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REVIEW ARTICLE

Exosome therapy in hair regeneration: A literature review of the evidence, challenges, and future opportunities

Yana Kost BA[1] | Ahava Muskat BA[1] | Nour Mhaimeed BA, MS[2] | Roya S. Nazarian MD[1] | Kseniya Kobets MD[1]

[1]Department of Medicine, Division of Dermatology, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York, USA

[2]Eastern Virginal Medical School, Norfolk, Virginia, USA

Correspondence
Kseniya Kobets, MD, Department of Medicine, Division of Dermatology, Montefiore Medical Center, Albert Einstein College of Medicine, 3411 Wayne Avenue, 2nd Floor Dermatology Suite, Bronx, New York, USA.
Email: kkobets@montefiore.org

Abstract

Background: Alopecia is a common chief complaint and is challenging to treat. As such, regenerative treatments to promote hair growth are an emerging area of research. Exosomes, which are extracellular vesicles involved in cell communication, homeostasis, differentiation, and organogenesis, have been shown to play a central role in hair morphogenesis and regeneration with potential for use as alopecia treatment.

Aims: This review summarizes and assesses the body of literature surrounding exosomes as regenerative therapeutics for alopecia and identifies areas for improvement in future research.

Methods: A review was conducted using a comprehensive list of keywords including "exosome," "alopecia," and "hair loss" on PubMed, EMBASE, and Google Scholar databases published from inception to February 2022. Reference lists of identified articles were included. 47 studies were included. Clinical trial databases were searched using the term "exosome"; however, no trials relevant to hair growth were identified.

Results: Our updated and comprehensive review details the history of exosome use in medicine, postulated underlying mechanisms in treating hair loss, and current clinical studies. Preclinical studies demonstrate clear benefits of exosome therapeutics in regenerative medicine and for hair loss treatment. Clinical trials demonstrate safety of exosome use in medicine, but data showing efficacy and safety of exosome therapy for alopecia are lacking. We identified several gaps in knowledge required for effective clinical translation including safety, exosome source, and optimal treatment delivery mechanism and dosage.

Conclusion: Exosomes are on the horizon as an exciting therapeutic for the treatment of alopecia. Further studies and clinical trials are required.

1 | INTRODUCTION

Alopecia is a leading indication for dermatology visits, but treatment remains challenging. Androgenic alopecia is the most common type of non-scarring alopecia, affecting up to 80% of Caucasian men and 50% of women by 70 years of age while central centrifugal cicatricial alopecia is the most frequent cause of alopecia in African Americans.[1] Alopecia has a significant negative psychological impact on patients.[1]

Due to the prevalence of alopecia, significant research has been conducted in hopes of finding safe and effective treatments. Current FDA-approved treatments such as topical minoxidil and oral/topical finasteride have partial efficacy in arresting hair loss but are limited in promoting hair growth. Furthermore, adverse effects and difficulty adhering to daily use of such treatments may further limit use of these medications.[1] Low-level laser therapy is also FDA-approved but its efficacy is unclear.[2] Hair transplantation is surgical treatment

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option available to patients, however, may be unattainable due to cost.[2]

As such, regenerative treatments that not only inhibit hair loss but promote growth are an emerging area of research. Platelet-rich plasma injection therapy (PRP) is one such treatment with minimal side effects that has demonstrated benefit in improving hair volume and density in multiple clinical studies.[3] More recently exosomes, cell-derived vesicles secreted by most cells in the body containing various molecules, have emerged as a new therapy with remarkable efficacy in early studies.[3] Although literature is currently limited, we provide a comprehensive review to clinicians regarding this innovative treatment.

2 | METHODS

A broad review was conducted using a comprehensive list of keywords including "exosome," "alopecia," and "hair loss" on PubMed, EMBASE, and Google Scholar databases published from inception to February 2022. Reference lists on identified articles were included to augment the research. 47 studies were included. Additionally, two clinical trial databases, clinicaltrials.gov and clinicaltrialsregister.eu, were searched using the term "exosome," and all results were screened for trials mentioning hair. No clinical trials investigating the effects of exosomes on hair were found.

3 | RESULTS AND DISCUSSION

3.1 | What are exosomes?

Exosomes are classified as small extracellular vesicles with a diameter of 40–120 nm.[4] All cells release extracellular vesicles during normal physiologic activity. While ectosomes are released via outward budding of the plasma membrane, exosomes are formed by sequential invagination of membranes between multiple intracellular endosomes and organelles. In this process, the contents of the exosome are diversified by inclusion of DNA, RNA, lipids, metabolites, and cytosolic and cell-surface proteins.[4]

Exosomes were incidentally discovered in 1983, observed to be released from reticulocytes as they lost volume to mature into erythrocytes.[5] At the time, exosomes were thought to be simple cell debris. In the last two decades, exosomes have gained importance and have been found to serve many functions including cell signaling via delivery of peptides, receptor transfer between cells, as well as functioning as "cargo-delivery" packets of mRNA in order to maintain stem cell populations.[5,6]

Due to their vesicular structure, exosomes can protect proteins and nucleic acids from rapid degradation.[7] Moreover, exosomes can potentially be engineered to target specific tissues with a "homing" mechanism.[4] Of note, exosomes induce only a minimal immune response as they are natural materials, evenly if synthetically developed or modified, and therefore are highly biocompatible.[4,8,9]

Given their unique ability to preserve and deliver molecules in a targeted fashion, use of exosomes is being explored in many disease states, including alopecia.[10]

3.2 | Exosomes for alopecia treatment: Supporting evidence

3.2.1 | Preclinical studies

As discussed, exosomes play an important role in cell communication, tissue homeostasis, cell differentiation, organogenesis, and tissue remodeling.[5] Hair growth cycles rely on tight control of the hair follicle (HF), which requires a system of diffusible factors between cells, cell-surface ligands, and cell-surface receptors. Because the hair follicle is a compartmentalized organ, it has been hypothesized that such interactions are at least partially mediated by exosomes.[2,11,12] Interestingly, exosomes have been shown to carry Wnt proteins on their surface to induce the activation of β-catenin, a key signaling pathway hair morphogenesis and regeneration.[13,14] β-catenin promotes the induction and maintenance of the anagen portion of the hair cycle, in addition to regulation and differentiation of keratinocytes.[15] Anatomic regions of the hair follicle thought to be implicated in hair growth related to exosome treatment include the dermal papilla, outer root sheath, and bulge, which have shown response to exosomes secreted by regions of the hair follicle itself as well as exosomes from other tissue sources.

Numerous in vitro and animal studies have investigated the role of exosomes from various tissue sources. Preclinical evidence for the use of exosomes in alopecia is the most abundant in exosomes derived from dermal papilla cells (DPCs), an accumulation of specialized mesenchymal cells that are located at the bottom of the HFs[16] which have been shown to play a critical role in the regulation of HF growth, formation, and cycling.[17] Injection of DPC exosomes has been shown to accelerate the onset of HF anagen and delayed catagen in mice, as seen by H&E-stained tissue sections showing anagen VI phase in treated mice and immunohistochemical analyses showing upregulation β-catenin and Shh levels, important regulators of the hair cycle, in treated skin.[17] Upregulated levels of β-catenin and Shh10 following treatment with DPC exosomes were also confirmed in vitro after treating outer root sheath cells with DPC exosomes.[17] DPC-exosome treatment was shown to enhance outer root sheath cells proliferation and migration, including hair follicle bulge stem cells.[17] These findings were similar to those reported by Kwack et al., who used exosomes from DPCs to induce prolonged anagen of hair follicles in mice-injected subcutaneously.[18] DPC exosomes have also been shown to decrease hair loss and reduced inflammation around hair follicles in a mouse model of alopecia areata.[19]

Furthermore, DPCs play an important role in the differentiation of HF stem cells. During catagen and telogen, the epithelial cells at the base of the follicle undergo apoptosis, but the DP remains intact and migrates upward to the HF bulge, where it releases signals that stimulate the differentiation of HF stem cells and trigger the regeneration

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of HFs to start the anagen phase.[20] Yan et al. showed that during co-culture of HF stem cells with DPCs, HF stem cell differentiation was induced, and furthermore, DPC exosomes were shown to be attached to the surface of HFSCs via transmission electron microscopy during co-culture.[21] Finally, they observed 111 differentially expressed miRNAs in the DPC exosomes compared with DPCs, indicating that DPC exosomes play a key role in HF regeneration.[21] Of note, DPC exosomes have also been shown to act on adipose-derived stem cells to transdifferentiate them into DPC-like cells that express hair-inductive genes, β-Catenin, and hair-inductive miRNAs.[22]

Preclinical evidence supporting the use of exosomes from adipose-derived stem cells is also strong. Exosomes from adipose-derived stem cells have been shown to positively affect hair regrowth by promoting DPC proliferation via upregulating the Wnt/β-catenin, TNF-α signaling pathways, and vascular endothelial growth factor expression.[23-25] Exosomes from adipose-derived stem cells have been shown to significantly increase ALP, versican and α-SMA protein expression and DPC proliferation and migration in culture compared to a control group.[26]

Several other sources of exosomes for hair growth have been identified. Exosomes from hair outer root sheath cells were shown to maintain hair human dermal papilla cells in vitro.[27] Additionally, with hair outer root sheath cell exosome treatments, markers of hair growth induction increased by a factor of 2.1, 1.7and 1.3, respectively, compared to a control group.[27]

Additionally, bone marrow-derived exosomes were shown to activate dermal papillae cell proliferation and migration, upregulation of the Wnt/β-catenin pathway, and increase secretion of growth factors.[28] Separately, exosomes from human dermal fibroblasts have been shown to activate the β-catenin pathway in cell culture.[29,30]

Finally, immune cell-derived exosomes have also shown promise in alopecia treatment. Exosomes from myeloid-derived suppressor cells, innate immune cells which are known to inhibit T-cell proliferation, have been shown to increase in immunoregulatory mRNA levels, including FoxP3 and arginase 1 to prohibit T-cell hyperreactivity in a mouse model of alopecia areata.[31] Also, macrophage exosomes have shown significantly enhanced levels of hair-inductive markers of DPCs in a mouse model and human hair follicles in vitro.[32] Finally, exosomes derived from *Leuconostoc holzapfelii*, a bacteria isolated from human scalp tissue, have been shown to promote hair growth by regulation via the Wnt/β-catenin signal transduction pathway.[33]

Taken together, studies show that within the HF dermal papilla, outer root sheath, and HF bulge cells, exosomes from various tissue sources may have significant benefit for hair regrowth and rejuvenation.

3.2.2 | Clinical studies

After their initial discovery in 1983[34] with a pivotal study demonstrating that exosomes are derived from mesenchymal stem cells and have the capacity to promote proliferation and survival of cells in 2009,[35] clinical trials investigating their therapeutic use have gained traction. There are currently no completed clinical trials regarding the use of exosomes for the treatment of hair loss; however, anecdotal evidence and case reports from various hair restoration specialists show promising results.[36-39]

Additionally, several patents specific for the treatment of alopecia with exosomes are being developed. A European patented study demonstrated that a pharmaceutical composition comprising mesenchymal stem cell-derived exosomes may be capable of promoting hair growth in a mouse model.[40] Another patent-pending product in which the active ingredient consists of exosomes isolated from 0- to 5-month-old human newborn foreskin stem cells has also shown to increase hair growth in a mouse model.[41] Additionally, an active Japanese patent similarly describes a composition for promoting hair growth consisting of exosomes derived from mesenchymal stem cells.[42]

Several pilot studies have demonstrated exciting promise for the treatment of alopecia with exosomes. A recent presentation at the International Society of Hair Restoration Surgeons World Congress in 2020 revealed promising preliminary results from ongoing trials of exosome treatment for alopecia areata and androgenetic alopecia.[7,43,44] Furthermore, a recent pilot study in Korea conducted on 20 patients with male/female pattern hair loss reported the efficacy of exosome therapy based on enhancement in hair thickness (increased from 57.5 to 64.0 mm, $p \leq .001$) and hair density (increased from 105.4 to 122.7 counts/cm,^{2} $p \leq .001$) after 12 weeks of treatment.[45] While early studies show promise, additional clinical and preclinical studies are needed to determine the efficacy and mechanism of exosome treatment for alopecia.

3.3 | Exosomes for alopecia treatment: Use in a clinical setting

3.3.1 | Safety

While several exosome products are in clinical use, there are currently no United States Food and Drugs Administration (FDA)-approved exosome products. In 2019 and reiterated in 2020, the FDA issued a statement warning that exosomes are not approved, nor have they been proven effective, as response to reports of five patients experiencing serious adverse events, including infection and sepsis, within 2 months of being treated with exosome products.[46] While information regarding exosome therapy adverse events is limited, stem cell therapy adverse events are well documented and include but are not limited to tumor and ectopic tissue formation, physical trapping in the microvasculature, infusional toxicities, and cellular rejection by the host.[47] Exosomes are stem cell products but these adverse events have not been associated with their use given their inability to form tumors, smaller size that decreases the risk for physical trapping, and decreased likelihood of producing a host immune response.[47,48]

Various studies on exosomes have cited no significant adverse events, including a study assessing efficacy and safety of exosome

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TABLE 1 Commercial therapeutic exosome products for alopecia

Company name	Exosome product	Exosome source
Aegle Therapeutics[57]	AGLE-102	Allogeneic bone marrow mesenchymal stem cells
Benev[58]	Exosome Regenerative Complex	Stem cells
Direct Biologics[59]	ExoFlo™	Human bone marrow mesenchymal stem cells
Exocel Bio[60]	EXOVEX	–
ExoCoBio[61]	ASCE	Stem cells
Kimera Labs[62]	XoGlo®	MSCs

technology as a carrier for melanoma vaccination; however, these studies were not conducted in alopecia patients.[8,49] Given that exosomes are used allogeneically and require manipulation, and have potential risks of transferring genetic information and activating immune responses,[37] the FDA has categorized them as drug products, requiring extensive review before approval. Furthermore, questions relating to their biodistribution and pharmacokinetic profile are still unanswered.[29]

3.3.2 | *Treatment optimization*

Few studies have been performed to determine the optimal delivery mechanism, exosome source, and dose. Regarding delivery mechanism, a microneedle-based transdermal drug delivery approach has been shown to have improved efficacy compared to subcutaneous injection or topical administration of exosomes.[50] Another group demonstrated that combination therapy of microneedle patches containing exosomes of human amniotic mesenchymal stem cells combined with low-color-temperature yellow light synergistically facilitated hair regrowth in 7 days compared to monotherapy.[51] Another treatment using DPC exosomes encapsulated in oxidized sodium alginate has shown promise.[52] However, all such studies are conducted in animal models. Finally, a case report of significant hair regrowth in a patient with alopecia universalis following treatment with nonablative Er:YAG laser treatment, PRP, and exosome injections has been described.[53] Further definitive research is required in human clinical trials.

As noted previously, several sources of exosomes exist including bone marrow, adipose, and amniotic stem cell exosomes. In the preclinical setting, it has been shown that exosomes increased cell proliferation and survival independent of the tissue source in a dose-dependent manner.[54] Of note, compared with exosomes derived from human bone marrow mesenchymal stem cells, the yield of exosomes isolated from human amniotic fluid mesenchymal stem cells is higher, and thus may be more effective in a clinical setting.[55,56] Moreover, the appropriate dose and the number of doses of exosomes to be given for alopecia have not been determined. Higher concentrations of exosomes potentially may show better results. Additionally, different pharmaceutical companies may produce exosome products differently and of different final quality, which may affect treatment. A current list of companies producing therapeutic are listed in Table 1.

4 | CONCLUSION

The current body of literature surrounding hair regeneration capabilities of exosomes assures their place as an exciting and effective therapeutic for hair loss. However, most publications thus far are either preclinical or have very few participants. Questions remain regarding underlying mechanisms, safety, and most efficacious treatment protocols including treatment delivery mechanism, source, and dose. We urge scientists and innovators in the field to address this knowledge gap through collaboration on high-quality studies and randomized controlled clinical trials.

AUTHORS CONTRIBUTION

Y.K., A.M., N.M., and R.M. performed the research. Y.K. wrote the paper. A.M., N.M, R.N., and K.K. reviewed the paper and contributed essential edits. K.K. conceived of and supervised the project. All authors have read and approved the final manuscript.

ETHICS STATEMENT

No ethics review board approval was utilized for this literature review.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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