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FACIAL PLASTICS: FACIAL SKIN REJUVENATION (PJ CARNIOL AND AE BRISSETT, SECTION EDITORS)

Advances in Hair Restoration

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Abstract

Purpose of Review Treatment for alopecia remains limited in terms of medication side effect profile, patient adherence to treatment, and clinical response. We sought to review the literature for burgeoning therapies affecting hair growth through regulation of paracrine signaling and its effect on dermal papilla cells.

Recent Findings Newly proposed treatments for alopecia, including stem cell therapy derived from adipose tissue, hair follicles, umbilical cord blood, or bone marrow, and extracellular vesicles, such as exosomes, are tied to hair follicle regulation and regeneration through paracrine factor signaling, specifically through the Wnt/β-catenin signaling pathway.

Summary Recent advances in hair follicle regeneration and regulation, including stem cell therapy or treatment with exosomes, modulate alopecia through dermal papilla cell regulation and promoting hair follicle growth through anagen phase induction. Randomized, high-quality studies are needed to determine safety, efficacy, and appropriate treatment protocols using these newest therapies.

Keywords Hair restoration · Wnt pathway · Alopecia · Androgenetic hair loss · Exosomes · Stem cells · Adipose-derived stem cells

Introduction

Hair loss poses significant psychosocial sequelae in both men and women. The desire to pursue prevention and treatment is evident in the global valuation of the alopecia market, which was valued above $9.08 billion in 2019 and is expected to reach over $13.65 billion by 2027 [1]. Androgenetic alopecia (AGA) represents a vast majority of hair loss cases, affecting around 50 million men and 30 million women in the USA alone [2].

The most common types of non-scarring alopecia include involutional alopecia, that which occurs with age, AGA, telogen effluvium, and alopecia areata (AA). AGA, otherwise known as male or female pattern hair loss, is a hereditary condition causing progressive thinning of the hair secondary to increased androgen receptors and 5-alpha reductase resulting in diminution/miniaturization of dermal papilla cells (DPCs), which are mesenchymal stem cells of the hair follicle and play a major role in hair follicle morphogenesis and regeneration. A defect in conversion from stem cell to progenitor cell phenotype may play a role in patients suffering from AGA, as the amount of hair follicle stem cells remains stable while the number of proliferating progenitor cells decreases [3]. Telogen effluvium can be acute or chronic and most commonly secondary to acute severe illness, surgery, iron deficiency, thyroid pathology, malnutrition, chronic disease, and medications, such as oral contraceptives and lithium 4. AA is autoimmune inflammatory in etiology and most often results in non-scarring patches of hair loss, but may be diffuse in nature.

This article is part of the Topical collection on *FACIAL PLASTICS: Facial Skin Rejuvenation*

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Hair follicles each have their own lifecycle divided into three phases occurring simultaneously: anagen, catagen, and telogen. The anagen phase is the active phase, during which time the cells within the hair bulb divide rapidly resulting in hair growth, which lasts 2–6 years, and 85% of hair on the head is in this phase. The catagen phase is a transitional phase that lasts 2–3 weeks wherein hair growth halts, as its blood supply is disconnected. The telogen phase is a resting phase lasting 2–3 months during which time the hair sheds as new hair replaces it within 2 weeks. Hair is in telogen for 10–15% of one's life.

When evaluating patients with alopecia, it is important to obtain from the patient a thorough family and medical history, medication list, hair styling practices, hormonal imbalance history, menstrual cycle history, and menopausal symptoms. Depending upon history and presenting symptoms, laboratory work-up may be warranted, including hormonal profile, thyroid function testing, iron panels, vitamin D, and possibly skin biopsy to rule out underlying pathology as a cause for alopecia, such as polycystic ovarian syndrome, thyroid disease, or scarring alopecia.

Only two FDA-approved medications for hair loss exist: minoxidil and finasteride. These medications can be administered either topically or orally; however, both therapies may result in significant adverse effects, which may limit use or adherence to therapy. Although non-pharmacologic therapies, such as platelet-rich plasma and low-level laser therapy, may prove beneficial in the treatment of hair loss, the quality of evidence to support the use of these treatments is considered to be generally low [4, 5].

Emerging injectable therapies, such as stem cells and exosomes, are proposed to stimulate hair follicle regeneration and growth through the activation of specific signaling pathways, such as Wnt-mediating signaling. Herein, we will review these recent advances in hair restoration therapy and their proposed mechanism of action through paracrine signaling.

Importance of Wnt-Mediated Signaling in Hair Growth

The Wnt signaling pathway is a primary player in the regulation of hair morphogenesis, cycling, and regeneration, promoting hair follicle growth by advancing the hair follicle from telogen to anagen phase and increasing hair-related and anagen gene expression [6, 7, 8••, 9–14, 14•, 16–19]. Various Wnt proteins promote hair cycling and regeneration through the activation of β-catenin signaling, thereby inducing anagen and new hair follicles [8••, 17, 20–23]. Wnt-mediated signaling also plays a significant role in the maintenance and proliferation of stem cell reservoirs; Wnt/β-catenin signaling is paramount to the growth and maintenance of DPCs [10, 24, 25].

Circulating androgens have been proposed to inhibit canonical Wnt-β-catenin pathway causing hair loss in AGA [26]. Downregulated genes in AGA belong to that of the Wnt and TGF-β signaling pathways, further implicating the importance of the Wnt signaling pathway in alopecia [27]. Furthermore, the aging process causes a gradual loss of sex hormones, by which the hair follicle is negatively impacted. This is perhaps best realized in menopausal females, wherein substantial decreases in hair density and diameter are seen, as is decreased anagen phase and transition to greater amounts of finer vellus hair, likely secondary to lack of ovarian estrogen production [28–30]. Likewise, when treating osteoporosis in menopausal women, the primary therapies induce osteoblast differentiation from bone marrow stem cells via Wnt/ β-catenin signaling, an element necessitating further consideration when evaluating response of alopecia in menopausal women during treatment with these therapies [31, 32].

Newly proposed treatments for alopecia, including stem cell therapy and exosomes, are tied to hair follicle regulation and regeneration through paracrine factor signaling, specifically affecting the Wnt/β-catenin pathway, and may prove to be exciting treatment options for patients with alopecia.

Stem Cell Therapy

Stem cells secrete molecules, such as nucleic acids, extracellular vesicles, and proteins, which play a role in paracrine factor signaling, thereby regulating hair follicle cycles and regeneration [15•, 33, 34]. Stem cells may be derived from adipose tissue, bone marrow, hair follicles, or umbilical cord blood [19, 35–38]. Patients who underwent one treatment of intradermal injection of autologous stem cells, either from follicular or bone marrow-derived stem cells, demonstrated significant improvement in both AA and AGA [36]. Furthermore, stem cells derived from hair follicles have been shown to increase hair density in patients with AGA [37].

Adipose-derived stem cells (ADSCs) are mesenchymal stem cells (MSCs) found in subcutaneous adipose tissue. MSC-derived signaling and growth factors stimulate hair follicle development through β-catenin 39. ADSCs increase proliferation of DPCs and have been shown to decrease healing time in transplant-induced wounds, shorten telogen phase, and improve hair growth following hair transplantation [35, 39–42]. When combined with microneedling, ADSCs increased both hair density and thickness in women [43]. Response to ADSCs may be augmented by its surrounding environment. For example, when placed in conditioned medium (CM), a nutrient-rich medium with signaling molecules including nucleic acids, extracellular

vesicles, and proteins from stem cells, ADSCs have been shown to improve hair growth and hair numbers in both men and women, increase anagen hair rate and human follicular cell proliferation, improve hair growth, and protect human DPCs against cytotoxic injury by androgen and reactive oxygen species [44–50]. Additionally, when combined with nappage mesotherapy, multiple treatments with ADSC-CM demonstrated increased hair numbers without reported complications [46]. Similarly, adipose-derived stromal vascular cells demonstrated improvement in hair thickness in 19/20 patients and increase in hair density and decrease in hair-pull test scores in 18/20 patients, while adipose-derived regenerative cells increased mean hair counts following injection into the subcutaneous scalp in patients with AGA [51, 52].

Bu et al. through the use of CK15 expression, demonstrated that hair follicle cells can be differentiated from umbilical cord blood MSCs [53]. Human umbilical cord blood–derived MSCs prevent hair regression resulting from dexamethasone in mouse catagen induction models and increase proliferation of human DPCs [54].

Although reported side effects have been minimal when using stem cells, with the exception of procedural pain affecting patient compliance, CM preparation and contents vary widely, and degradation of CM factors may require both frequent administration and large quantities for effect thereby limiting clinical application [47, 55, 56].

Exosome Therapy

Exosomes are 30–150-nm extracellular vesicles responsible for transmission of transcription factors, cytokines, mRNA, and microRNA [57–60]. Exosomes transport Wnt proteins, which induce activation of β-catenin signaling pathways [7, 13, 14, 61]. Studies have shown that exosomes promote hair follicle stem cell proliferation and differentiation and cell migration and angiogenesis and aid in tissue repair [9, 19, 62–65].

Exosomes derived from MSCs increase proliferation, migration, and growth factor expression and release in DPCs66 and, thus, have been evaluated for their role in hair follicle regeneration and growth. MSC-derived extracellular vesicles both activate DPC hair inductivity and regulate DPC proliferation and have been shown to convert hair follicles from telogen to anagen phase [61, 64, 66].

DPC-derived exosomes may augment hair follicle regeneration through regulation of hair follicle growth via paracrine mechanisms [64, 67, 68]. DPC-derived exosomes regulate growth and development of hair follicles through proliferation of DPCs, hair matrix cells, and outer root sheath cells and increase growth factors in DPCs [67, 69, 70]. Additionally, DPC-derived exosomes have also been shown to prolong anagen phase and increase hair shaft elongation [67, 69, 70]. For example, human DP exosomes, when injected into mouse skin, promote hair growth through an induction of β-catenin and Shh levels [67].

Although there are no published clinical trials evaluating exosomes in hair restoration, exosomes have been shown to stimulate hair follicle proliferation with an increased hair density and thickness in patients with AGA after 12 weeks of treatment without reported serious adverse reactions [71]. Although no significant adverse events are cited, there are potential risks of transferring genetic information and immune responses [72–74]. See Figs. 1, 2, and 3 for clinical examples of patients treated with exosomes.

Gene Engineering

Wnt protein expression can be modified to positively impact the hair cycle. CM derived from gene-engineered retroviral-mediated Wnt1a-overexpressing bone marrow MSCs has been shown to result in hair regrowth through effect on DPCs when injected intradermally, while Wnt7a-MSC-CM induces more hair follicle regeneration when compared to MSC-CM, further demonstrating the importance of Wnt signaling in hair growth [19, 75, 76].

Fig. 1 5-ml exosomes at 6 months post injection

Fig. 2 5-ml exosomes at 4 months post injection

Fig. 3 5-ml exosomes at 4 months post injection

Choi et al. introduced genes of three trichogenic platelet-derived growth factor-A, SOX2, and β-catenin to ADSCs and demonstrated that these ADSCs with trichogenic factors were similar to DPCs in terms of mRNA expression and have enhanced hair-regenerative potential, as they accelerate the telogen to anagen transition [77].

Conclusion

Recent advances in hair follicle regeneration and regulation, including stem cell therapy or treatment with exosomes, modulate alopecia through DPC regulation and promoting hair follicle growth through anagen phase induction. Wnt-mediating signaling seems to play an important role in the response of DPCs to stem cell and exosomal therapies. Burgeoning therapies using stem cells or exosomes for alopecia still require randomized, double-blinded, high-quality human studies with adequate power to determine safety, efficacy, and appropriate treatment protocols. Further data collection is also needed to ensure appropriate preparation and administration of product and gather information pertaining to side effects and expected treatment response in patients.

Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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