

Conventional and novel stem cell based therapies for androgenic alopecia

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Abstract: The prevalence of androgenic alopecia (AGA) increases with age and it affects both men and women. Patients diagnosed with AGA may experience decreased quality of life, depression, and feel self-conscious. There are a variety of therapeutic options ranging from prescription drugs to non-prescription medications. Currently, AGA involves an annual global market revenue of US\$4 billion and a growth rate of 1.8%, indicating a growing consumer market. Although natural and synthetic ingredients can promote hair growth and, therefore, be useful to treat AGA, some of them have important adverse effects and unknown mechanisms of action that limit their use and benefits. Biologic factors that include signaling from stem cells, dermal papilla cells, and platelet-rich plasma are some of the current therapeutic agents being studied for hair restoration with milder side effects. However, most of the mechanisms exerted by these factors in hair restoration are still being researched. In this review, we analyze the therapeutic agents that have been used for AGA and emphasize the potential of new therapies based on advances in stem cell technologies and regenerative medicine.

Keywords: stem cells, stem cell therapies, hair follicle, dermal papilla, androgenic alopecia, laser, hair regeneration

Introduction

The prevalence of androgenic alopecia (AGA) increases with age, and is estimated to affect about 80% of Caucasian men.¹ Female AGA, also known as female pattern hair loss, affects 32% of women in the ninth decade of life.² The consumer market for products that promote hair growth has been increasing dramatically.³ These products promote hair regeneration based on the knowledge about the hair follicle (HF) cycle.^{4,5} However, in most cases, the mechanisms of action of these products are not well characterized and the results are variable or with undesirable side effects.⁶ At present, only two treatments for AGA have been approved by the US Food and Drug Administration (FDA): Minoxidil and Finasteride.⁷⁻¹⁰ Although these medications have proved to be effective in some cases, their use is limited by their side effects.^{11,12} With the emergence of stem cells (SCs), many mechanisms that lead to tissue regeneration have been discovered.¹³ Hair regeneration has become one of the targets for SC technologies to restore the hair in AGA.¹⁴ Several SC factors such as peptides exert essential signals to promote hair regrowth.^{15,16} Some of these signals stimulate differentiation of SCs to keratinocytes which are important for HF growth.¹⁷ Other signals can stimulate dermal papilla cells (DPCs) that promote SC proliferation in the HF.^{18,19} In this review, we describe HF characteristics and discuss different therapies used currently for AGA and possible novel agents for hair regeneration. These therapies include FDA-approved

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medications, non-prescription physical or chemical agents, natural ingredients, small molecules, biologic factors, and signals derived from SCs.

HF and SC niche

The HF undergoes biologic changes from an actively growing stage (anagen) to a quiescent stage (telogen) with an intermediate remodeling stage (catagen).⁴ HFSCs are located in the bulge region of the follicle and they interact with mesenchymal SCs (MSCs) located in the dermal papilla (DP).¹⁸ These signal exchanges promote activation of some cellular pathways that are essential for DPC growth, function, and survival, such as the activation of Wnt signaling pathway.^{19–21} Other signals, such as those from endothelial cells (ECs) located at the DP, are also essential for HF maintenance.²² EC dysfunction that impairs adequate blood supply may limit or inhibit hair growth.²² For instance, Minoxidil, a synthetic agent, is able to promote hair growth by increasing blood flow and the production of prostaglandin E2 (PGE2).⁷ It has been shown that proteins that belong to the transforming growth factor (TGF) superfamily, such as bone morphogenetic proteins (BMPs), also exert signals to maintain the capacity of DPCs to induce HF growing in vivo and in vitro.²³ These BMPs may be released by several cells that compose the follicle, including ECs.^{24–26} ECs may provide signals for

BMP receptor activation in DPCs similar to those signals that promote survival of MSCs in human embryoid bodies composed of multipotent cells.^{24,25} DPCs have been derived from pluripotent SCs in an attempt to study their potential for hair regeneration in vitro and in vivo.²⁷ Together, dermal blood vessels and DPCs orchestrate a suitable microenvironment for the growth and survival of HFSCs.^{28,29} Interestingly, the expression of Forkhead box C1 regulates the quiescence of HFSCs located in the bulge region (Figure 1).³⁰ HFSCs are quiescent during mid-anagen and maintain this stage until the next hair cycle.^{29,30} However, during early anagen stage, these cells undergo a short proliferative phase in which they self-renew and produce new hair.³⁰ Therefore, the bulge region constitutes a SC niche that makes multiple signals toward quiescence or proliferation stages.^{30–34} It is known that fibroblasts and adipocyte signals are able to inhibit the proliferation of HFSCs.³⁴ Additionally, BMP6 and fibroblast growth factor 18 (FGF18) from bulge cells exert inhibitory effects on HFSC proliferation.³⁴ Dihydrotestosterone (DHT) also inhibits HF growth.³⁵ Agents that reduce DHT, such as Finasteride, promote hair regrowth by inhibiting Type II 5 α -reductase.^{8,14,36} In contrast to these inhibitory effects, DPCs located at the base of the HF provide activation signals (Figure 1).^{18,34} The crosstalk between DPCs and HFSCs leads to inhibition of inhibitory effects with the resultant cell

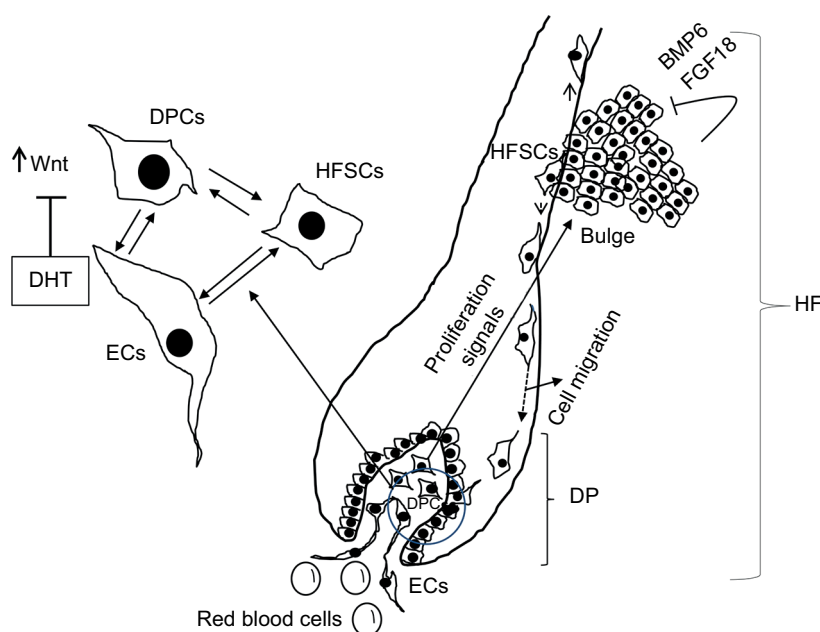


Figure 1 Diagram of the HF and factors involved in hair regeneration.

Notes: The HF is composed of different cell types including HFSCs, DPCs, and ECs, among others. HFSCs migrate from the bulge area after activation by growth factors released by DPCs. However, BMP6 and FGF18 from the bulge cells exert autocrine inhibitory effects in HFSC proliferation. Once the HFSCs are closer to DPCs and ECs, they differentiate and proliferate during anagen phase, forming new hair. Activation of Wnt signaling is essential for DPCs to release the factors that promote differentiation and proliferation of HFSCs. DHT interferes with this Wnt signaling and, in this way, inhibits hair growth and promotes hair miniaturization. Effective cell–cell interactions between HFSCs, DPCs, and ECs are essential for hair growth.

Abbreviations: BMP6, bone morphogenetic protein 6; DHT, dihydrotestosterone; DP, dermal papilla; DPCs, dermal papilla cells; ECs, endothelial cells; FGF18, fibroblast growth factor 18; HF, hair follicle; HFSCs, hair follicle stem cells.

proliferation toward hair regeneration (anagen).^{30,31,37} With the self-renewal of HFSCs, the outer root sheath (ORS) forms, and signals from DPCs to the bulge cells diminish in a way that the bulge cells start again with their quiescent stage.^{4,34} As mentioned earlier, Forkhead box C1 transcription factor has an important role in maintaining the threshold for HFSC activation.³⁰ The knockdown of these factors in bulge cells reduces the cells' threshold for proliferation, and the anagen cycle starts more frequently due to promotion of HFSC proliferation in shorter periods of time.³⁰

Prescribed and non-prescription products that promote hair growth and possible mechanisms of action

FDA-approved chemical agents

At present, the only therapeutic agents for AGA approved by the FDA in the USA are Finasteride and Minoxidil.^{9,10} Minoxidil promotes hair growth by increasing the blood flow and by PGE2 production.⁷ Although Minoxidil is now a non-prescription medication, Finasteride and other drugs require a medical prescription for AGA treatment (Table 1). Dutasteride and Finasteride inhibit 5 α -reductase, blocking the conversion of testosterone to DHT.^{36,38} While Finasteride is a selective inhibitor of type II 5 α -reductase, Dutasteride inhibits type I and type II 5 α -reductases. These medications have also been used to treat benign prostatic hyperplasia.³⁹

Natural ingredients

In addition to prescribed medications, some natural ingredients have been used to promote hair growth (Table 2). For example, procyanidin B-2 (found in apples and in several plants) is able to inhibit the translocation of protein kinase C (PKC) in hair epithelial cells.⁴⁰ PKC isozymes, such as PKC- β I and - β II, play an important role in hair cycle progression and inhibiting their translocation can promote hair growth.⁴⁰ Procyanidin B-3 can promote hair growth by inhibiting TGF- β 1.⁴¹ Another group of natural ingredients, such as saw palmetto, alfatradiol, and green tea (*Epigallocatechin gallate*), have the capacity to inhibit 5 α -reductase and block DHT production.^{42–44} The natural ingredients and their proposed mechanisms of action are summarized in Table 2

(the commercial web page is included, since there are no formal studies about their mechanisms of action).

Laser therapy

Light amplification by stimulated emission of radiation (LASER) generates electromagnetic radiation which is uniform in polarization, phase, and wavelength.⁴⁵ Low-level laser therapy (LLLT), also called “cold laser” therapy, since it utilizes lower power densities than those needed to produce heating of tissue. Transdermal LLLT has been used for therapeutic purposes via photobiomodulation.^{46,47} Several clinical conditions, such as rheumatoid arthritis, mucositis, pain, and other inflammatory diseases, have been treated with these laser devices.^{48–50} LLLT promotes cell proliferation by stimulating cellular production of adenosine triphosphate and creating a shift in overall cell redox potential toward greater intracellular oxidation.⁵¹ The redox state of the cell regulates activation of signaling pathways that ultimately promotes high transcription factor activity and gene expression of factors associated with the cell cycle.⁵² Physical agents such as lasers have been also used to prevent hair loss in a wavelength range in the red and near infrared (600–1,070 nm).^{5,47,51,53} Laser therapy emits light that penetrates the scalp and promotes hair growth by increasing the blood flow.⁵⁴ This increase gives rise to EC proliferation and migration due to upregulation of vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase.^{55,56} In addition, the laser energy itself stimulates metabolism in catagen or telogen follicles, resulting in the production of anagen hair.^{53,54} A specific effect of LLLT has been demonstrated to promote proliferation of HFSCs, forcing the hair to start the anagen phase.⁵⁷

Biologic agents that promote hair growth and their mechanisms of action

SC signaling

Recently, it has been found that SCs release factors that can promote hair growth.¹⁶ These factors and their mechanisms of action have been summarized in Table 3. These factors, known as “secretomes”, are able to promote skin regeneration, wound healing, and immunologic modulation, among other effects.^{58,59}

Table 1 Prescribed products used for AGA

Prescribed products	Source	Mechanism of action
Finasteride/Dutasteride ^{9,10}	Synthetic (small molecule)	Inhibits type II, 5 α -reductase
Latanoprost and Bimatoprost ^{36,38,39,79,80}	Synthetic prostaglandin analog of PGF2 α (originally used to decrease ocular pressure in glaucoma)	Activates prostaglandin receptor

Abbreviation: AGA, androgenic alopecia; PGF2 α , prostaglandin F2 α .

Table 2 Non-prescription products used for AGA and their proposed mechanisms of action

Non-prescription product	Source	Proposed mechanism of action
Minoxidyl (FDA approved) ⁹	Synthetic (small molecule)	Potassium channel opener and powerful vasodilator used in hypertension
Apple Procyanidin B-2 (extract from apples) ⁴⁰	Natural (apples and several plants)	Inhibitor of translocation of PKC isozymes in hair epithelial cells
Procerin (saw palmetto extract and other ingredients such as iodine, gotu kola, magnesium, grape seed extract, biotin, niacin, and vitamin B12) ⁴²	Natural (small plant named saw palmetto)	Used to treat benign prostatic hyperplasia. Inhibits type I and II 5 α -reductase and blocks DHT production
Provillus (www.provillus.com)	Formulation (Minoxidil 2 or 5%, biotin, Zn, Fe, Mg, Ca, B6 complex)	Contains Minoxidil and more vitamins (similar ingredients to Procerin)
Follicusan (https://www.ulprospector.com/en/na/PersonalCare/Detail/1381216299/Follicusan-DP)	Natural (milk-based bioactive compound)	Stimulates cellular functioning in the scalp and hair follicle. Stimulates dermal papilla cells. Improve hair density and thickness
Musol 20 (http://www.cosmeticingredients.co.uk/Ingredient/musol-20-pf)	Natural (yeast extract, mucoprotein)	Physically deposited as a protective covering to create thicker hair
Capixyl (http://lucasmeyercosmetics.com/en/products/product.php?id=6)	Synthetic and natural (four amino acids biomimetic peptide with red clover extract; rich in biochanin A [antioxidant])	Inhibitor of 5 α -reductase, improves ECM proteins; it reduces inflammation
EMortal Pep (http://www.revagain.co.kr/goods/catalog?code=0002)	Synthetic and natural	Blocks upregulation of TGF- β 1 induced by DHT. Activates dermal papilla cells
Planoxia-RG (https://www.ulprospector.com/en/na/PersonalCare/Detail/5314195870/PLAN_OXIA-RG)	Natural	Promotes transition from telogen phase to anagen phase
Tricholastyl (http://dir.cosmeticsandtoiletries.com/detail/tradeName.html?id=17820)	Natural (water, mannitol, <i>Pterocarpus marsupium</i> bark extract, disodium succinate, glutamic acid)	Antiglycation activity. In this way, it restores the hair growth cycle
Keramino-25 (http://www.lonza.com/productsservices/consumercare/personalcare/proteins/animal-proteins/keramino-25.aspx)	Synthetic	Increases the strength of the hair (because of its great penetration)
Seveov (http://www.naturex.asia/uk_1/markets/personal-care/natbeautytm/seveov.html)	Natural (maca root extract)	It protects the hair bulb and shaft. It stimulates cell division in the hair shaft and bulb
Hairomega (http://thehairlossreview.com/hairomega_review.html/)	Natural (formulation that contains [200 mg] saw palmetto and [300 mg] β -sitosterol as the main ingredients)	Inhibits 5 α -reductase and formation of DHT
Green tea (<i>Epigallocatechin gallate</i>) ^{43,91}	Natural (polyphenol antioxidant)	Inhibits 5 α -reductase and formation of DHT
Nioxin (formulation of Coenzyme Q10 and other coenzymes) http://www.nioxin.com/en-US?utm_source=google&utm_medium=cpc&utm_term=nioxin&utm_campaign=Nioxin_Search_Brand+Awareness&utm_content=sMPLlfxa dc_452731_95217_e_nioxin&clid=CJSy3JbH0cgCFY17fodMTIDKQ	Synthetic	Inhibits 5 α -reductase and formation of DHT
Alfatradiol (17 α -estradiol) ⁴⁴	Synthetic (small molecule)	Inhibits type II 5 α -reductase
Quercetin ⁸⁴	Natural (flavonoid found in several non-citrus fruits, vegetables, leaves, and grains)	Inhibits PGD2

Abbreviations: AGA, androgenic alopecia; DHT, dihydrotestosterone; ECM, extracellular matrix; FDA, US Food and Drug Administration; PGD2, prostaglandin D2; PKC, protein kinase C; TGF- β 1, transforming growth factor β 1.

Some of these factors, such as epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF) and HGF activator, VEGF, insulin-like growth factor (IGF), TGF- β , and platelet-derived growth factor (PDGF), are able to provide signals that promote hair growth.^{15,60–64} As mentioned before, DPCs provide signals to HFSCs located in the bulge that proliferate and migrate either to the DP or to the epidermis

to repopulate the basal layer (Figure 1).^{32,65} Enhancement in growth factor expression (except for EGF) has been reported when the adipose SCs are cultured in hypoxic conditions.¹⁵ Also, SCs increase their self-renewal capacity under these conditions.^{66–68} Low oxygen concentrations (1%–5%) increase the level of expression of SC factors that include VEGF, basic fibroblast growth factor, IGF binding protein 1 (IGFBP-1), IGF

Table 3 Stem cell factors and small molecules that promote hair growth and their mechanisms of action

Factor	Mechanism of action
HGF and HGF activator ⁶¹	Factor secreted by DPC that promotes proliferation of epithelial follicular cells
EGF ⁶⁰	Promotes growth and migration of follicle ORS cells by activation of Wnt/ β -catenin signaling
bFGF ⁶²	Promotes the development of hair follicle
IL-6 ⁹³	Involved in WIHN through STAT3 activation
VEGF ⁷²	Promotes perifollicular angiogenesis
TGF- β ⁶³	Stimulates the signaling pathways that regulate hair cycle
IGF-I ⁶⁹	Promotes proliferation, survival, and migration of hair follicle cells
IGFBP-I to -6 ⁷⁰	Regulates IGF-I effects and its interaction with extracellular matrix proteins at the hair follicle level
BMP ²³	Maintains DPC phenotype which is crucial for stimulation of hair follicle stem cell
BMPIa ²³	Maintains the proper identity of DPCs that is essential for specific DPC function
M-CSF ⁷¹	Involved in wound-induced hair regrowth
M-CSFR ⁷¹	Involved in wound-induced hair regrowth
PDGF and PDGFR- β /- α ⁶⁴	Upregulates the genes involved in hair follicle differentiation. Induction and regulation of anagen phase. PDGF and its receptors are essential for follicular development
Wnt3a ⁹⁷	Involved in hair follicle development through β -catenin signaling
PGE2 ^{79,80}	Stimulates anagen phase in hair follicles
PGF2 α and analogs ^{79,80}	Promotes transition from telogen to anagen phase of the hair cycle
BIO ⁹⁸	GSK-3 inhibitor
PGE2 or inhibition of PGD2 or PGD2 receptor D2/GPR44 ⁷⁷	Promotes follicle regeneration
Iron and l-lysine ⁹⁵	Under investigation

Abbreviations: bFGF, basic fibroblast growth factor; BIO, (2'Z,3'E)-6-bromoindirubin-3'-oxime; BMP, bone morphogenetic protein; DPCs, dermal papilla cells; EGF, epidermal growth factor; GSK-3, glycogen synthase kinase-3; HGF, hepatocyte growth factor; IGF-I, insulin-like growth factor I; IGFBP-I, insulin-like growth factor-binding protein I; IL-6, interleukin-6; M-CSF, macrophage colony-stimulating factor; M-CSFR, macrophage colony-stimulating factor receptor; ORS, outer root sheath; PDGF, platelet-derived growth factor; PDGFR- α , platelet-derived growth factor receptor alpha; PDGFR- β , platelet-derived growth factor receptor beta; PGD2, prostaglandin D2; PGE2, prostaglandin E2; TGF- β 1, transforming growth factor β 1; VEGF, vascular endothelial growth factor; WIHN, wound-induced hair neogenesis; Wnt3a, wingless-type MMTV integration site family, member 3A.

binding protein 2 (IGFBP-2), macrophage colony-stimulating factor (M-CSF), M-CSF receptor (M-CSFR), and PDGF receptor β (PDGFR- β).^{15,69,70} While these groups of factors promote HF growth in intact skin, another group of factors, such as M-CSF, M-CSFR, and interleukin-6, are involved in wound-induced hair neogenesis.⁷¹ HGF and HGF activator stimulate DPCs to promote proliferation of epithelial follicular cells.⁶¹ Epidermal growth factor promotes cellular migration via the activation of Wnt/ β -catenin signaling.⁶⁰ VEGF promotes hair growth and increases the follicle size mainly by perifollicular angiogenesis.⁷² Blocking VEGF activity by neutralizing antibodies reduced the size and growth of the HF.⁷² PDGF and its receptor (PDGFR- α) are essential for follicular development by promoting upregulation of genes involved in HF differentiation and regulating the anagen phase in HFs.^{64,73} They are also expressed in neonatal skin cells that surround the HF.⁷³ Monoclonal antibodies to PDGFR- α (APA5) produced failure in hair germ induction, supporting that PDGFR- α and its ligand have an essential role in hair differentiation and development.⁷³ IGF-1 promotes proliferation, survival, and migration of HF cells.^{69,74} In addition, IGF binding proteins (IGFBPs) also promote hair growth and hair cell survival by

regulating IGF-1 effects and its interaction with extracellular matrix proteins in the HF.⁷⁰ Higher levels of IGF-1 and IGFBPs in beard DPCs suggest that IGF-1 levels are associated with androgens.⁷⁴ Furthermore, DPCs from non-balding scalps showed significantly higher levels of IGF-1 and IGFBP-6, in contrast to DPCs from balding scalps.⁷⁴

Small molecules

Small molecules with low molecular weight (<900 Da) and the size of 10^{-9} m are organic compounds that are able to regulate some biologic processes.⁷⁵ Some small molecules have been tested for their role in hair growth.⁷⁶ Synthetic, non-peptidyl small molecules that act as agonists of the hedgehog pathway have the ability to promote follicular cycling in adult mouse skin.⁷⁶ PGE2 and prostaglandin D2 (PGD2) have also been associated with the hair cycle (Table 3).⁷⁷ PGD2 is elevated in the scalp of balding men and inhibits hair lengthening via GPR44 receptor.⁷⁸ Also, it is known that PGE2 and PGF2 α promote hair growth, while PGD2 inhibits this process.^{77,79} Prostaglandin analogs of PGF2 α have been used originally to decrease ocular pressure in glaucoma with parallel effects in the growth of eyelashes, which suggests a

specific effect in HF activation.⁸⁰ PGD2 receptors are located in the upper and lower ORS region and in the DP, suggesting that these prostaglandins play an important role in hair cycle.⁸¹ Molecules such as quercetin are able to inhibit PGD2 and, in this way, promote hair growth.^{82–84} Antagonists of PGD2 receptor (formally named chemoattractant receptor-homologous expressed in Th2 cells) such as setipiprant have been used to treat allergic diseases such as asthma, but they also have beneficial effects in AGA.^{85–87} Another small molecule l-ascorbic acid 2-phosphate promotes proliferation of ORS keratinocytes through the secretion of IGF-1 from DPCs via phosphatidylinositol 3-kinase.⁸⁸ Recently, it has been described that small-molecule inhibitors of Janus kinase–signal transducer and activator of transcription (JAK-STAT) pathway promote hair regrowth in humans.⁸⁹ Janus kinase inhibitors are currently approved by the FDA for the treatment of some specific diseases such as psoriasis and other autoimmune-mediated diseases.^{90–94} Also, another group of small molecules such as iron and the amino acid l-Lysine are essential for hair growth (Table 3).⁹⁵

Cellular therapy

The multipotent SCs in the bulge region of the HF receive signals from DPCs in order to proliferate and survive.^{27,28,65,84,96} It has been shown that Wnt/ β -catenin signaling is essential for the growth and maintenance of DPCs.^{19,97} These cells can be isolated and cultured in vitro with media supplemented with 10% fetal bovine serum and FGF-2.^{37,98} However, they lose versican expression that correlates with decrease in follicle-inducing activity in culture.⁹⁸ Versican is the most abundant component of HF extracellular matrix.⁹⁹ Inhibition of glycogen synthase kinase-3 by (2'Z,3'E)-6-bromindirubin-3'-oxime (BIO) promotes hair growth in mouse vibrissa follicles in culture by activation of Wnt signaling.⁹⁸ Therefore, the increase of Wnt signaling in DPCs apparently is one of the main factors that promote hair growth.¹⁹ DPCs have been also generated from human embryonic SCs that induced HF formation after murine transplantation.²⁷

Platelet-rich plasma

Platelets are anucleate cells generated by fragmentation of megakaryocytes in the bone marrow.¹⁰⁰ These cells are actively involved in the hemostatic process after releasing biologically active molecules (cytokines).^{100–102} Because of the platelets' higher capacity to produce and release these factors, autologous platelet-rich plasma (PRP) has been used to treat chronic wounds.¹⁰³ Therefore, PRP can be used as autologous therapy for regenerative purposes, for

example, chondrogenic differentiation, wound healing, fat grafting, AGA, alopecia areata, facial scars, and dermal volume augmentation.^{101,104–108} PRP contains human platelets in a small volume that is five to seven times higher than in normal blood and it has been proven to be beneficial to treat AGA.^{10,105,109–111} The factors released by these platelets after their activation, such as PDGFs (PDGF $\alpha\alpha$, PDGF $\beta\beta$, PDGF $\alpha\beta$), TGF- β 1, TGF- β 2, EGF, VEGF, and FGF, promote proliferation of DPCs and, therefore, may be beneficial for AGA treatment.^{109,112–114} Clinical experiments indicate that patients with AGA treated with autologous PRP show improved hair count and thickness.¹⁰⁹

In search of novel therapies

In this paper, we reviewed and discussed the use of therapeutic agents for hair regeneration and the knowledge to promote the development of new therapies for AGA based on the advances in regenerative medicine. The HF is a complex structure that grows when adequate signaling is provided to the HFSCs. These cells are located in the follicle bulge and receive signals from MSCs located in the dermis that are called DPCs. The secretory phenotype of DPCs is determined by local and circulatory signals or hormones. Recent discoveries have demonstrated that SCs in culture are able to activate DPCs and HFSCs and, in this way, promote hair growth. The study of these cellular signals can provide the necessary knowledge for developing more effective therapeutic agents for the treatment of AGA with minimal side effects. Therefore, advancements in the field of regenerative medicine may generate novel therapeutic alternatives. However, further research and clinical studies are needed to evaluate their efficacy.

Disclosure

The authors report no conflicts of interest in this work.

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