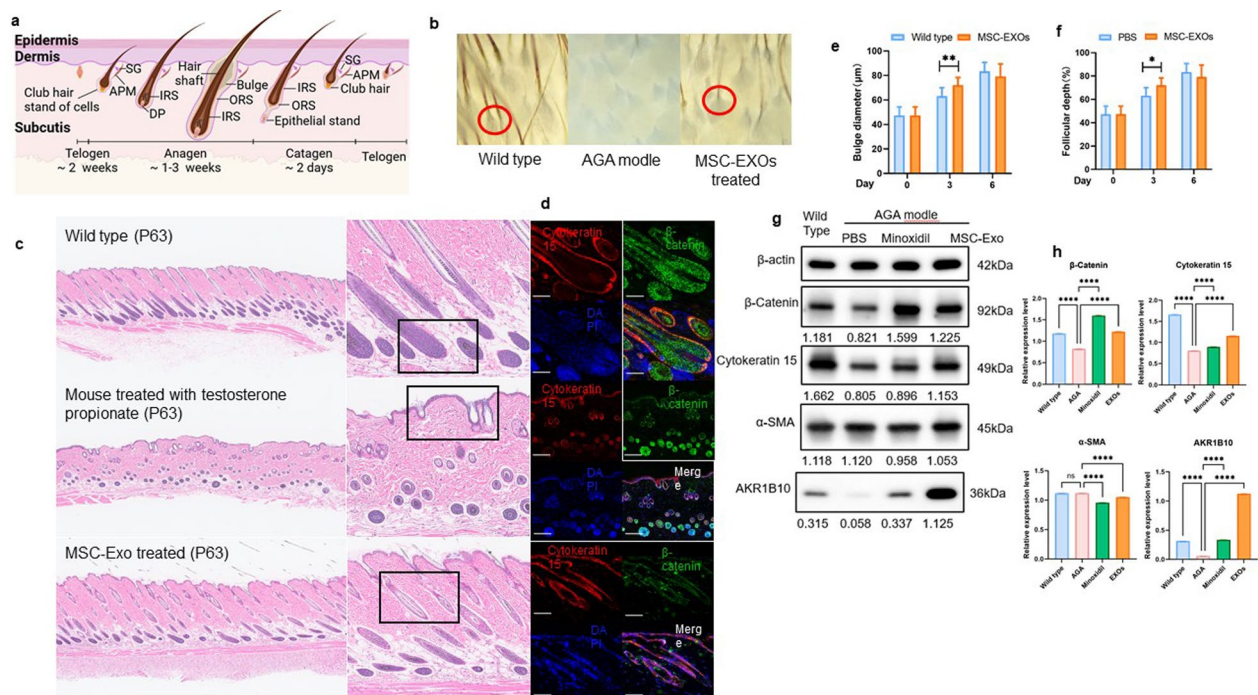


Fig. 3 Histological and WB analysis of AGA mouse skin. **a** Schematic depiction of the hair growth cycle. **b** Transparent visualization of mouse skin tissues under a dissecting microscope. The red circle marks the hair follicle opening on the skin surface, $n = 5$ mice/group, Scale bar: 20 μm . **c** HE and immunofluorescence staining of the mouse skin. HE images of each group (left panel) are whole-view HE images of the skin under $5\times$ magnification, displaying the relative position and development of hair follicles and skin structure; (middle panel) representative views under $63\times$ magnification, demonstrating the structure of hair follicles and the development of hair shafts; black boxes mark the classical characteristics of hair follicles, $n = 5$ mice/group. **d** Immunofluorescence staining of the hair follicle structure. Nuclei are stained with DAPI (blue). Cytokeratin 15 marks keratin (red), indicating the structure of the hair root sheath. β -catenin (green) is a characteristic protein of hair growth. White scale bar: 200 μm . **e** Statistics of the diameter of the hair follicle bulge. The maximum diameter of the bulge of hair follicles in at least 5 HE-stained views from different mice in the same group was randomly selected, detected, and statistically analyzed. Student's t -test was applied to analyze the difference. **f** Statistics of hair follicle depth. The depth of the bottom of the hair follicle to the epidermis layer, and the percentage of the total depth of the epidermis to the dermis layer were randomly selected for at least 5 HE-stained views of the back skin from different mice in the same group and detected and calculated. Student's t -test was applied to analyze the difference. **g** Western blotting of mouse skin tissues. The grayscale statistical results are shown in **h**. Each bar represents the mean $\pm$ s.d. for triplicate experiments, $*p \leq 0.05$, $**p \leq 0.005$. Full-length blots/gels are presented in Supplementary Fig. 2

enhanced cellular proliferation associated with hair growth stimulation.

Figure 3f illustrates early-stage changes in follicle depth within the skin structure between days 3 and 6. By day 3, the distance from the follicle base to the dermal layer in the treated group significantly differed from that in untreated controls, indicating accelerated follicular remodeling. Western blot analysis of mouse skin further demonstrated that β -catenin protein levels were substantially reduced in the AGA model relative to wild-type controls. Treatment with either minoxidil or MSC-Exo effectively restored β -catenin expression to near-normal levels. In contrast, α -smooth muscle actin (α -SMA) levels showed no significant variation between wild-type and model groups. Furthermore, keratin 15 protein expression, which was markedly diminished in all AGA model groups, showed the most pronounced recovery following

MSC-Exo treatment, underscoring its restorative effects on follicular keratinocyte health.

MSC-exo regulates the ECM ((extracellular matrix, ECM) of hDPCs and indirectly promotes cell differentiation

MSC-Exo exerts its regulatory influence on target cells predominantly through paracrine signaling mechanisms [10, 11]. Given the critical role of hDPCs in modulating the hair follicle growth cycle, we focused our investigation on the transcriptomic alterations in hDPCs following MSC-Exo treatment. Using RNA sequencing and differential expression analysis of long non-coding RNAs (lncRNAs) at 24 h post-treatment, we aimed to elucidate the early regulatory responses of hDPCs mediated by MSC-Exo. Applying stringent criteria of $\log_2\text{FC} > 2.0$ and $P < 0.05$, a total of 974 differentially expressed lncRNAs were identified between the extracellular vesicle-treated

and control groups, comprising 495 upregulated and 479 downregulated transcripts. The hierarchical clustering heatmap illustrating these expression patterns is shown in Fig. 4a, while Fig. 4b presents a bubble plot highlighting the top 20 significantly enriched pathways. Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis revealed significant downregulation of the ECM–receptor interaction pathway, consistent with the extensive structural remodeling observed in the dermal components of hair follicles during the germinal phase. This was accompanied by enrichment in pathways related to protein digestion and absorption. The Notch signaling pathway, known to critically regulate hair follicle germination and maintain stemness of follicular stem cells—particularly via NOTCH3—was also downregulated, suggesting a shift towards cellular differentiation. Conversely, the TGF- β signaling pathway, which is typically growth-inhibitory, showed reduced activity, indicating that treated hDPCs adopted features consistent with proliferative or growth phases.

For lncRNA characterization, transcript lengths were compared with annotated human transcripts, focusing on coding potential (Fig. 4c). The majority of identified lncRNAs ranged between 100 and 500 base pairs in length (Fig. 4d). Applying the same differential expression thresholds ($\log_2\text{FC} > 2.0$, $P < 0.05$), 12 lncRNAs exhibited significant regulation following MSC-Exo treatment—5

upregulated and 7 downregulated. These common differentially expressed lncRNAs are illustrated in heatmaps and volcano plots (Fig. 4e, f).

GO enrichment analysis of lncRNA target genes, visualized as directed acyclic graphs, highlighted significant terms such as serine endopeptidase activity (GO:0021680) and positive regulation of mitogen-activated protein kinase activity (GO:0055091), implying a modulatory role of lncRNAs in regulating phosphorylation cascades within hDPCs (Supplementary Fig. S1A and S1B).

Collectively, these high-throughput data suggest that MSC-Exo initiates early regulatory effects on hDPCs by modulating ECM composition, activating phosphorylation-related signaling pathways, and stimulating secretion of differentiation-associated factors. The relatively modest differential expression observed may be attributable to the brief 24 h treatment window, reflecting early-stage cellular responses. The pronounced effects seen *in vivo* likely result from subsequent autocrine signaling within hDPCs following their initial activation by MSC-Exo.

MSC-exo activates Wnt pathway genes and upregulates GSK3A

MSC-Exo regulates hair growth primarily through modulation of Wnt-related signaling pathways [16–19]. To

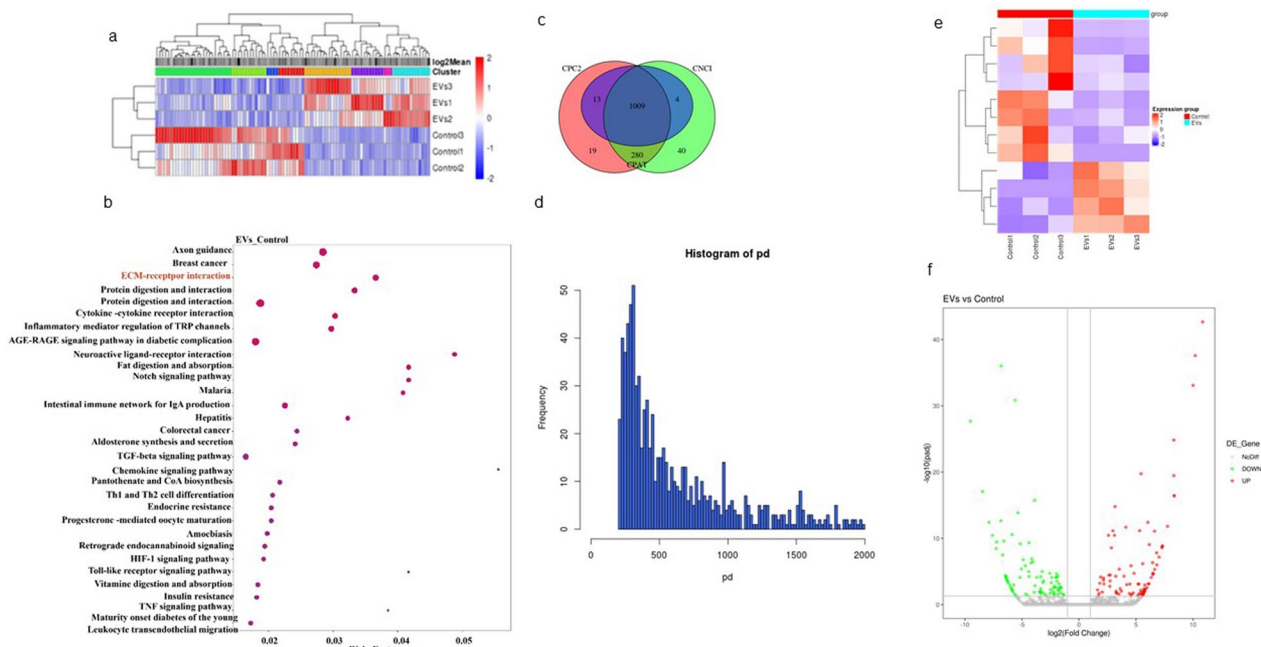


Fig. 4 RNA-Seq analysis of hDPCs. **a** Transcriptome analysis reveals distinct gene expression patterns in hDPCs cultured alone or with exosome supplementation. **b** The KEGG pathway analysis identified active signaling pathways in exosome-treated hDPCs, including ECM-receptor interaction and TGF- β signaling. **c** Venn diagram depicting the identification of valid lncRNAs. The overlapping lncRNAs were considered valid and underwent further analysis. **d** The distribution of lncRNA lengths. **e** lncRNA-seq heatmap. **f** Heatmap of differentially expressed lncRNAs

further elucidate the effects of MSC-Exo on hDPCs, we conducted a series of high-throughput and functional assays. DiI-labeled MSC-Exo were used to monitor their uptake by hDPCs after a 4 h incubation followed by medium replacement (Fig. 5a). Dose–response experiments revealed that increasing concentrations of MSC-Exo induced a corresponding, dose-dependent enhancement in hDPC proliferation, with maximal cell viability observed at 80 $\mu\text{g/mL}$ (Fig. 5b, c).

In wound healing assays, MSC-Exo facilitated scratch closure in a non-linear, concentration-dependent manner, peaking at 60 $\mu\text{g/mL}$ (Fig. 5d). After 24 h of treatment, MSC-Exo significantly decreased the expression of TGF- β —a known growth inhibitor—while markedly elevating levels of insulin-like growth factor (IGF) and vascular endothelial growth factor (VEGF) (Fig. 5e) [16]. These ELISA results confirmed a robust, dose-dependent increase in VEGF secretion (Fig. 5f). Gene expression analysis further demonstrated that MSC-Exo treatment upregulated components of the Wnt/ β -catenin pathway, including LEF1, while concurrently downregulating TGF- β 1 within the TGF- β /SMAD signaling axis. Interestingly, GSK3A expression was also elevated, indicating complex modulation of intracellular signaling cascades (Fig. 5g). Collectively, these data suggest that MSC-Exo stimulates hair follicle transition into the anagen phase by enhancing LEF1 expression and reshaping the autocrine secretory profile of hDPCs.

Key microRNAs in MSC-exo play a synergistic regulatory role on hDPCs

To explore the molecular mediators of these effects, phosphorylation levels of key signaling pathways—AKT and ERK—were evaluated via Western blot following MSC-Exo treatment. Although the p-AKT/AKT ratio showed a non-significant increase, phosphorylation of ERK (p-ERK/ERK ratio) was significantly and dose-dependently elevated (Fig. 6a), implicating ERK pathway activation in MSC-Exo-induced proliferation. Next, we performed absolute quantification by digital PCR of eight candidate microRNAs within MSC-Exo derived from hUCMSCs, focusing on those previously implicated in hair growth regulation [20]. This analysis revealed that miR-21-5p and let-7b-5p were present at levels over ten-fold higher than other microRNAs, identifying them as dominant regulatory components (Fig. 6b).

To delineate their functional roles, synthetic miR-21-5p and let-7b-5p were individually administered to hDPC cultures. Both microRNAs significantly upregulated the expression of proliferation and hair growth-associated genes Cyclin D1, c-MET, and LEF1, while simultaneously suppressing the expression of c-JUN. Notably, neither microRNA significantly affected c-Myc expression

(Fig. 6c). These results indicate that miR-21-5p and let-7b-5p act synergistically to modulate hDPC function.

Our data support a model whereby these key microRNAs coordinate to activate the Wnt/ β -catenin pathway through LEF1 upregulation, thereby enhancing the transcription of genes essential for hair regeneration. This effect is further potentiated by c-MET-mediated cross-talk that amplifies Wnt signaling. Crucially, the miRNAs exert a finely tuned regulatory balance—promoting cell proliferation via Cyclin D1 upregulation while maintaining c-Myc at basal levels to preserve microenvironmental homeostasis and prevent aberrant growth. The detailed molecular mechanisms underlying the synergistic regulation by miR-21-5p and let-7b-5p in hDPCs remain to be elucidated and warrant further investigation.

Discussion

Mesenchymal stem cells derived from hUCMSCs facilitate skin regeneration through multiple coordinated mechanisms, including modulation of inflammatory responses, promotion of a vascularized granulation matrix, enhancement of skin cell proliferation and migration, and inhibition of apoptosis [18]. MSC-Exo has demonstrated a capacity to accelerate epithelialization and stimulate skin cell growth effectively. In murine models of cutaneous injury, MSC-Exo reduces myofibroblast accumulation and attenuates scar formation via specific microRNA-mediated pathways, highlighting their anti-fibrotic potential [25]. By promoting the remodeling of the ECM, MSC-Exo mitigates excessive fibrotic scarring, thereby facilitating the restoration of functional epidermal tissue architecture.

Our current investigation extends these findings by demonstrating that MSC-Exo influences gene expression profiles associated with ECM regulation, which likely supports the dynamic extension and migration of hair follicles within the dermal layer. Interestingly, α -smooth muscle actin expression was comparable between wild-type and untreated model groups but significantly diminished in both MSC-Exo-treated groups. This reduction may correlate with the observed decrease in hair follicle density within treated mouse skin samples. Importantly, changes in hair growth dynamics corresponded with decreased intercellular fibrosis, suggesting a link between reduced fibrotic burden and hair follicle activation.

Keratin 15 (K15), a pivotal structural protein in epithelial cells that contributes to the integrity of skin and hair follicles, was markedly downregulated across all experimental modeling groups relative to wild-type controls. Notably, MSC-Exo administration elicited the most robust recovery of K15 expression, significantly surpassing levels observed in untreated models. This is consistent with the known biology of keratinocytes, wherein

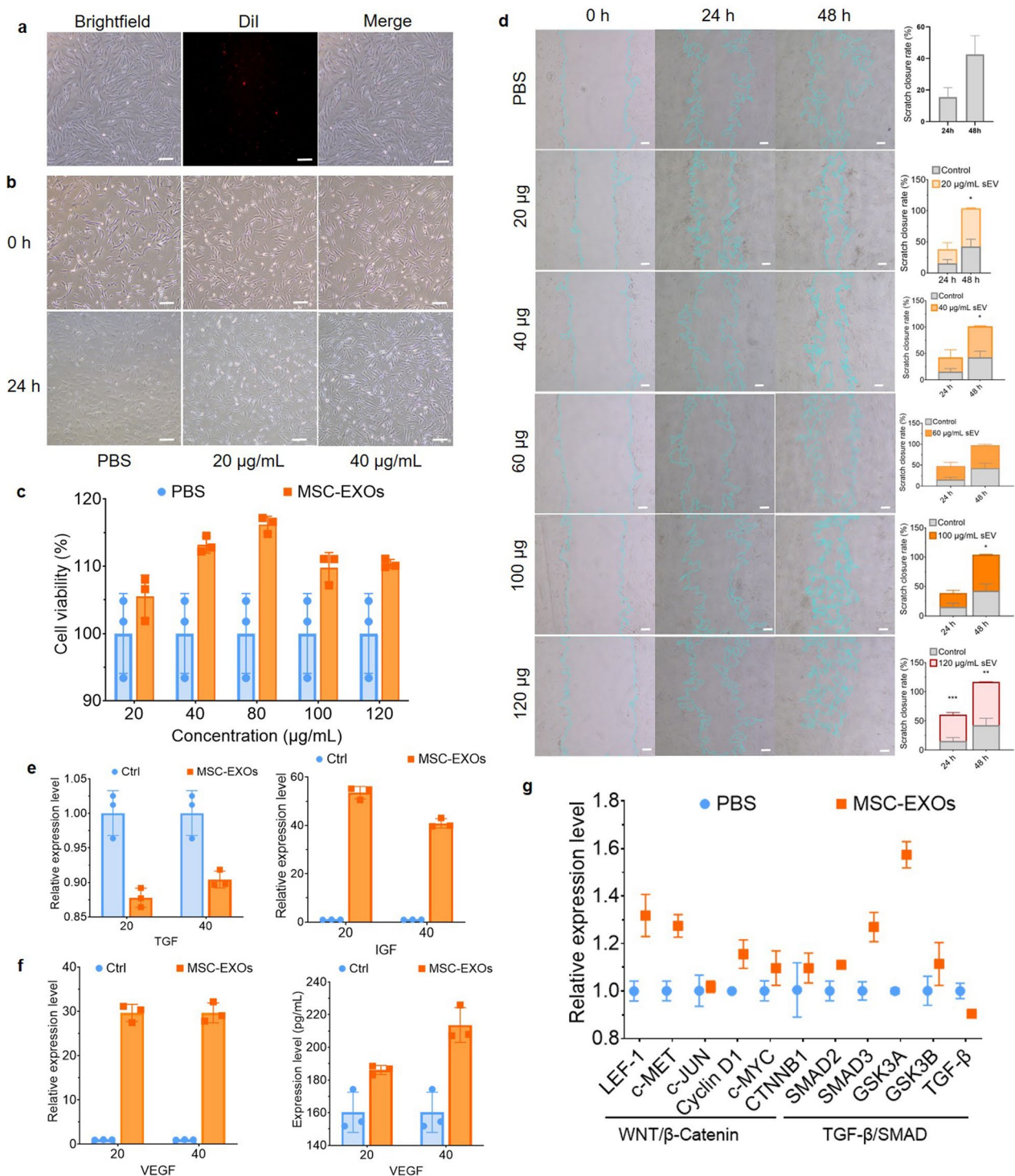


Fig. 5 MSC-Exo promotes hDPCs proliferation and regulate the expression of growth-related genes. **a** Schematic diagram of MSC-Exo treatment of DP cells. Bright-field fluorescence microscopy was used to observe the growth of hDPCs (left panel). Fluorescence field was applied to observe red-labeled Dil-stained MSC-Exo (middle panel), while the Merge image is on the right, Scale bar: 200 μ m. **b** Observation diagram of hDPCs proliferation treated with different concentrations of MSC-Exo, Scale bar: 200 μ m. **c** CCK8 assay to detect the proliferation ability of hDPCs treated with different concentrations. **d** Scratch healing assay exhibiting the migration ability of hDPCs under different treatments. The bar chart on the right shows the percentage of the scratch width at different time points with respect to the initial scratch width. Scale bar: 200 μ m. **e** Real-time PCR was performed to detect the mRNA expressions. **f** VEGF expression, Real-time PCR detection (left panel), and ELISA detection of hDPCs-secreted VEGF level. **g** Real-time PCR was performed to detect the mRNA expression of hDPCs after MSC-Exo treatment

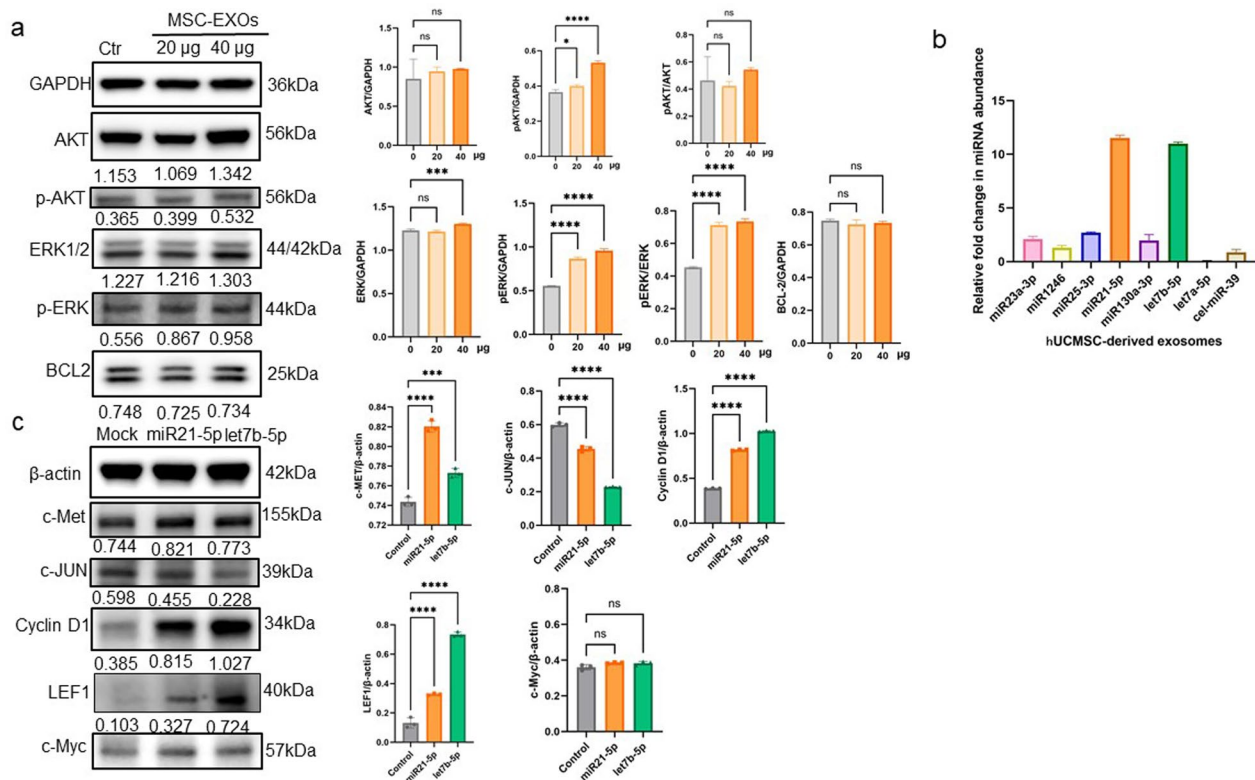


Fig. 6 Effect of MSC-Exo treatment on AKT phosphorylation in hDPCs. **a** The regulation of AKT and ERK pathways in hDPCs by MSC-Exo. **b** Absolute quantification of hair growth-associated microRNAs in exosomes using digital PCR (dPCR). **c** Modulation of hair follicle-related gene expression in hDPCs cells by synthetic microRNAs. Each bar represents the mean $\pm$ s.d. for triplicate experiments, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, n.s., no significance. Full-length blots/gels are presented in Supplementary Fig. 3

K15 is downregulated as hair follicles enter growth phases and keratinocytes migrate out of the basal layer [16]. The regulation of genes related to hair follicle architecture and skin microenvironment by MSC-Exo appears to be multifaceted and bidirectional; MSC-Exo promotes an initial phase of controlled cellular proliferation and differentiation but subsequently, temper gene activation to prevent excessive repair responses, thereby maintaining tissue homeostasis.

hDPCs contribute to dermal sheath formation and generate non-follicular fibroblasts critical for skin regeneration and wound healing, with a demonstrated ability to induce hair follicle neogenesis [16–18]. However, hDPC functionality is highly context-dependent. In the present study, expression of the anti-apoptotic marker BCL2 remained stable within hDPCs, consistent with its established role in maintaining hair follicle cell survival throughout the hair cycle [12–14]. MSC-Exo treatment enhanced ERK pathway phosphorylation, promoting differentiation of hDPCs. Conversely, high doses of MSC-Exo reduced AKT phosphorylation, correlating with decreased cellular proliferation. This effect likely involves the microRNA let-7b-5p, which is known to modulate

key signaling pathways governing proliferation and differentiation.

An increase in GSK3A activity in hDPCs was observed following MSC-Exo exposure, potentiating negative regulation of downstream Wnt signaling phosphorylation events and contributing to decreased p-AKT levels [15, 16]. This gene expression shift favors initiation of differentiation programs over continued proliferation, resulting in moderate enlargement of the hair follicle bulge and subsequent elongation of the hair shaft. Beyond these direct intracellular effects, MSC-Exo exerts important paracrine and endocrine-level regulation on hDPC function. Similar to minoxidil—which induces VEGF secretion in cultured hDPCs—MSC-Exo treatment elicited a significant increase in VEGF levels alongside a reduction in TGF- β 1 expression, further supporting a pro-angiogenic and regenerative microenvironment [17].

Due to their lipid bilayer membrane structure, MSC-Exo delivers potent but transient signals to adjacent cells, directly activating and modulating hDPC behavior. This positions MSC-Exo as an early initiators of hair follicle regeneration. Furthermore, MSC-Exo orchestrates changes in the secretory profile of hDPCs, which is

crucial for sustaining hair growth during the mid-to-late anagen phase of the hair cycle. Despite these promising findings, the mechanistic insights and therapeutic implications of MSC-Exo in AGA remain preliminary. Comprehensive animal studies are required to delineate the precise molecular pathways and multifactorial regulatory networks underlying hair regeneration and cyclic follicular changes in AGA.

Conclusions

Exosomes derived from hUCMSCs promote the proliferation and migration of hDPCs primarily via activation of the Wnt/ β -catenin signaling pathway, resulting in enhanced hair shaft regrowth in an AGA mouse model. These results identify MSC-Exo as a promising therapeutic agent and novel target for the treatment of androgen-dependent alopecia.

ARRIVE checklist

The work has been reported in line with the ARRIVE guidelines 2.0.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13287-025-04538-5>.

Additional file 1.
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Additional file 3.
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Author contributions

Conceptualization: Yujun Zhang and Aiqing Yu. Data curation: Yujun Zhang, Zhizhen Yang, Saifeng Zhong. Formal analysis: Yujun Zhang, Saifeng Zhong, Zhizhen Yang, and Mingming Xie. Investigation: Yujun Zhang, Saifeng Zhong, and Zhizhen Yang. Methodology: Yujun Zhang, Saifeng Zhong, and Zhizhen Yang. Project administration: Yujun Zhang and Aiqing Yu. Resources: Yujun Zhang and Aiqing Yu. Supervision: Mingming Xie and Aiqing Yu. Validation: Yujun Zhang, Saifeng Zhong, and Zhizhen Yang. Visualization: Yujun Zhang, Saifeng Zhong, and Zhizhen Yang. Writing -original draft: Yujun Zhang, Saifeng Zhong, and Mingming Xie. Writing-review & editing: Yujun Zhang, Aiqing Yu, and Mingming Xie.

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Data availability

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Declarations

Ethics approval and consent to participate

All experiments involving the handling of mice or murine tissues were approved by the Animal Ethics Committee of the Hubei University of Medicine (Approval No: HMC-AEC-2024-112 HMC-AEC-(experiments)2024-112, Title of the approved project: Aging & Regeneration Research Project, Date of approval: September 2, 2024). No human studies are involved in this study.

Competing interests

There are no financial conflicts of interest to disclose.

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