

The Roles of Exosomes in Regulating Hair Follicle Growth

Ming Cheng ^{1,2}, Cong Ma ¹⁻³, Hong-Duo Chen ^{1,2}, Yan Wu ^{1,2}, Xue-Gang Xu ^{1,2}

¹Department of Dermatology, The First Hospital of China Medical University, Shenyang, 110000, People's Republic of China; ²Key Laboratory of Immunodermatology, Ministry of Education and NHC; National Joint Engineering Research Center for Theranostics of Immunological Skin Diseases, Shenyang, 110000, People's Republic of China; ³Department of Dermatology and Sexually Transmitted Diseases, The First Hospital of Inner Mongolia University for Nationalities, Tongliao, 028000, People's Republic of China

Correspondence: Xue-Gang Xu; Yan Wu, Department of Dermatology, The First Hospital of China Medical University, Shenyang, 110000, People's Republic of China, Email xuxuegang2749290@163.com; jlwuyan@126.com

Abstract: Alopecia is considered a widespread yet troubling health issue, with limited treatment options. As membranous structures derived from cells carrying proteins, nucleic acids and lipids, exosomes functionally mediate intercellular communication and alter the responses of recipient cells, resulting in disease restraint or promotion. Exosomes have broad prospects in diagnosis and treatment of diseases. Studies using animal models and at the cellular level have clearly shown that exosomes from several types of cells, including dermal papilla cells and mesenchymal stem cells, have a notable capacity to promote hair growth, suggesting that exosomes may provide a new option to treat alopecia. Here, we present a thorough review of the most recent progress in the application of exosomes to hair growth.

Keywords: exosome, hair follicle, alopecia

Introduction

Alopecia is considered a widespread yet troubling health issue, which could be categorized primarily into nonscarring (non-cicatricial) alopecia and scarring (cicatricial) alopecia.¹ Clinically, the most prevalent forms of alopecia are androgenetic alopecia (AGA) and alopecia areata (AA).¹ AGA impacts 70% of males and 50% of females by 50 years old,¹ with AA's lifetime occurrence around 2% globally.^{2,3} As a common disease, alopecia affects not only patients' appearance, but also their psychosocial and social health. However, treatment options for alopecia are limited. Currently, therapies for AGA approved by the FDA encompass topical minoxidil, oral finasteride, and low-level light therapy.⁴ Options for AA include topical and intralesional corticosteroids, contact immunotherapy, topical minoxidil, phototherapy, and oral Janus kinase (JAK) inhibitors,^{1,5-9} none of which has been approved by the FDA.

Exosomes, which are membranous structures derived by cells carrying proteins, nucleic acids and lipids, have an essential function in facilitating intercellular communication and altering response of recipient cells with a result of disease restraining or promoting.¹⁰ Exosomes are also associated with immune reactions, the advancement of cancer, the virulence of viruses, heart-related illnesses, disorders related to the central nervous system, and pregnancy.¹⁰ In addition, exosomes have broad prospects in diagnosis and treatment of diseases. Their intrinsic properties in regulating intracellular pathways have advanced their potential utility to treat many diseases, including cancer and neurodegenerative conditions.¹⁰ Additionally, they can be modified to transport therapeutic substances to specific targets, which have the advantages of high bioavailability and fewer adverse reactions.¹⁰ Furthermore, they have the potential to assist in disease diagnosis through liquid biopsies, owing to their presence in all biological fluids.¹⁰

Given their unique and newly discovered biological characteristics, exosomes have become a hot topic of intensive investigation. Recent studies have shown that exosomes promote hair growth, making them an innovative treatment choice for alopecia. Here, we present a thorough review of the latest advancements in using exosomes for hair growth.

What are Exosomes?

Extracellular vesicles (EVs), originating from cells, are membranous formations.¹¹ EVs allow the exchange of proteins, lipids, and nucleic acids among cells, serving as an extra method for cell-to-cell communication.¹¹ According to size and different biogenesis pathways, EVs can be divided into exosomes (50–150 nm), microvesicles (100–1000 nm), apoptotic bodies (100–5000 nm) and large oncosomes (1000–10,000 nm).¹²

Exosomes are generated by endocytosis and secreted by exocytosis of the plasma membrane.¹³ There are four phases involved in the biogenesis of exosomes: transporting cargo to multivesicular bodies (MVBs), creating MVB, transporting MVB, and merging MVB with the plasma membrane.¹³ When exosomes arrive at the recipient cell, they may interact with the surface molecules to induce subsequent signaling, merge with the plasma membrane to discharge their substances into the cytoplasm, or get internalized through various routes.¹⁴

In the laboratory, strategies of exosome separation include ultra-centrifugation, ultra-filtration, immunoaffinity capture, charge neutralization-based polymer precipitation, size-exclusion chromatograph, ion-exchange chromatograph, microfluidic techniques, and membrane-based isolation techniques, among which ultracentrifugation is the most preferred choice.^{15–17} The identification of exosomes involves examining their shape, particle dimensions and surface markers.¹⁸ Their microstructure could be characterized by transmission electron microscopy (TEM), scanning electron microscopy (SEM), cryo-electron microscopy and atomic force microscopy (AFM).¹⁸ Nano particle tracking analysis (NTA) and dynamic light scattering (DLS) could be used to assess the distribution of suspended particles.¹⁸ Generating from endosomes, all exosomes have identical membrane transport proteins and fusion proteins (Annexins, Flotillin, GTPases), MVB formation-related proteins (Alix, TSG101), heat shock proteins (Hsp20, Hsp60 and Hsp70), tetraspanins (CD9, CD63, CD81 and CD82), phospholipase and lipid-associated membrane proteins, which could be identified by Western blotting, trypsin digestion, mass spectrometry, ELISA analysis and flow cytometry.¹⁸ Exosomes normally could not be stored for a long period, and the current storage methods include freezing, freeze-drying and spray-drying, among which freezing at -80°C is considered as the best storage method.¹⁹

Hair Anatomy and Growth Cycle

Derived from the epidermis, hair comprises two distinct parts: a visible shaft on the skin's surface and a follicle within it (Figure 1).²⁰ Among the growth phase, the hair shaft (HS) has three primary concentric areas: the medulla, cortex and cuticle.²¹ The hair follicle (HF) has an essential role in hair growth,²⁰ forming a pilosebaceous unit alongside the sebaceous gland (SG) and arrector pili muscle (APM).²² The HF consists of three segments, which are lower, middle, and upper: the lower segment is the region from the base of the HF to the insertion of APM and could be divided into the bulb and suprabulb

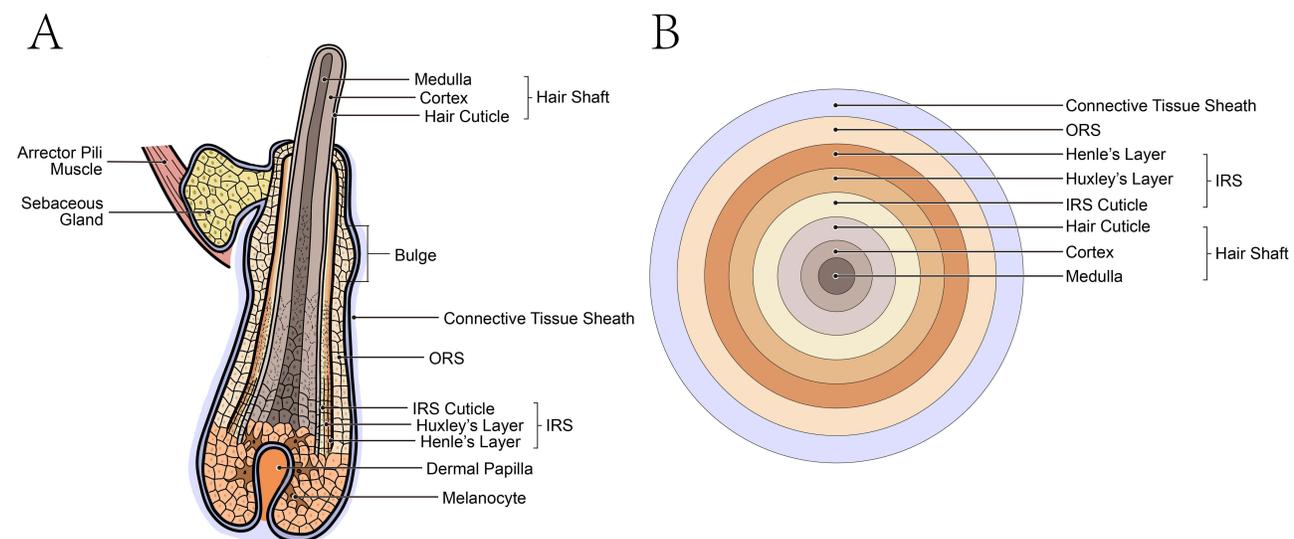


Figure 1 Hair anatomy. (A) A human scalp hair follicle (anagen). (B) The concentric layers of the hair follicle bulb.

Abbreviation: IRS, inner root sheath; ORS, outer root sheath.

regions; the middle segment (isthmus) is short and extends from the insertion of APM to the meatus of the SG duct; the upper segment (infundibulum) spans from the meatus of the SG duct to the follicular orifice.²¹ The suprabulb region lies between the isthmus and the hair bulb (HB), consisting of the HS, inner root sheath (IRS), outer root sheath (ORS), vitreous layer (VR) and fibrous root sheath (FRS).²¹ IRS has three layers: Henle's layer, Huxley's layer, and cuticle, the latter layer being adjacent to the cuticle of HS and thus anchors HS to HF.²⁰ The IRS acts as a divider between the HS and ORS.²⁰ The ORS shields the IRS while it rises from the matrix cells at the bottom side of the HB to the meatus of the SG duct.²¹ When the ORS arrives at the level of the infundibulum, the keratinization transforms into normal epidermal keratinization, accompanied by the development of the granular cell layer and the stratum corneum.²¹ The bulge region is densely populated with pluripotent cells, surrounded by the APM.²¹ It is believed that these stem cells located in the bulge have an essential role in generating new hair.²¹ The vitreous (glossy) layer forms an acellular, eosinophilic region surrounding the ORS and extending to the basement membrane of epidermis.²¹ The FRS is the external most layer of the HF and encases the VR, seamlessly extends to the dermal papilla (DP) and the papillary dermis above it, and comprises densely packed collagen bundles coating the entire HF.²¹ The HB is the part of the HF generating hair actively and encloses the follicular DP, DP cells (DPCs), mucopolysaccharide-rich stroma, nerve fibers, and a single capillary loop.²¹ The DP has an essential role in determining the size, shape, color and the frequency of hair regeneration.²³

Throughout the whole life process, the HF has regular growth cycles, which are mainly manifested by alterations in the DP's morphology and structure, development of new shaft and removal of aged hair.²⁴ The HF cycle could be divided into anagen, catagen and telogen: the anagen stage marks the peak of HF growth, characterized by swift hair growth and full HS formation, with the HF infiltrating the subcutaneous tissue; when the HF enters catagen, the HS halts growth, with reduced cell proliferation and differentiation capacity, cell apoptosis, and quick HF degeneration; after catagen, the HF undergoes telogen, leading to the HF's diminished biological activity and the HS reduction, alongside a significant rise in the expression and activity of the HF's regulatory factors for subsequent growth cycles.^{24,25} About 84% of scalp hairs in humans are in the anagen phase, 1% to 2% in catagen, and 10% to 15% in telogen.²¹ DPCs have an essential role in activating the hair follicle stem cells (HFSCs) and initiating new hair cycles: during telogen, DPCs move to the lower region of HB and thus interact with HFSCs in HB directly; HFSCs proliferate after activation, the amount of which arrives at a pivotal value, and the next anagen stage starts.^{24,25} The regeneration of the HF is closely associated with the turnover of the whole skin, and it is believed that HFSCs are at the center of this dynamic process.²⁶ The behavior of HFSCs is choreographed by complicated intrinsic and extrinsic signaling pathways, the latter of which could come from vasculature, nerves, APM, melanocyte stem cells (McSCs), mesenchymal cells, adipose tissue, immune cells, non-HFSC epithelial cells and extracellular matrix.²⁶ HF formation and growth encompass a variety of conserved signaling pathways, notably Wnt/ β -catenin, Sonic hedgehog (Shh), BMP, TGF- β , FGF, Notch, Edar, and AKT pathways, among others.^{22,24,27-29}

Hair pigmentation depends on the McSC system.³⁰ Situated in the HB and hair germ (HG) region of HFs in telogen-phase, McSCs are encircled by HFSCs and progenitor cells (HG cells) that make up the McSC niche.³⁰ When anagen starts, McSCs rejuvenate melanocytes that descend into HB, and produce pigment for hair.³⁰ It remains a mystery why, the fail of McSC system is sooner than other adult stem cell groups, resulting in hair greying.³⁰ It is shown that most McSCs toggle between stem cell states and transit-amplifying for both self-renewal and production of mature offspring.³⁰ Their mobility, moving between HFSCs and transit-amplifying areas, allows them to temporarily transition into different states of differentiation influenced by local microenvironmental signals.³⁰ Reverted McSCs, rather than reserved stem cells resistant to reversible alterations, sustain the McSC system.³⁰ There is build-up of stranded McSCs that fail to assist in the renewal of melanocyte offspring during ageing.³⁰ These findings show that dedifferentiation is essential for maintaining stem cells at homeostasis and indicates that adjusting McSC mobility may provide a novel and promising choice for preventing hair greying.³⁰

The Progress of Exosomes Applied in Hair Growth

DPC Exosomes

Given the critical function of DPCs in the HF growth cycle, researches have concentrated on the role of DPC exosomes (DPC-Exos) in hair. In vitro, migration and proliferation of ORS cells (ORSCs) could be promoted, and the expression of β -catenin and Shh could be stimulated by human DPC-Exos.³¹ Injection of human DPC-Exos could accelerate the start of

anagen, delay catagen in mice (depilation hair cycle model) and upregulate Shh and β -catenin levels in skin.³¹ Human DPC-Exos could also enhance proliferation of human ORSCs and DPCs, increase level of growth factors (HGF, KGF and IGF-1) in DPCs, and increase HS elongation in cultured human HFs.³² Implanted with mouse epidermal cells, human DP spheres treated by DPC-Exos could augment HF neogenesis.³² Through injection of DPC-Exos in mice (natural hair cycle model), anagen from telogen could be induced and anagen could be prolonged.³²

Mouse DP spheroid-derived exosomes containing miR-218-5p could facilitate the development of HF by diminishing the function of the Wnt/ β -catenin signaling inhibitor SFRP2, thus up-regulating β -catenin.³³ Photobiomodulation could promote hair generation in injured mouse skin by promoting the migration of mouse DPCs and secretion of DPC-Exos.³⁴

DPC-Exos from Angora rabbits could mediate the proliferation of Angora rabbit HFSC by the Wnt3a/ β -catenin signaling pathway.³⁵ Through targeting the Wnt inhibitor WIF1, exosomal miR-181a-5p from Angora rabbits DPC-Exos could activate the Wnt/ β -catenin signaling pathway, thus modulating genes associated with HF growth and development and suppressing HFSC apoptosis, but promoting HFSC proliferation.³⁶

When exposed to Angora rabbit DPC-Exos, a total of 3702 genes are differentially expressed in Angora rabbit HFSCs, such as BMP4, IGF1R, KRT17, LEF1, TGF α , and TGF β 3, which are abundant in pathways related to HF growth and development, and LEF1 is identified to play a key role in HFSCs proliferation.³⁷

In addition, through miRNA high-throughput sequencing, 111 miRNAs were identified to be differentially expressed between Shannbei White Cashmere goat DPC-Exos and DPCs.³⁸ Overexpression of miR-22-5p inhibits HFSC proliferation by targeting LEF1,³⁸ suggesting that DPC-Exos also contain molecules that negatively regulate HF growth.

Mesenchymal Stem Cell Exosomes

In addition to DPC-Exos, mesenchymal stem cell exosomes are another focus, specifically adipose stem cell exosomes (ADSC-Exos). Compared with the same concentration of platelet-rich plasma exosomes, human ADSC-Exos could significantly enhance migration and proliferation of human DPCs in culture, and expression of ALP, α -SMA and versican in DPCs.³⁹ Human ADSC-Exos could elevate the level of β -catenin, BMP2, cyclin and versican in DPCs, mitigate the suppressive impact of dihydrotestosterone (DHT) on DPCs and down-regulate TGF- β 1 along with its downstream genes.⁴⁰ Furthermore, through targeting SMAD3, ADSC-Exos containing miR-122-5p could antagonize DHT suppression of HF, promote the level of β -catenin and versican in mice, restore dermal thickness and HB size, and promote the normal growth of HF.⁴⁰

By inhibiting miR-22 and the TNF- α signaling pathways and stimulating the Wnt/ β -catenin signaling pathway, mouse ADSC-Exos facilitate migration and proliferation, reduce apoptosis of rat DPCs, and enhance mouse hair growth through injection.⁴¹ Mouse ADSC-Exos co-transplanted with dermal and epidermal cells into mouse skin could induce more significant hair regeneration than dermal and epidermal cells alone.⁴² A divisionable microneedle patch made of chitosan lactate (CL) and mouse ADSC-Exos could sustainably release CL and ADSC-Exos.⁴³ ADSC-Exos could promote mouse DPCs proliferation through stimulating the Wnt/ β -catenin signaling pathway, and the L-lactate secreted by CL could enhance DPCs growth through stimulating lactate dehydrogenase.⁴³ CL and ADSC-Exos synergistically promote growth of mouse tentacular HF in vitro and mouse hair regrowth in vivo.⁴³

A retrospective analysis in South Korea found that in 39 patients with alopecia, 12 weeks of ADSC-Exos treatment led to notable enhancements in hair density and thickness,⁴⁴ which has thus far been the only study in which exosomes have been used in treating alopecia.

Additional varieties of mesenchymal stem cell exosomes have been employed in hair growth. A removable microneedle patch-based medication dispensing mechanism, primarily composed of keratin from hair, could integrate with human bone marrow mesenchymal stem (BMSC) exosomes and a minor molecular medication UK5099, and induce pigmentation and hair regrowth in mouse.⁴⁵ Mouse HF mesenchymal stem cell exosomes could also enhance mouse hair growth in vivo and in vitro.⁴⁶

Other Cellular Exosomes

Furthermore, several studies have been directed towards examining the effects of other cellular exosomes. Human ORSC exosomes can increase the expression of ALP, α -SMA and versican in human DPCs, which could support the hair inductivity of DPCs.⁴⁷ Fisetin is a type of polyphenol in fruits and vegetables. Exosomes originating from Fisetin-treated human keratinocytes (HaCaT) could stimulate mitochondria and β -catenin in human HFSCs and

trigger their proliferation *in vitro*.⁴⁸ Through stimulating the Wnt/ β -catenin signaling pathway, exosomes of bovine colostrum (milk exosomes, Milk-Exos) promote human DPCs proliferation, rescue DHT-induced halt of follicle development, and induce mouse dorsal hair regrowth at the level comparable to the treatment of minoxidil.⁴⁹

Myeloid-derived suppressor cell exosomes could prevent AA progression and suffice for partial hair growth in mice, with a marked rise in Tregs, decreased T helper proliferation, lessened cytotoxic effects, a minor uptick in lymphocyte apoptosis, and a notable surge in immunoregulatory mRNA, such as FoxP3 and arginase 1.⁵⁰

EVs and EV Mimetics

In addition to exosomes, studies have been conducted on EVs and EV mimetics in hair research.

miR-140-5p enriched in human DPC-EVs could directly repress BMP2, thus promote proliferation of human ORSCs and hair matrix cells *in vitro*, and accelerate human HF elongation *ex vivo*.⁵¹ Human DP-EVs are encased in semi-oxidized sodium alginate (OSA) hydrogels. They produce OSA-encapsulated EVs (OSA-EVs), and establish a continuous-release mechanism that improves the preservation of EVs and the steadiness of vesicular proteins both *in vivo* and *in vitro*.⁵² OSA-EVs could facilitate human hair matrix cells proliferation, prolong anagen in cultured human hairs, and accelerate the regeneration of mouse dorsal hair after depilation.⁵²

Human BMSC-EVs could stimulate the proliferation of human DPCs and ORSCs *in vitro*, boost level of β -catenin target transcription factors LEF1, EP2 and Axin2 in DPCs, promote migration of ORSCs, enhance the level of keratin differentiation markers K6, K16, K17 and K75 in ORSCs, and augment HS growth in cultured human HFs.⁵³ Mouse BMSC-EVs could increase human DPCs migration and proliferation *in vitro*, increase expression and secretion of IGF-1 and VEGF in DPCs, enhance transformation from telogen to anagen and amplify the level of versican, Wnt5a and Wnt3a in mice.⁵⁴ In a retrospective study in America, 22 females and 9 males suffering alopecia were enrolled, treated with human BMSC-EVs injections and followed for a minimum of 6 months. Over 50% of female patients and close to 80% of male patients showed improvements in hair growth.⁵⁵

EVs from mesenchymal stem cells of adipose tissue and dental pulp show obvious transcriptomic traits that human ADSCs and ADSC-EVs highly express genes related to angiogenesis, dermal matrices, and hair growth.⁵⁶ Polygonum multiflorum Thunb extract, which is bio-pulsed reagents, could improve production of chicken embryonic mesenchymal stem cell EVs, and thus enhance the proliferation of human DPCs *in vitro*, increase expression of follicle activity-related genes IGF-1 and RAC1, cell proliferative genes PNCA and CCND1, and decrease the expression of apoptosis genes TP53 and CASP2 in DPCs.⁵⁷ A case report shows that human placenta mesenchymal stem cell EVs could have an effect on permanent chemotherapy-induced alopecia.⁵⁸

Human dermal fibroblast EVs promote human HF length *ex vivo*, stimulate the Wnt/ β -catenin pathway in human DPCs, and enhance the migration, differentiation and proliferation of human ORSCs.^{59,60} Engineered nanovesicles from mouse fibroblasts could boost the proliferation and migration of human DPC *in vitro*, raise the expression of pERK, pAKT, PCNA, and VEGF-receptor-2 in DPCs, and promote human HS size *ex vivo*.⁶¹

Mouse macrophage-derived EVs could promote proliferation, migration, and activation of the Wnt/ β -catenin pathway in human DPCs, enhance levels of VEGF and KGF in DPCs, increase HS size in cultured human HFs, and promote HF growth in mice.⁶² Engineered EV mimetics from mouse macrophage could activate human DPCs *in vitro*, induce HS elongation in cultured human HFs and hair regrowth in mice.⁶³

ReN cell VM (ReN) cells are a neural progenitor cell line. Prepared by extruding ReN cells, exosome-mimetic nanovesicles could stimulate human DPCs proliferation and accelerate the HF cycling transition in mice through miR-100 by stimulating the Wnt/ β -catenin pathway.⁶⁴

EVs originating from *Leuconostoc holzapfelii* existing in the human scalp can promote the migration and proliferation of human DPCs, diminish apoptosis by altering the cell cycle, and increase hair-inductive activity by the Wnt/ β -catenin pathway.⁶⁵

Summary

Studies using animal models and at the cellular level have shown that exosomes promote hair growth (Figure 2). Table 1 summarizes the effects of exosomes, EVs and EV mimetics on hair growth. Exosome therapy stands out from cell therapy due

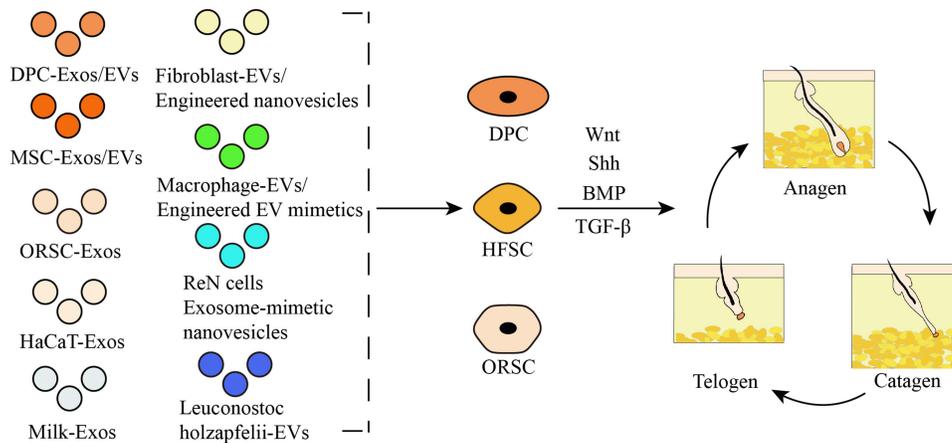


Figure 2 The role of exosomes, EVs and EV mimetics in regulating hair growth. Exosomes/EVs/EV mimetics act on DPCs, HFSCs, ORSCs and affect hair growth cycle through Wnt, Shh, BMP and TGF-β signaling pathways.

Abbreviations: DPC, dermal papilla cell; EVs, extracellular vesicles; Exos, exosomes; HFSC, hair follicle stem cell; MSC, mesenchymal stem cell; ORSC, outer root sheath cell.

to its low immunogenicity and fewer adverse reactions. At present, research on the effect of exosomes on hair remains in its infancy, and the underlying mechanism and efficacy remain to be elucidated. Thus, the use of exosomes in clinical settings for hair growth remains behind the curve: uncertainties persist about the fundamental processes, safety, and the most effective treatment methods, encompassing the delivery of treatment, its origin, and dosage. However, it is envisioned that this novel exosomal therapy will eventually become a novel and hopeful choice for treating alopecia.

Table 1 Effects of Exosomes, EVs and EV Mimetics on Hair Growth

Source	Type	Content	Effects in vitro/ex vivo	Effects in vivo	Combination	References
Human DPCs	Exos	–	Migration↑, proliferation↑, β-catenin↑, Shh↑ in ORSCs	Accelerating the start of anagen, delaying catagen, β-catenin↑, Shh↑ in mice	–	[31]
Human DPCs	Exos	–	Proliferation↑ of ORSCs and DPCs, HGF↑, KGF↑, IGF-1↑ in DPCs, HS elongation↑ in cultured HFs	HF neogenesis↑, inducing anagen from telogen, anagen↑ in mice	–	[32]
Human DPCs	EVs	miR-140-5p	Proliferation↑, BMP2↓ in ORSCs and hair matrix cells, HF elongation↑	–	–	[51]
Human DPCs	EVs	–	Proliferation↑ of hair matrix cells, anagen↑ in cultured HF	Regeneration of dorsal hair↑ in mice	OSA hydrogels	[52]
Mouse DPCs	Exos	miR-218-5p	–	HF development↑, SFRP2↓, β-catenin↑ in mice	–	[33]
Mouse DPCs	Exos	–	–	Hair generation↑ in injured mouse skin	Photobiomodulation	[34]
Angora rabbits DPCs	Exos	–	Proliferation↑, Wnt3a/β-catenin signaling pathway↑ in HFSCs	–	–	[35]
Angora rabbits DPCs	Exos	miR-181a-5p	Proliferation↑, apoptosis↓, WIF1↓, Wnt/β-catenin signaling pathway↑ in HFSCs	–	–	[36]
Angora rabbits DPCs	Exos	–	LEF1↑ in HFSCs	–	–	[37]
Human ADSCs	Exos	–	Migration↑, proliferation↑, ALP↑, α-SMA↑, versican↑ in DPCs	–	–	[39]
Human ADSCs	Exos	miR-122-5p	β-catenin↑, BMP2↑, cyclin↑, versican↑, TGF-β1↓ in DPCs, suppressive impact of DHT on DPCs↓	DHT suppression of HF↓, normal growth of HF↑, SMAD3↑, β-catenin↑, versican↑ in mice	–	[40]

(Continued)

Table 1 (Continued).

Source	Type	Content	Effects in vitro/ex vivo	Effects in vivo	Combination	References
Mouse ADSCs	Exos	–	Migration↑, proliferation↑, apoptosis↓, miR-22↓, TNF-α signaling pathways↓, Wnt/β-catenin signaling pathway↑ in DPCs	Hair growth↑ in mice	–	[41]
Mouse ADSCs	Exos	–	–	Hair regeneration↑ in mice	Dermal and epidermal cells (co-transplantation)	[42]
Mouse ADSCs	Exos	–	Proliferation↑, Wnt/β-catenin signaling pathway↑ in DPCs, growth of mouse tentacular HF↑	Hair regrowth↑ in mice	CL in a separable microneedle patch	[43]
ADSCs	Exos	–	–	Hair density↑ and thickness↑ in human	–	[44]
Human BMSCs	Exos	–	–	Hair regrowth↑ in mice	UK5099 in a removable microneedle patch	[45]
Human BMSCs	EVs	–	Proliferation↑ of DPCs and ORSCs, LEF1↑, EP2↑ Axin2↑ in DPCs, migration↑, K6↑, KI6↑, K17↑, K75↑ in ORSCs, HS growth↑ in cultured HFs	–	–	[53]
Human BMSCs	EVs	–	–	Hair growth↑ in human	–	[55]
Mouse BMSCs	EVs	–	Migration↑, proliferation↑, IGF-1↑, VEGF↑, in DPCs	Transformation from telogen to anagen↑, versican↑, Wnt5a↑, Wnt3a↑ in mice	–	[54]
Mouse HF-MSCs	Exos	–	HF growth↑	Hair growth↑ in mice	–	[46]
Human placenta MSCs	EVs	–	–	Permanent chemotherapy-induced alopecia↓ in human	–	[58]
Chicken embryonic MSCs	EVs	–	Proliferation↑, IGF-1↑, RAC1↑, PNCA↑, CCND1↑, TP53↓, CASP2↓ in DPCs	–	Polygonum multiflorum Thunb extract	[57]
Human ORSCs	Exos	–	ALP↑, α-SMA↑, versican↑ in DPCs	–	–	[47]
Human HaCaT cells	Exos	–	Proliferation↑, mitochondria↑, β-catenin↑ in HFSCs	–	Fisetin	[48]
Human dermal fibroblasts	EVs	–	Migration↑, differentiation↑, proliferation↑ of ORSCs, Wnt/β-catenin pathway↑ in DPCs, HF length↑	–	–	[59,60]
Mouse fibroblasts	Engineered nanovesicles	–	Proliferation↑, migration↑, pERK↑, pAKT↑, PCNA↑, VEGF-receptor-2↑ in DPCs, HS size↑	–	–	[61]
Mouse macrophages	EVs	–	Proliferation↑, migration↑, Wnt/β-catenin pathway↑, VEGF↑, KGF↑ in DPCs, HS size↑ in cultured HFs	HF growth↑ in mice	–	[62]
Mouse macrophages	Engineered EV mimetics	–	Proliferation↑, β-catenin↑, versican↑, ALP↑, pAKT↑, pERK↑, Bcl-2↑, PCNA↑ in DPCs, HS elongation↑ in cultured HFs	Hair regrowth↑ in mice	–	[63]
Bovine colostrum	Exos	–	Proliferation↑, Wnt/β-catenin signaling pathway↑ in DPCs, DHT-induced halt of HF development↓	Hair regrowth↑ in mice	–	[49]

(Continued)

Table 1 (Continued).

Source	Type	Content	Effects in vitro/ex vivo	Effects in vivo	Combination	References
Mouse MDSCs	Exos	–	–	Tregs↑, T helper proliferation↓, cytotoxic effects↓, lymphocyte apoptosis↑, FoxP3↑, arginase I↑, AA progression↓ and suffice for partial hair growth↑ in mice	–	[50]
ReN cells	Exosome-mimetic nanovesicles	miR-100	Proliferation↑ of DPCs	HF cycling transition↑, Wnt/β-catenin pathway↑ in mice	–	[64]
Leuconostoc holzapfelii	EVs	–	Migration↑, proliferation↑, apoptosis↓, Wnt/β-catenin pathway↑ in DPCs	–	–	[65]

Notes: ↑: upregulation. ↓: downregulation.

Abbreviations: AA, alopecia areata; ADSCs, adipose-derived stem cells; ALP, alkaline phosphatase; α-SMA, alpha-smooth muscle actin; Axin2, axis inhibition protein 2; BMP2, bone morphogenetic protein 2; BMSCs, bone marrow-derived stem cells; CASP2, caspase 2; CCND1, cyclin D1; CL, chitosan lactate; DHT, dihydrotestosterone; DPCs, dermal papilla cells; EP2, Prostaglandin E2 receptor 2; EVs, extracellular vesicles; Exos, exosomes; FoxP3, Forkhead box protein P3; HF, hair follicles; HFSCs, hair follicle stem cells; HGF, hepatocyte growth factor; HS, hair shaft; IGF-1, insulin growth factor 1; K6, keratin 6; K16, keratin 16; K17, keratin 17; K75, keratin 75; KGF, keratinocyte growth factor; LEF1, lymphoid enhancer binding factor 1; MDSCs, myeloid-derived suppressor cells; miR, microRNA; MSCs, mesenchymal stem cells; ORSCs, outer root sheath cells; OSA, oxidized sodium alginate; pAKT, phospho-protein kinase B; PCNA, proliferating cell nuclear antigen; pERK, phospho-extracellular regulated protein kinase; RAC1, Ras-related C3 botulinum toxin substrate 1; SFRP2, secreted frizzled related protein 2; Shh, Sonic hedgehog; SMAD3, small mother against decapentaplegic family member 3; TGF-β1, transforming growth factor beta 1; TNF-α, tumor necrosis factor-alpha; TP53, tumor suppressor p53; Tregs, regulatory T cells; VEGF, vascular endothelial growth factors; WIFI, Wnt inhibitory factor 1; Wnt3a, Wnt family member 3a; Wnt5a, Wnt family member 5a.

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Disclosure

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