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Advances in Stem Cell-Based Therapy for Hair Loss

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Abstract

OBJECTIVE: Hair loss is a quite common condition observed in both men and women. Pattern hair loss also known as androgenetic alopecia is the most common form of hair loss that is thought to affect up to 80% of Caucasian men and up to 40% of Caucasian women by age of 70, and it can have quite devastating consequences on one's well-being, including lower self-esteem, depression and lower quality of life. To date there have only been 2 FDA approved medications, minoxidil and finasteride, but their effects are often unsatisfactory and temporary, in addition to having various adverse effects. Stem cell-based therapies have recently received lots of attention as potential novel treatments that focus on reactivating hair follicle stem cells and in this way enhance hair follicle growth, regeneration and development. Stem cell-based therapy approaches include stem cell transplant, stem cell-derived conditioned medium and stem cell-derived exosomes.

MATERIALS AND METHODS: A combination of following key words was utilized for a PubMed search: cell-based therapy, hair loss, alopecia, hair regrowth; abstracts were screened and included based on the content relevant to hair loss and stem-cell based therapy.

RESULTS: Preclinical research utilizing these approaches has blossomed in the past decade along with a more limited number of clinical studies, overall demonstrating very promising findings.

CONCLUSION: However, stem cell-based therapies for hair loss are still at their infancy and more robust clinical studies are needed to better evaluate their mechanisms of action, efficacy, safety, benefits and limitations. In this review, we provide the resources to the latest preclinical studies and a more detailed description of the latest clinical studies concerning stem cell-based therapies in hair loss.

Keywords

hair loss; alopecia; stem cell-based therapy; transplant; conditioned medium; exosome; hair regrowth; hair regeneration

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Introduction:

Hair loss, particularly, pattern hair loss (PHL) as its most common form, occurs quite commonly in both women and men, and often leads to a significant decrease in quality of life[1]. It is believed that over 80% of Caucasian men and up to 42% of Caucasian women at the age of 70 are affected by male pattern hair loss/androgenetic alopecia (MPHL/AGA) and female pattern hair loss (FPHL), respectively[1]. Hair is considered a major feature of beauty and esthetic appearance; hence hair loss has a major impact on one's self-perception, self-esteem, and can lead to depression and other mood disorders[2]. Furthermore, some postulate early onset of AGA to be associated with a heightened risk of development of myocardial infarction and metabolic syndrome[3].

It is thought that the Wnt- β-catenin pathway plays a major role in pathogenesis of hair loss.[4] To date, there are only 2 FDA approved medications for treatment of hair loss, minoxidil (a vasodilator) and finasteride (a selective inhibitor of the type II and III isoforms of 5α-reductase). However, these medications have been far from perfect; both have been associated with limited efficacy, duration of effect, and several important side effects[5, 6].

PHL is a form of non-scarring alopecia. PHL is characterized by defects in and loss of hair progenitor cells, while hair follicle stem cells (HFSCs) remain viable. This notion in particular makes PHL a reversible condition[7, 8], and current and novel treatment modalities attempt to utilize the existent viability and responsiveness of HFSCs as to reverse hair loss pathology and promote hair growth. Providing adequate signals and environment to reactivate HFSCs and regrow a hair follicle is of particular interest to the hair regeneration scientific and clinical community. In the past decade, hair regeneration research has plummeted, including the discoveries regarding stem-cell based therapies leading to many preclinical and some clinical studies with encouraging outcomes. Stem-cell transplant, stem cell-derived conditioned medium (CM) and stem cell-derived exosomes have recently gained a lot of attention as potential new agents to modify and enhance the signaling pathways that could induce HFSC reactivation, hair cycle and hair follicle regeneration. In this review, we will provide resources to the preclinical studies, but our major focus will be on the latest clinical research as it relates to stem-cell based therapies, hair loss, and hair regeneration potential.

Discussion:

As briefly mentioned previously, stem-cell based therapies include three distinct prospective mechanisms: transplantation of multipotent stem cells from different sources, application of stem cell-derived CM and application of stem-cell derived exosomes[9]. Herein, we will address each of them individually by discussing current clinical studies, their results, respective benefits and limitations.

Transplantation of multipotent stem cells has become a well-accepted treatment option for hair loss (especially AGA). The sources of multipotent stem cells with regenerative potentials of hair follicles in the skin include adipose tissue[10], bone marrow[11], hair follicles from unaffected areas[12], and umbilical cord blood[13].

Owczarczyk-Saczonek et al[8] provide a thorough review of pre-clinical discoveries of promising results and benefits of stem-cell based transplant therapies. Results of clinical studies are further discussed below.

Elmaadawi et al[14] studied the safety and efficacy of the autologous bone marrow-derived mononuclear cells (BMMCs) including stem cells in comparison to follicular stem cells (FSCs) obtained from the unaffected scalp areas in 20 patients with alopecia areata (AA) and 20 patients with AGA. All patients underwent one treatment session with autologous stem cells (BMMCs or FSCs) that were injected intradermally. Evaluation by immunostaining and digital dermoscopy 6 months post-treatment demonstrated significant improvement of both conditions with no significant difference between treatment groups and no adverse events.

Rigenera® is a technology that obtains autologous mature stem cells from biopsies of a patient using a preparation system for mechanical disintegration and filtering of solid tissues. In a study the cell suspension was injected into the scalp of 11 patients affected by AGA. 23 weeks post-treatment there was a 29%±5% increase in hair density in the scalp area receiving treatment as compared to the area receiving placebo[15]. Gentile et al[15] suggested that bulge-derived HFSCs can be isolated with this newly discovered method to avoid the challenges concerning cell culturing and more importantly that they have the ability to enhance hair density in patients with AGA.

Multipotent stem cells arising from the adipose tissue – the adipose-derived stromal vascular cells (ADSVCs) or adipose-derived regenerative cells (ADRCs) refer to the stromal vascular fraction-derived freshly used primary multipotent stem cells. When these cells are cultured, they attain additional features and become a population of mesenchymal stem cells (MSCs) which are referred to as adipose-derived stem cells (ADSCs)[16, 17]. Anderi et al[16] studied ADSVCs in a total of 20 patients suffering from AA[16]. There was a statistically significant improvement of hair thickness especially 6 months post-treatment. Only 1 out of 20 patients did not demonstrate any increase in hair diameter. Furthermore, there was a statistically significant increase in hair density 3 and 6 months post-treatment; 18 out of 20 patients demonstrated improvement while only 2 out of 20 patients did not show any increase in hair density. Lastly, there was also a statistically significant decrease in hair-pull test results 3 and 6 months post-treatment; only 2 out of 20 patients did not demonstrate any decrease in hair-pull test scores. Anderi et al[16] suggested autologous ADSVCs graft to be safe and effective treatment modality for AA.

Zanzottera et al[10] utilized the Rigenera® device to prepare autologous ADMSCs obtained during hair transplant procedure. The suspension was then applied to the scalp areas undergoing hair transplant in 3 patients suffering from AGA. Monthly follow up revealed a more rapid healing of transplant-induced wounds. Furthermore, there was a continuous improvement in hair growth and a shorter telogen phase two months post-treatment.

Another study found benefit of primary pluripotent ADRCs in enhancing hair growth. Particularly, addition of stromal vascular fraction-derived stem cells to the adipose tissue in a transplant procedure involving 6 patients suffering from male or female PHL demonstrated a

statistically significant 23% increase in mean hair count compared to 7.5% increase in patients treated with adipose tissue alone[17].

The dermal papilla (DP) region is an important area of the hair follicle that contains MSCs which participate in inducing hair growth and controlling hair cycle. DP cells are surrounded by dermal sheath cup (DSC) cells which are essential for DP cell regeneration and proliferation and therefore hair growth, as well[18]. It is proposed that circulating androgens deregulate DP cell-derived signaling leading to inhibition of canonical Wnt-β-catenin pathway and hair loss in AGA_4. Besides DP cells, the multipotent stem cells from the bulge region are also thought to depend on DSC cells[19]. In a study by Tsuboi et al[20], 50 male and 15 female patients received a single injection treatment of autologous DSC cells at concentrations 7.5×10^6, 1.5×10^6, or 3.0×10^5 DSC cells or a placebo in 4 randomized distinctive scalp regions and were followed-up at 3, 6, 9 and 12 months post-treatment. There was a significant increase in total hair density and cumulative hair diameter at the 3.0×10^5 DSC cell injection location 6 and 9 months post-treatment. These results suggested that autologous DSC cell injection at minimal concentration is a potential safe and useful additional modality for treatment of PHL in both males and females.

A new focus is being placed on stem-cell secreted bioactive molecules such as growth factors, cytokines, chemokines, and others, as potential key regulators of hair follicle cycle and regeneration[9]. Particularly, it is thought that up to 80% of regenerative properties of transplanted stem cells come from paracrine factor signaling[21, 22]. Stem cells secrete such factors including nucleic acids, extracellular vesicles (exosomes included) and proteins, thus inducing paracrine signaling[23, 24]. These factors are components of a secretome. In other words, secretome represents a set of signaling molecules including nucleic acids, extracellular vesicles, and proteins secreted by stem cells. When a cultured stem cell-derived secretome is present in a nutrient-rich medium it is referred to as a stem cell-derived "conditioned medium" (CM)[25].

Several studies focusing specifically on the ability of the extracellular matrix (EM) to induce hair regeneration are available and overall their results are promising[9]. Moreover, in comparison to other modalities, stem cell-derived CM provides additional benefits. For instance, the donor-recipient match that is normally required in a cell-based type of treatment is surpassed with CM because it represents a cell-free medium[26]. Additionally, there appears to be less risk of tumor development as well as benefits of easier preparation and lower cost[27, 28]. Although stem cell-derived CM-based therapy is at its early beginnings, many preclinical[9] and several clinical studies have shown encouraging results. The clinical studies will be discussed below.

Fukuoka et al[29] evaluated efficacy and safety of ADSC-CM in 25 patients (12 women and 13 men) diagnosed with female or male PHL; 1 male patient received a diagnosis of both AGA and AA. In this study, ADSCs were pretreated under hypoxic conditions that were previously shown to have the ability to induce secretion of various growth factors and cytokines with potential benefits for hair regrowth as compared to normoxic ADSCs[29, 30]. The ADSC-derived secretome is composed of hepatocyte growth factor, vascular endothelial growth factor, keratinocyte growth factor and platelet-derived growth factor[29]. This medium

was applied every 3–5 weeks by utilizing nappage and papule injection methods. All patients demonstrated a statically significant improvement in hair growth; 4 treatment sessions over a 3–4-month-period resulted in best results[29].

In another study of the same group on 22 patients (11 men and 11 women) with alopecia received ADSC-CM injections every 3–5 weeks for a total of 6 sessions. 10 patients (8 men and 2 women) were also part of a half-side comparison study. Trichogram evaluations before and after treatment demonstrated a statistically significant increase in hair numbers in both genders. In the half-side comparison study, the side receiving treatment exhibited a significant increase in hair numbers compared to the side of placebo[31]. Adverse events included post-procedural pain which negatively affected patient compliance.

ADSC-CM was also evaluated in 27 female patients suffering from FPHL. This group utilized a microneedle roller to apply ADSC-CM weekly for 12 consecutive weeks. Phototrichographic analysis revealed a statistically significant increase in both hair density and hair thickness, and no adverse events (including pain)[32].

Narita et al[33] evaluated efficacy of ADSC-CM in a total of 40 patients (21 men and 19 women) diagnosed with alopecia[33]. Patients underwent ADSC-CM intradermal injections monthly for a total of 6 months and had follow-up evaluations before and at 2, 4 and 6 months post-treatment. There was a significant increase in hair density and anagen hair rate in this study, as well as, dermal echogenicity and dermal thickness of the treated scalp.

Undoubtedly, CM demonstrates potential as a future hair regrowth therapy; however, like any treatment modality it poses certain limitations. Particularly, the type and level of factors present in a stem cell-derived CM can be highly variable, and standardization of its preparation will be of utmost importance to improve its clinical use and results[22]. Additionally, fast turnover and depletion of CM factors *in vivo* may necessitate large quantities and frequent application[34, 35]. We will now briefly discuss one particular component of CM that is considered an additional alternative stem-cell based therapeutic approach: the exosome.

Exosomes are extracellular vesicles of the smallest size, that act as cell-to-cell transporters and messengers by carrying signaling molecules including transcription factors, cytokines, and RNA[22, 36, 37]. Exosomes have been demonstrated as important modulators of paracrine signaling, and particularly, DP cell-derived exosomes could be of major importance for hair follicle regeneration[38]. Many of the preclinical studies show favorable outcomes; however, there are currently no clinical studies employing extracellular vesicle or exosome therapy for hair growth[9]. More preclinical and new clinical studies are needed to further characterize exosomes as a novel regenerative treatment for hair loss.

More robust studies are encouraged for the other two stem cell-based therapy approaches: the stem cell-based transplant and the stem cell-derived CM; several clinical trials currently are underway (ClinicalTrials.gov Identifiers: NCT01673789, NCT02865421, NCT03078686, NCT02849470, NCT03676400, NCT03662854, NCT 01501617). Several aforementioned studies have been completed and are awaiting results.

Conclusion:

Novel discoveries revolving around stem-cell based therapies provide encouraging steps towards developing more effective and successful hair loss treatments. Although these initial steps towards such discoveries are hopeful, there is still a limited amount of clinical data to fully support stem-cell based therapies. While stem-cell transplant, CM and exosome therapies demonstrate preclinical and some clinical success, each one of them has its own limitations that will need to be overcome. Stem cell transplant is a costly procedure, and it also raises concerns for tumorigenicity[24]. While CM and exosomes may be more affordable[26] and safe in terms of tumor development[27, 28] they both pose some problems. The cell-free nature of CM provides a safer and more immunocompatible environment, but makes isolating a composition-consistent CM challenging[26]. Similarly, there are currently no standard effective isolation methods for exosomes[39]. While results are certainly hopeful, larger and more robust double blind controlled clinical trials are needed to further assess the exact mechanisms, therapeutic potential and safety of stem-cell based approaches to hair loss management.

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