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Review Article

Exosome-based Therapies for Androgenetic Alopecia: Mechanisms, MicroRNAs, and Clinical Prospects

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Abstract

Characteristic signs of alopecia are gradual thinning, disruption of structural features, and the hair development cycle (anagen, catagen, telogen) against the background of miniaturization of hair follicles, which leads to baldness and psychological stress in patients. Despite the rapid development and clinical application of synthetic pharmacological, cellular/acellular, and molecular drugs, no effective therapeutic agent against alopecia has yet been developed. Great hopes are pinned on the improvement of therapeutic strategies with the introduction of exosomes into practical application, which contain a wide array of active substances for the targeted stimulation of hair follicle activity (anagen inducers) through the regulation of intracellular signaling cascades, growth factors, and microRNAs. The review discusses in detail the microRNAs and their intracellular targets that control hair follicle morphogenesis. It also focuses on the prospects of using stem cell exosomes from various sources for the treatment of alopecia, providing a clinical rationale for potential benefits and risks.

Introduction

Alopecia is a disease characterized by progressive hair loss caused by various mechanisms, among which genetic and environmental factors, as well as sensitivity to hormonal changes, play an important role.[1,2] Alopecia, therefore, has a multifactorial predisposition and is divided into different types.[3] Alopecia is associated with a number of comorbidities and remains an economic and psychosomatic burden for the individual and society.

The most common form of hair thinning and baldness is androgenetic alopecia (AGA), which varies in its pathogenetic and clinical features and affects between 23% and 87% of the world's population. The pathogenesis of the disease is characterized by multifactoriality, based on a combination of genetic predisposition (autosomal dominant inheritance with variable penetrance is most typical) and external factors (androgens) that negatively influence the development of the hair follicles (HFs) and lead to metabolic aging of hair.[4–6]

The development of AGA is based on the vellus-like transformation of the hair during repeated growth cycles (regeneration) of the scalp, the shortening of the anagen phase,[7] and the miniaturization of the HFs with disruption of their structure and the cyclical development of the hair. The disease affects HFs and their structures, including the dermal papilla (DP), which is a niche for the development of epithelial progenitor cells, and the DP microenvironment, which regulates hair regeneration (anagen, catagen, telogen). AGA is associated with a weakening of the DPs, a spheroidal structure that supplies the HF with nutrients and oxygen. A direct correlation has been found between the thickness of the hair shaft and the number of DPs.[8] A gradual progression of the disease is observed, which cannot be controlled with conventional therapeutic approaches based on the use of vasodilators and 5-alpha-reductase inhibitors, and in some cases is only partially effective in halting disease progression (partial regrowth of hair).[9] At the same time, the process of progressive hair loss inevitably causes cosmetic and psychological problems, leading to a negative perception of the body, social functioning, the patient's self-perception,[10] and psychological stress, regardless of age or stage of baldness.[2,9] The pathogenesis of AGA is caused by excessive production or activity of male sex hormones as the main factor of cytokine action on the microenvironment and the genetically determined expression of androgen receptors.[6] Type II 5α-reductase converts the male sex hormone (testosterone) into the potent androgen dihydrotestosterone, which binds to the androgen receptors of the follicle in the scalp, leading to a progressive depletion of HF, manifesting as miniaturization of the HF,[6,11] against the background of increasing active hypertrophy of the sebaceous glands (SGs) in response to the action of sex hormones.[12]

The therapy of AGA aims to stop follicle miniaturization by blocking the enzyme type II 5α-reductase, improving blood supply

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(as a factor for potential stem cell differentiation), stimulating follicle growth through the use of stem growth factors and platelet-rich plasma products, and increasing hair density. Therefore, the most accessible method of treating AGA is palliative treatment with drugs (finasteride—a blocker of the enzyme type II 5α-reductase, minoxidil—a drug with an angioprotective effect),[12,13] as well as the use of prostaglandins. The drugs have a number of limitations and side effects. The use of finasteride carries the risk of developing irritability and sexual dysfunction,[6] against the background of a short-term effect in patients with AGA.[3] The main antiandrogens used in women with AGA include cyproterone acetate, spironolactone, and flutamide.[14] Surgical treatment—the transplantation of autologous HFs from the occipital and temporal areas (donor zone) to the frontal and parietal areas (recipient zone)—is currently an effective method of treating alopecia with a good and stable aesthetic result in the medium term (six months).[1] However, the method has limitations for its wide application in patients with AGA due to the duration and painfulness of the surgical procedures and the limited, non-renewable number of autologous graft HFs in the donor areas.[1,11] As a result, in the late stages of AGA, there are not enough donor HFs available for transplantation (more than 10,000 HFs) to achieve an aesthetic result after surgery. In addition, limiting factors for surgical treatment of AGA include the postoperative three- to six-month rehabilitation period, the desocializing effect of surgery, and the risk of dysfunction of the transplanted HFs as a result of an unaltered microenvironment (to which the HFs are transferred).[15] Among the therapeutic (and early postoperative) strategies for the treatment of alopecia, a method of photobiomodulation using a laser to stimulate HFs is used.[12] Microneedling therapy is also used. In addition, a technique is employed in which microscopically small punctures are made in the scalp using a special device or thin needles (microneedling). The micro-injuries increase blood circulation and the local concentration of growth factors, which promotes the activation of HFs.[12]

In the treatment of autoimmune alopecia, JAK inhibitors are used to block the activity of JAK enzymes, which are involved in the regulation of cellular immune-inflammatory reactions.[12] Experience of positive use in the treatment of AGA has not been confirmed. Alternative methods for the treatment of AGA include the search for new properties and the combined use of compounds of biologically active substances (e.g., caffeine) with non-steroidal anti-inflammatory drugs.[13] The most recent promising and actively developing therapeutic approach, which enables a personalized approach to the problem of each individual patient with AGA, is molecular cell therapy.[1] Cell therapy utilizes multipotent/pluripotent stem cells from various tissue sources, as well as blood- and fibroblast-based products. When comparing the efficacy of blood products, which include platelet-rich plasma and platelet lysate, it should be noted that the latter has an advantage due to an additional processing step that leads to an increase in the concentration of growth factors.[13]

Cell-free therapy mainly uses extracellular vesicles/exosomes derived from mesenchymal stem cells (MSCs), MSCs derived from MSC (pre-) conditioned medium or supernatant,[16] microRNAs (miRs), and growth factors to activate hair follicle stem cells (HFSCs).[11] Exosomes are nanoscale or microscale bilayer structures (vesicles) that are surrounded by a lipid layer and have a diameter of up to 200 nm. They are secreted by cells and contain proteins, bioactive substances, and nucleic acids that regulate the vital functions of the recipient cells.[17,18] Studies show that exosomes stimulate the regeneration of HFs due to their high content of active components and miRs.[19,20] In particular, exosomes from stem cells come into contact with recipient cells via membrane molecules (receptors) and trigger intracellular signals that activate HFs. The interaction and subsequent fusion of exosomes with the target cell membrane ensure the intracellular transfer of exosomes contents and have a positive effect on the functional potential and growth of HFs.[19,21,22] The research areas dealing with the regenerative potential of exosomes, whose main source is stem cells, are actively developing. An important aspect is the inexhaustible potential and theoretically proven safety of exosomes (which needs further investigation) in regulating the growth and development of HFs. It is expected that a sufficient number of future studies that practically confirm the high regenerative and biotherapeutic potential of exosomes *in vitro* and in animal models will allow the field to enter the clinical trials phase and open up new opportunities for the development of molecular drugs that can solve the problem of treating AGA and specifically control the development of HFs.[19,23] However, an effective, safe, and widely accepted treatment for AGA with long-term efficacy has not yet been developed.[9,24]

Alopecia is characterized by a progressive disturbance in the alteration and ratio of HFSCs and dermal papillary cells (DPCs).[25] Functional changes in stem cells are associated with a disruption of molecular signaling cascades, against a background of differential expression of miRs and growth factors, accompanied by a change in the microenvironment of HFs. In particular, HFs from different scalp regions (frontal, occipital) of AGA patients were characterized by transcriptomic alterations associated with ephrin and Hippo signaling cascades, leading to dysregulated HF growth and miniaturization.[26] The miRs that have been upregulated in human DPCs include miR-106a/b, miR-125b, miR-221, and miR-410.[27] In the context of AGA, miR-133b expression was impaired at various scalp sites, affecting the Wnt signaling pathway and the subsequent processes of DPC proliferation,[28] HF growth, and development. In addition, pathological development and differentiation of keratinocytes were observed in AGA due to the low expression of miR-324-3p in HFSCs.[29]

This review aims to describe the molecular genetic aspects of exosomes derived from different tissues and cells, and the molecular components (growth factors, miRs) they contain in exos, in the control of vital activity and activation of HFSCs through intracellular signaling, considering the hair growth cycle in relation to the morphological stages (anagen, catagen, telogen), and to identify the main potential pathogenetic pathways for the development of AGA, taking into account the role of exosomes.

Anatomy of the HF

The HF is an appendage of the skin and regulates the growth and regeneration of the cuticle and scalp in the postnatal period.[30] The HF is a self-renewing miniature organ of the skin consisting of eight cell layers and is the result of a neuroectodermal-mesodermal interaction whose morphogenesis (induction, organogenesis, cytodifferentiation) is regulated by exogenous and endogenous factors,[3,31] including various signaling pathways (Wnt, Hedgehog, Notch, bone morphogenetic protein (BMP)), genetic, epigenetic factors, growth factors, and cytokines associated with the HF microenvironment formed by the epidermal component, the dermis, and the hypodermis (loose connective tissue and adipose tissue).[12,30,32–36]

Four morphological regions can be distinguished in the hair, which are subdivided from the dermis downwards and comprise the infundibulum, the isthmus, the suprabulbar zone, and the bulb. The hair shaft originates in the funnel region, which is morpholog-

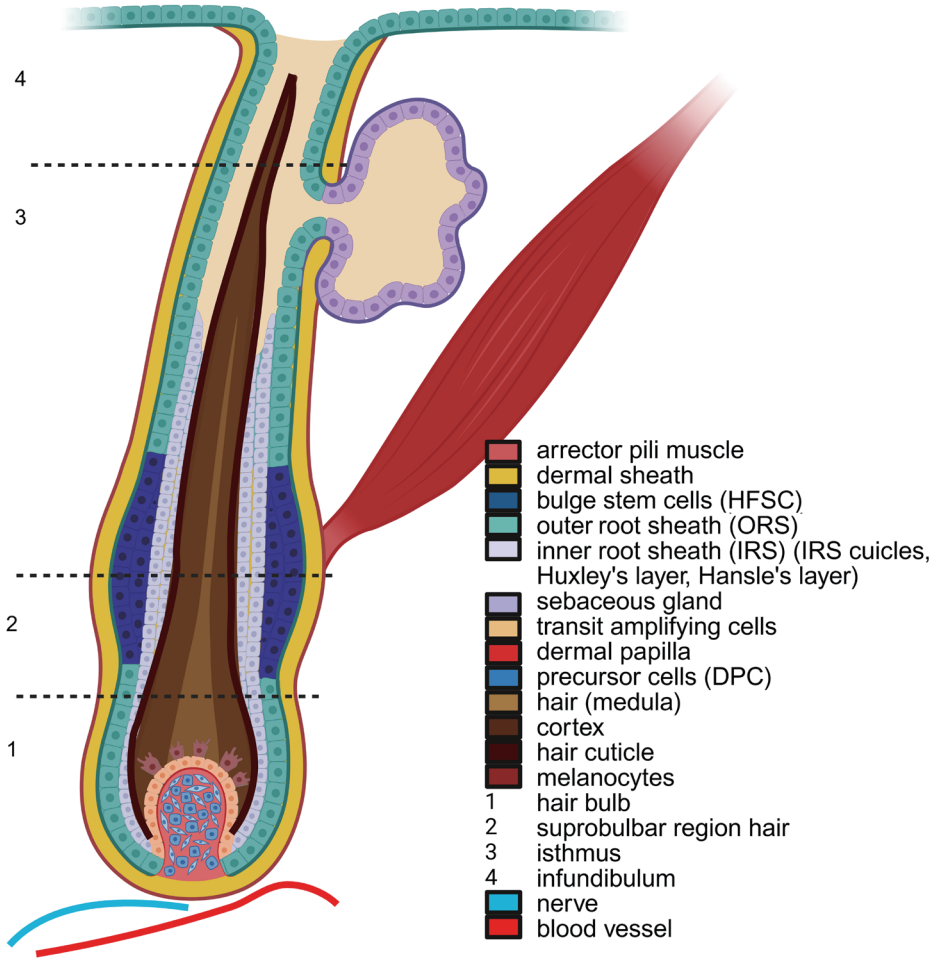


Fig. 1. Anatomy of the hair. The hair follicle consists of eight cell layers and four morphological regions can be distinguished in the hair, which are subdivided from the dermis downwards and comprise the infundibulum, the isthmus, the suprabulbar zone and the bulb. DPC, dermal papillary cells; HFSC, hair follicle stem cells.

ically defined by the area between the openings of the HF and the SG and has a relatively constant cellular composition. Next comes the isthmus—the area between the opening and the smooth muscle fibers (arrector pili muscle (APM)) that raise the hair, which is located in the papillary dermis. The isthmus contains a population of stem cells involved in epidermal regeneration (Gli1+Lgr6+). Below the isthmus, where the APM attaches, is the suprabulbar region or lower segment of the HF (lower follicle, hair bulge). Beneath the suprabulbar region is a spherical structure—the hair bulb, which includes the DP, which forms the base of the HF, outer root sheath (ORS), and inner root sheath (IRS).[3,25] The DP is supplied by the neurovascular network in the neighboring layer of the hair matrix (Fig. 1). The precursor and matrix cells of the HF colonize the bulb and the dermal sheath by proliferative processes. The matrix cells act as germ cells and support the hair cycle, while the progenitor cells have high regenerative potential and prevent skin damage and restore the DP.[3]

HFSCs colonize HF segments,15 but HFSCs from the isthmus and the zone between APM and ORS are highly clonogenic and can form cells of the interfollicular epidermis, HF, and SG.[32] Human HFSC markers include pleckstrin homology-like domain, family A, member 1 (PHLDA1),[37] EpCAM/Ber-EP4, and characteristic molecules of telogenic hair germs.[38] Purified human bulge HFSCs express keratin 15 and cluster of differentiation 200 (CD200). The HF goes through cyclical physiological phases: anagen (growth), catagen (involution), telogen (resting phase), and exogen (release of telogen effluvium or hair breakage). The signals that control the processes occurring in HFSCs are generated directly in the HF and control the cyclicity of the phases of HF regeneration/morphogenesis,[39] including the long phase of hair growth—anagen (two to six years on the scalp and in the area of a person's mustache and beard, two years on the body),[12] which is characterized by the priming and rapid proliferation of HFSCs in the hair germ, generating transit-amplifying cells that form the hair shaft and IRS,[32] and the subsequent activation of HFSCs in the bulge, which mediates the formation of ORS.[12] This is followed by a two-week catagen phase characterized by a decline in the cell cycle, short-term regression of the matrix and hair ORS, mediated by apoptosis in the cells of the bulb,[32] triggered by fibroblast growth factor (FGF) 5, brain-derived neurotrophic factor (BDNF), p75, p53, transforming growth factor beta (TGFβ)1, and bone morphogenetic protein receptor type 1A (BMPRIa).

This is followed by the telogen phase—two to three months of quiescence of the HFSCs, during which some HFSCs undergo mi-

gration.[35] The lower ORS cells differentiate into the inner bulge cells (Krt6+), the hair germ develops from the middle cells, and the upper cells form a new bulge.[32] At the same time, telogen is associated with high expression of estrogen receptors. The action of 17-β-estradiol has an inhibitory effect on the HF cycle and stops the anagen phase.[33] HFSCs therefore exhibit heterogeneity: part of the cells of the follicular layer do not participate in HF regeneration (isthmic stem cells), while the cells of the lower part can regenerate ORS HF.[40] Isthmic stem cells are characterized by low content of α6-integrin and are CD34-negative. A universal pluripotent population of HFSCs located near the SG, whose progeny reside in the ORS of the HF, has also been described.[41]

Epidermal stem cells of the central isthmus above the bulge are Wnt-independent, Lgr6-positive, and give rise to HF, SG, and interfollicular epidermis.[42] In addition, HFSCs in the isthmus and inferior bulge can form HF and epidermis (cell line and mouse studies) by migrating into the epidermis.[43] HFSCs can form a pool of transient-amplifying cells, which are involved in the healing of acute wounds.[12] The stem cells of the upper bulge are normally quiescent but have the potential to self-renew and form hair and SG.[41] In particular, K15+, Lgr5+, Gli1+ stem cell progeny from the upper bulge promote the formation of sebocytes and also neuronal, endothelial, and fat cells outside the HF via β-catenin, mediating wound healing.[41] The activation and vital activity of stem cells in the bulge is subject to strict control by the daughter stem cells of the bulge, which initiate self-renewal processes in the anagen stages.[44] The stem cells act on the DP by interacting with the germinal matrix cells isolated by the basement membrane. They are important for the activation of hair growth and for signal transmission during repair.[38,45]

Fat formation is synchronized with the activation of HFSCs. In this case, the maximum number of progenitor cells in the subcutaneous adipose tissue is recorded at the time of HFSC activation.[30] Severe stages of cachexia with a lack of subcutaneous adipose tissue are accompanied by severe alopecia.

The lower part of the hair bulb contains a multicellular tissue structure—the DP—which supports hair growth and the HF by interacting with capillaries and nerve endings.[30] The DP contains a pool of dermal stem cells involved in the regeneration of the new dermal sheath (outer layer of the HF) during the phases of the hair cycle.[30] DPCs are found at the base of the HF and are responsible for its formation and regeneration. The DPC markers alkaline phosphatase (ALP) and versican induce HF formation. ALP is directly related to HF formation and is a biomarker of this process induced by DPCs.[46,47] Versican expression is β-catenin-dependent and maintains or stimulates the growth of DPCs, initiating the HF cycle.[47,48] Thus, HFSCs of different localizations mediate normal function and passage of the hair through cyclic stages and actively respond to the microenvironment and molecular factors.

Intracellular signaling cascades and molecules that regulate the phases of HF development

The entry of some HF stem cells into the anagen phase occurs when a certain concentration of stem cell-activating factors is reached in the microenvironment.[49] Activated HFSCs ensure hair growth and tissue regeneration.[41,50]

In the final stage of telogen, the secondary hair germ cells and the DP are activated and produce proteins that initiate anagen. Two important molecular participants have been identified—insulin-like growth factor (IGF) 1 and FGF7—which are synthesized by the DP. These factors interact with the surface glycoproteins of matrix keratinocytes and control the development and cyclicity of the HF. In addition to IGF1 and FGF7, anagen induction depends on molecules belonging to the TGF-β, BMP, WNT, Sonic Hedgehog, Homeobox, and neurotrophin (NT) families.[39]

WNT

The molecular intracellular WNT cascade regulates HF formation and growth through basal plate and placodes, regulates morphogenesis, and mediates the transition to the HF stage.[30] The canonical WNT signaling cascade comprises the protein families WNT, Frizzled, Dishevelled, β-catenin, and the Axin/glycogen synthase kinase (GSK)-3/APC protein complex. WNT is secreted under the influence of the transmembrane transporter Wntless, the expression of which is observed in HF after hair formation. Wnt proteins act as morphogens in the induction of primary HF,[6] the formation of placodes,[39] and the transition to anagen.[39] The WNT family includes primary WNTs (WNT3, WNT4, WNT6), which are required for HF induction, and secondary WNTs (WNT2, WNT7b, WNT10a, WNT10b), which are involved in HF development.[30] Overexpression of versican and WNT/β-catenin leads to aggregation of specialized mesenchymal fibroblasts under the epidermis, giving rise to the placode.[3]

The first WNT that triggers HF initiation is unknown; the second is Wnt5a. Stable β-catenin activity in the dermis controls epithelial thickening and plaque formation. Subsequently, fibroblasts regulate the formation of the dermal condensate, the precursor of DP,[3] via WNT/β-catenin and FGF20. Wnt1a regulates the stability of DP properties and is involved in HF recovery processes.[3] During IRS formation, Wnt1a is activated by BMP secretion, upregulating the transcription factor GATA-3 and modulating the differentiation of IRS precursors, or maintaining sufficient levels of the intracellular protein Lef1 (target of Dlx3) and stabilized β-catenin for hair shaft growth.[3] WNT3a is expressed in HF in the anagen bulge zone and in melanocytes and regulates proliferation, differentiation, and pigment deposition.[51] The expression of WNT3a was analyzed in the progenitor cells of the root sheath, bulb, hair bulge, epidermis, and melanin stem cells of HF.

Wnt10b regulates placode border formation and is directly dependent on nuclear factor kappa B (NF-κB) induced by WNT/β-catenin signaling.[3] The size of the placode is determined by the interaction of NF-κB with dickkopf-related protein 4 (DKK4).[3] WNT10b is expressed during anagen and promotes epithelial differentiation and early HF development.[52] Wnt10b regulates the formation of IRS from primary epithelial cells.[3] During telogen, the critical moment for anagen activation is the presence and high expression of WNT10b in the HF microenvironment.[53]

Wnt1a, 3a, 7a, and 7b stimulate the WNT/β-catenin pathway in DPCs, which is responsible for hair development.[36] GSK-3β, which regulates self-renewal and cell function, also negatively regulates Wnt signaling through phosphorylation at Ser9 and stabilizes β-catenin.[6] Thus, activation of the Wnt cascade is accompanied by intracellular accumulation of β-catenin and its transfer to the nucleus, stimulating the expression of target genes for renewal and proliferation: Axin2, Lef1,[6,36] WNT3A, and secreted frizzled-related protein 1 (SFRP1).[20] Hair removal stimulates the production of tumor necrosis factor (TNF)-α, which leads to activation of scalp keratinocytes and increased expression of the *WNT3*, *WNT10a*, and *WNT10b* genes. In addition to activating the WNT signaling cascade, TNF-α also activates NF-κB and thus regulates hair regeneration processes.[30] β-Catenin is expressed in HF stem cells, hair germs, and hair bulges during HF regeneration and interacts with the nuclear complex of DNA-binding proteins T cell

factor/lymphoid enhancer factor family (LEF/TCF), initiating the transcription of genes (c-myc, Cyclin D1) responsible for cell proliferation, apoptosis, cell cycle, and differentiation of HFSCs.

The Wnt cascade controls the exit from the quiescent stage and the activation of the anagen stage through the development of stem cells in the bulge area. In AGA, a violation of the functional potential of stem cells is associated with impaired Wnt signaling. Probability loci associated with Wnt ligand biogenesis and class B/2 molecular pathways are involved in the pathogenesis of hair loss. The Wnt/β-catenin cascade was found to control and maintain the development of DPCs.[54] Investigations revealed that the regulation of androgen receptors is controlled by six loci in seven genes, which are conditionally divided into groups. The genes in the first group include genes associated with Wnt (RSPO2, LGR4, WNT10A, WNT3, DKK2, SOX13, TWIST2, TWIST1, IQGAP1, PRKD1), genes associated with apoptosis (DFFA, BCL2, IRF4, TOP1, MAPT), and a group combining various genes, including androgen receptor and TGF-β signaling (RUNX3, RUNX2, ALPL, PTHLH, RUNX1, AR, SRD5A2, platelet-derived growth factor (PDGF)-A, PAX3, FGF5). It is assumed that the anagen stage is shortened by contrasts in genes that control apoptosis.[38] Activation of the WNT/β-catenin signaling cascade leads to nuclear expression of the genes Axin2, Tcf/Lef, Lgr5, WNT3A, SFRP1, and Blimp1. It has been shown (in mice) that Wnt ligands are continuously produced by the ORS and maintain HFSC activity. At the same time, the IRS-HFSC secretes Wnt inhibitors: DKK and SFRP1, which ensure a quiescent state during telogen.[35]

As mentioned, activation of the Wnt signaling pathway regulates intranuclear Tcf/Lef transcription factors. Tcf3/4 downregulates important genes of the Wnt signaling pathway and inhibits HFSC activation. When Tcf3/4 interacts with β-catenin, the suppressive effect is blocked.[55] The activation of β-catenin depends on Lef1 expression and regulates gene expression in HF cells.[11] Expression of the Lgr5 gene is upregulated in HFSCs (genetic marker) localized in the bulge, promoting their self-renewal and upregulating the Sonic hedgehog (Shh) pathway to promote differentiation of HFSCs during the anagen phase.[35] The Blimp1 gene is a target and mediator of DP-inducing signaling pathways including TGF-β and WNT/β-catenin.[56]

The high local concentration of dihydrotestosterone in AGA is associated with high expression of genes that inhibit WNT/β-catenin signaling: SFRP2, SERPINF1 (PEDF), DKK1, and IGFBP3, resulting in activation of TGF-β expression and reduced HF growth.[6,11] Reduced regulation of SERPINF1 stimulates the proliferation of DPCs, promotes HF growth, and prolongs the anagen stage. The use of recombinant PEDF protein produced unclear results. Reduced regulation of SFRP2 induces WNT signaling.[57,58] SFRP2 also increases the expression of WNT3a, enhancing WNT signaling pathway activity.[59] Exogenous SFRP2 inhibits DPC proliferation.[60] DKK1 has been shown to be a potential biomarker for obesity and reduces HF enlargement and hair width,[60,61] linking AGA development to age and obesity.[62,63]

Thus, the Wnt signaling pathway plays an important role in HFSC activation and promotes the transition to the anagen phase by regulating the expression of target genes responsible for placode formation and HF development. During the hair cycle, WNT protein expression changes, peaking in anagen and gradually decreasing until it ceases in telogen.[30]

Notch

Another membrane receptor that transmits a signal into the cell and regulates gene expression is Notch.[64] Notch regulates stem cell potential, adhesion, epidermal cell localization, and cellular differentiation by repressing p63.[3] Notch1 is an important regulator of hair growth due to its potentiating effect on Wnt5a expression in DP and its activating effect on FoxN1 expression in keratinocytes, which are localized in the hair cortex and induce their differentiation.[3] Notch is involved in the protection and maintenance of HF function by regulating the skin microbiota (preventing dysbiosis) and protecting stem cells from inflammatory destruction.[65]

Shh

The Shh glycoprotein is a signaling molecule and an inductive factor that regulates the signaling pathway determining cell fate. In the absence of Shh protein, the Patched and Smoothened (Smo) components of the signaling pathway interact, resulting in inhibition of Smo.[66] Shh interacts with Patched and releases Smo via the transcription factor Gli, which activates it and transports it into the nucleus to initiate gene transcription, including Cyclin D1 and N-myc.[67]

The Shh signaling pathway is involved in HF morphogenesis during embryonic development.[68] Although it is not required for HF development, it regulates epithelial proliferation and HF growth. During the anagen phase, Shh is strongly expressed in the follicular matrix and acts as a mitogen that accelerates telogen exit.[33,69] In addition, DP maturation is determined by dermal expression of Shh, which activates specific morphogenesis genes.[30]

The initial phase of hair formation is associated with the production of the proteins Noggin and Shh in the placode. Noggin inhibits BMP activity by increasing the expression of the transcription factor Lef1, leading to activation of the Shh signaling pathway that regulates DP maturation. Conversely, Noggin-BMP contact suppresses the expression of E-cadherin, which is overexpressed in HF-deficient mice.[3] Furthermore, activation of downstream targets of the Shh signaling pathway (Sm, Gli, etc.) can be controlled by formation of the laminin-511–β-integrin complex (ligand-receptor).

Shh is also secreted by perifollicular nerve endings to support Gli1+Lgr6+ HFSCs that regulate epidermal regeneration.[30] Shh is involved in root sheath cell differentiation via activation of Sox9. GATA-3 is expressed during epidermal cell stratification and IRS differentiation. Cult1 is required for epithelial HF differentiation.[3] Selective local expression of the Sox4 and Shh genes is observed in HF, whereas no expression occurs in the bulge.[33] Thus, activation of the Shh signaling pathway controls anagen and HF morphogenesis.

BMP

BMPs belong to the family of secreted glycoproteins of the TGF-β superfamily and influence tissue and organ development. BMPs regulate cellular processes through ligand-receptor interactions,[70] forming a heterodimeric complex that phosphorylates Smad1/5/8,[71] followed by interaction with Smad4 and translocation to the nucleus. Smad1/5/8 also activates transcription factors that regulate the proliferation and differentiation of HFSCs.[72] The activation of BMP is associated with cessation of hair growth, consistent with studies on the BMP antagonist Noggin, which shortens the refractory period and initiates hair regeneration.

The ratio of high BMP6 expression to low Sostd1 expression mediates hair shaft growth via Sox2.[3] BMP7 also influences HF stem differentiation after birth in cashmere goat.[73] BMP signaling influences the refractory period and regeneration time in telogen. Myofibroblasts can be reprogrammed into adipocytes via BMP signaling during wound healing of new HF by activating the expression of adipocyte transcription factors.[74]

TGF-β

TGF-β family proteins play an important role in the pathogenesis of AGA.[7] TGF-β2 activates Smad2/3 in HFSCs and promotes enhancement of the regeneration process.[3] TGF-β2 suppresses target genes of the BMP signaling cascade (BMP/Smad1/5 – ID3) by activating Tmeff1, stimulating HFSCs, and triggering anagen.[3,75] In anagen, gradual suppression of TGF-β signaling is observed, with increased WNT/β-catenin and Ki-67 activity.[11] Interaction of TGF-β with the specific surface glycoprotein endoglin (Egn) on the HFSC surface ensures switching between BMP and Wnt signaling. The effector of BMP and Wnt signaling pathways, Smad4, forms heterodimers to control Egn expression in HFSC homeostasis.[35]

During anagen in DPCs, interaction of the SMAD3 gene with SMAD2/SMAD4 was observed, leading to suppression of nuclear expression of versican and β-catenin, resulting in AGA development.[11]

Ectodysplasin A (EDA) receptor (EDAR)

EDA/EDAR/NF-κB maintains the primary placode and regulates Shh-mediated HF organogenesis via secretion of cyclin D1.[3]

The EDAR signaling pathway consists of the EDA ligand, the transmembrane receptor EDAR, and the intracellular binding protein EDARADD, and is involved in HF development and the HF cycle.[30] EDA and EDAR belong to the TNF superfamily. Structurally, EDAR is divided into an extracellular N-terminal ligand-binding domain, a single transmembrane domain, and an intracellular death domain.[30] The latter interacts with EDARADD to initiate transcription of target genes.[30] The highest expression of EDA, EDAR, and EDARADD is observed in late anagen, gradually decreasing throughout the HF cycle and reaching a minimum in telogen.[30] Thus, anagen activation is controlled by the EDAR signaling pathway and determines normal hair development.

Hypoxia-inducible factor 1-alpha (HIF-1α)

The hypoxic microenvironment provides signals that regulate stem cell self-renewal and differentiation.[76,77] HIF-1α, the major transcription factor in the hypoxic signaling pathway, is normally degraded by hydroxylation via proline hydroxylase. The HIF subunit is prolyl-hydroxylated under normoxic conditions by members of the egg-laying nine (EGLN) family (prolyl hydroxylase domain (PHD)-2), leading to its rapid degradation.[27] Under hypoxia, free radicals inhibit proline hydroxylase activity and increase HIF-1α gene expression.[78] Suppression of PHD-2 promotes HIF-1α activity and induces transcription of hypoxia response element (HRE) genes, including vascular endothelial growth factor (VEGF), chemokine (C-C motif) ligand 5, and endothelins ET-1 and ET-2.[27] Key genes associated with the HIF-1α signaling pathway include *EGLN1*, *EGLN3*, *SERPINE1*, *HMOX1*, *TIMP1*, and *IL6R*.[27]

The HIF signaling pathway regulates hair development, restoration, and regeneration. HIF controls HF regeneration by influencing the shape and size of the DP.[79,80] Hair growth is similar to wound healing, in which HIF-1α stimulates neovascularization and collagen/elastin formation.[8] Anagen is characterized by increased vascularization. HIF-enhancing factor binds and removes iron ions, which act as cofactors for PHD. Inactivation of PHD promotes the accumulation of uncleaved HIF-1α, which binds to HIF-1β, dimerizes, and generates active HIF. The activation of angiogenesis and regeneration processes is triggered by transcription of HRE genes.[80] In DPCs, exposure to hypoxia leads to increased proliferation via modulation of lactate dehydrogenase activity.[81] Additionally, hypoxia stimulates hair induction in a paracrine manner through the generation of reactive oxygen species and production of cytokines and growth factors.[82,83]

AGA is associated with decreased vascularization and nutrient supply due to reduced VEGF expression in HF.[27] In the scalp, AGA is associated with decreased HIF1A expression and indirect inhibition of hair growth genes.[83] Suppression of EGLN1/3 expression has been found to induce DPC proliferation by activating HF via the HIF-1α–VEGF signaling cascade.[27] Furthermore, blocking EGLN1 activates anaerobic glycolysis regulated by the HIF pathway, controlling HF metabolism in AGA.[84] Hypoxia activate the HIF signaling pathway, promoting new blood vessel formation and triggering regeneration processes in the DP cells.[8] Administration of HIF-stimulating factor has a positive effect on hair restoration *in vitro*.[80] Thus, proliferation and migration of DP daughter cells were observed in 3D DPC cultures (hanging drop method) when stimulators of the HIF-1α signaling pathway, such as deferoxamine and deferiprone, were added (similar to the effects of minoxidil and caffeine).[80] However, HIF modulators/PHD inhibitors have been shown to shorten the kenogenic phase and accelerate the onset of anagen.[8,83] Therefore, HIF-1α stimulates HF and mediates the onset of anagen phases while shortening HF latency.[83]

Exosomes

Molecular mediators control the formation and cyclic transitions of HF. Vesicles contain a considerable amount of them, release them from the cells, and change the functional potential and properties of the target cells. The concept of extracellular vesicles summarizes several classes of nanovesicles that are secreted by most cells as intercellular mediators, including exosomes (30–200 nm) and microvesicles (30–1,000 nm) containing miRs, messenger RNAs (mRNAs), non-coding RNAs, DNA,[1] and proteins, including cytokines and growth factors.

Exos are formed by endocytosis and excreted by the mechanism of exocytosis.[85] Exos that form from endosomes are characterized by a similar set of membrane glycoproteins. Annexins, flotillin, GTPases from the families of transport and fusion proteins, Alix, TSG101 (which regulates the formation of multivesicular bodies), Hsp20, Hsp60, Hsp70, tetraspanins (CD9, CD63, CD81, CD82), phospholipases, and proteins covalently bound to membrane lipid molecules are expressed on the surface of exos.[86] It was found that exosomes derived from DP,[87–90] dermal fibroblasts, keratinocytes,[91] HFSC,[92,93] adipose-derived stem cells (ADSC) and conditioned medium (containing exos) derived from MSC can be used to activate the proliferation of HFSC and hair growth. Human MSCs from the umbilical cord,[6,11,20,94–102] hSCs from the dental pulp.[103]

Exos can be of natural origin or produced artificially. However, the use of synthetic liposomes and nanovesicles for the delivery of therapeutic molecules (miRs) has encountered the problem of their biocompatibility and safety, which favors the use of exosomes of natural origin.[104] At the same time, the development of science in this direction is unstoppable, and several human clinical trials have already been registered using exos artificially enriched with certain miRs. However, a limiting factor is the lack of large-scale preclinical studies in animals that ensure an optimally developed scheme for the maintenance of cell cultures producing exosomes, as well as the dosage and conditions for drug administration.[104] At the same time, the nature of endogenous mechanisms for miR loading/sorting in exosomes is under active investigation, but the factors that determine active or passive loading have not yet been elucidated. Important features of exosomes are their composition, which is characterized by the content of lipids and proteins on their

surface, and their nanomechanical (colloidal) properties, which determine the interaction with the recipient cell.[104]

Composition of exosomes (miRs in hair growth)

miRs and hair growth

miRs are 18–25 nm long RNAs that regulate gene expression by influencing mRNA.[3,90] Exosomes protect miRs from degradation by RNases and mediate their effect within the recipient cells, thereby influencing biological processes.[90] The key epigenetic regulators responsible for the development and regeneration of HF are miRs, which are found in the skin and in HF.[105]

miR-1 influences the development of HF by controlling genes responsible for the proliferative potential and differentiation of HFSCs. miR-1 overtranscription suppresses the division processes of HFSC by inducing differentiation, affecting the expression of IGF1 receptor (*IGF1R*) and *LEF1* genes.[106] LEF1 has been found to be required for Wnt signal transduction. Anagen is characterized by high expression of the LEF1 transcription factor, leading to activation of the β-catenin signaling pathway, inducing differentiation of bulge stem cells and preventing apoptosis of HFSCs.[88]

miR-21 stimulates HF development by inactivating BMP4 and inhibiting the mRNA of Pten, Pdcd4, Tim4, Tmp1.[3] miR-22 is increased in catagen/telogen compared to anagen. miR-22 controls the HF cycle by regulating the formation of IRS and hair shaft and repressing the activity of DLX3, FOXN1, and HOXC13.[107,108] miR-22 is a post-transcriptional controller of the HF cycle, stimulating the transition to catagen, activating the Wnt/β-catenin cascade, and increasing the mRNA expression of WNT3A, AXIN2, LEF1, and SEPRP1 genes in DPC, which ensures hair regrowth.[20] miR-22-5p inhibits the proliferation of HFSC by targeting LEF1 and Foxn1.[87] miR-24 affects HFSC differentiation in mice by inhibiting Tcf-3 (keratinocyte stem cell regulator) during the anagen phase of HF, leading to HF developmental defects.[109] miR-29a/b1 affects LRP6, Ctnnb1, Bmpr1a and suppresses Wnt signaling and BMP, whose expression is induced during the HF cycle, shortening hair by suppressing HFSC and matrix cell differentiation.[3] It was found that the suppressive effect of miR-29a-5p on EDAR has a negative effect on the formation of hair placodes.[110] Since miR-29 can be characterized by multidirectional effects by grouping several miRs (miR-29a, miR-29b, miR-29c) under the term miR-29, overexpression of miR-29a/b1 in mouse HFSCs leads to inhibition of their activation by blocking the Wnt signaling pathway via the target LRP, resulting in hair loss.[111] Interesting results were obtained in animal models (mice), which showed a significant decrease in miR-29a expression in the anagen,[112] indicating the need for a detailed study of this miR.

miR-31 affects the development of HF, as evidenced by the high expression of this miR in mutant nude mice.[113] miR-31-5p specifically blocks the activity of AXIN1, which suppresses the Wnt signaling cascade by reducing β-catenin.[114,115] The miR-31 target genes also include DKK1,[116] SMAD3/4,[117] RAS p21 activator protein 1, which increases the level of mitogen-activated protein kinase (MAPK) 1/3 and promotes hair growth.[118] On the other hand, miR-31 impaired hair growth in transgenic mice.[119] In humans, miR-31 was upregulated in HF aging.[120]

miR-103/107 homologs target DKK1 and AXIN2.[121–123] It was found that the expression of miR-103/107 in epidermal keratinocytes decreases with increasing age of the organism (mice).[124] This may suggest a role for this miR in regulating the growth and development of HF. miR-122-5p induces angiogenesis by specifically activating VEGF and reducing endothelial cell metabolism. In addition, miR-122-5p acts as a blocker of the TGF-β signaling cascade and activates hair regeneration processes. These data are supported by the effect of Exos-miR-122-5p on DPC in AGA, the suppression of SMAD3/p-SMAD3, and the restoration of versican and β-catenin levels.[11] miR-122-5p affects Wnt2 mRNA.[3] miR-125 is highly expressed in alopecia DPCs.[125] miR-125b inhibits the expression of Blimp1 and vitamin D receptor genes, thereby arresting HFSC differentiation and disrupting stem cell renewal.[63] miR-126 is highly expressed in HF, but no further studies have been performed.[63]

miR-130b-5p targets Wnt10a and DKK1.[126,127] Overexpression of miR-133b is observed in AGA, which negatively affects the β-catenin signaling pathway in HFSCs.[28] NOTCH1 was found as a co-target gene for miR-133 in ovine HFs.[128] The target of miR-140-5p is BMP2, which leads to the activation of proliferative processes in the ORS and HF matrix.[3] miR-149 expression decreases during differentiation of HFSCs, and when overexpressed, limited proliferation/differentiation of HFSCs is observed by blocking MAPK1/ERK2 signaling, followed by a decrease in FGF2 and c-MYC gene expression.[129] miR-152 is expressed in HF, has one target—the mRNA of the *DKK1* gene—and inversely correlates with the level of DKK1.[130] miR-152 expression increases during aging of skin fibroblasts. miR-152 is involved in the regulation of inflammatory processes.[131]

miR-181a-5p stimulates the Wnt/β-catenin cascade and induces HFSC division.[90] Animal studies (sheep) have identified a target gene—the Galpha i2 protein—for miR-181a, which is able to stimulate the Wnt/β-catenin cascade in DPC, inhibit cell division processes, and trigger DPC.[132] miR-195-5p induces HF by targeting the LRP6 protein (in DPs) and blocking Wnt/β-catenin activity.[3,133] miR-195-5p is expressed in exosomes of DPCs and affects genes that induce proliferative processes that regulate hair growth.[134] However, induced overexpression of miR-195-5p in DPCs inhibits their proliferation.[135]

High expression of miR-203a-3p, which targets the *Smad1* gene, is observed in differentiated HFSCs. miR-203a-3p represses Smad1 expression and mediates BMP induction, thereby preserving the properties of HFSCs.[136] In addition, miR-203 inhibits its DKK1 mRNA,[137] activates the Wnt/β-catenin pathway, and induces anagen hair growth.[138] miR-205 is expressed in HFSCs. Lack of miR-205 expression leads to proliferation arrest in HFSCs by impairing the PI3K signaling pathway.[3] miR-214 inhibits β-catenin by targeting the Enhancer of Zeste homolog 2 and suppresses HFSC proliferation and differentiation.[3] miR-214 also affects Sox9 and polypyrimidine tract-binding protein 1 in HFSCs. On the other hand, high miR-214 expression leads to abnormal hair length.[3] The overexpression of miR-214 reduces the number of HFs and slows down the hair growth cycle. Lower miR-214 expression in exosomes of DPCs induces reprogramming of adipose tissue stem cells in DPCs.[134] miR-218-5p activates the regenerative potential of HFSCs by activating β-catenin signaling,[20,90] and by targeting (inhibiting) the *SFRP2* gene (mice).[3] miR-218-5p upregulates the *Ctnb* gene to promote HF neogenesis.[139] miR-339-5p is downregulated during HFSC differentiation, regulates *DLX5* and *Wnt3a* genes, and inhibits Wnt/β-catenin signaling.[140]

miR-1285-3p has the target genes *LEF1*, *Dlx3*, *Foxn1*, and *Sosdc1* and affects cellular differentiation by accelerating the transition from HF to telogen. Increased expression of miR-1285-3p impairs HFSC proliferation by decreasing the expression of KI67, PCNA, and AKT proteins, and increasing the expression of S100A3, K6, and Notch1 proteins, thereby blocking hair growth by activating the NOTCH signaling pathway.[64] In addition, miR-

1285-3p inhibits the proliferation of HFSCs through the activation of human HFSCs.[64] Let-7b modulates *EDA* gene expression via post-transcriptional regulation of the TGF-βI receptor.[3]

Infusion of DPC exosomes into HF affected the β-catenin and Shh signaling pathways, resulting in prolonged anagen and catagen phases during hair development.[141] The cellular microenvironment, consisting of dermal and subcutaneous fibroblasts, plays an important role in the functional potential of HFSCs. Melanocytes are formed from melanocyte-derived MSCs that are localized in a niche. Epithelial cells of the scalp produce TGF-β and Wnt and thus determine the viability and functional properties of MSCs. On the other hand, MSCs are influenced by cells of the extracellular matrix, in particular by the action of integrins in the basal layer.[38]

The expression of the following miRs was found to be increased in DP in AGA: miR-221, miR-125b, miR-106, miR-410.[3] High expression of miR-133b, miR-141-5p, miR-652-5p, miR-520d-5p, miR-1247-5p, and decreased expression of miR-378d, miR-4286, miR-3607-6p were observed in AGA-affected regions. The highest expression of miR-133b, miR-141-5p, miR-652-5p, and miR-1247-5p was observed in AGA areas compared to the control.[28] Thus, there is a long list of miRs expressed by single cells or localized in exosomes that influence the activation/quiescence of HFSCs. A closer examination of their properties and targets in relation to recipient cells and target genes will determine their clinical potential for the treatment of AGA.

Growth factors and hair growth

VEGF, PDGF, and bFGF induce HF growth. VEGF regulates the formation of blood vessels, the development of HF, and its properties.[36] PDGF has a stimulatory effect on the growth and development of HF in adipose tissue models (mice) through activation of HFSC.[142] The production of PDGF-AA with a paracrine effect was observed in the DPC, and its effect was directed toward the development and maintenance of HF.[134] PDGF and FGF2 have a synergistic effect by promoting proliferation and maintaining the inductive capacity of DPC.[47] FGF-2 contacts the receptor, activates signaling, and induces the expression of the *CTNB* gene.[134] CTNB controls genes responsible for the cell cycle and cell division (*Cyclin D1, c-Myc*, *and Ctnb*). After activation, Ctnb accumulates in the cytoplasm and is transported to the nucleus, where it regulates the transcriptional activity of anagen maintenance factors in the HF development cycle.[143] FGF7/keratinocyte growth factor (KGF) and epidermal growth factor (EGF) activate HF cells. The initiation phase is associated with high expression of ligands and low expression of receptors for these growth factors.[3] Anagen arrest is associated with the activity of FGF5, the absence of which leads to a prolonged anagen phase and the formation of extra-long hair shafts in mice.[39] Anagen arrest is also regulated by EGF receptors.[39]

IGF1 is a multifunctional cell growth factor that is involved in the basic life processes of cells.[144] IGF1 controls cell division, the synthesis of various proteins, hair growth, and hair loss.[145] IGF1 is involved in the processes of epidermal regeneration and HF (in rats). IGF1 exerts a stimulatory effect on bone marrow (BM)-MSCs by activating the ERK1/2 cascade, leading to suppression of the inflammatory response, inhibition of proinflammatory cytokine secretion, and activation of regenerative processes in skin and HF.[146] The development of AGA is accompanied by a high local concentration of dihydrotestosterone, which interacts with the androgen receptor, resulting in the inactivation of IGF1 and the initiation of MAPK and PI3K/AKT signaling under the influence of miR-221.[147] In addition, AGA is associated with increased expression of miR-122 in the HF, which triggers apoptosis of hDPC and downregulates the expression of the *IGF1R* gene.[148]

EGF ensures HF regeneration by mediating the activation of MSCs.[149]

Irisin, which belongs to the myokines (VEGF, IGF1, FGF), regulates hair growth. Irisin affects various cellular properties, increases proliferative activity and mitochondrial potential in hDPCs by stimulating GSK-3β/β-catenin, and induces target genes of the Wnt signaling pathway, leading to hair growth and hair shaft elongation (in humans).[150] Irisin induces rapid anagen onset and mediates accelerated hair growth in mice (C57BL/6).[150]

NTs regulate the formation of the most important morphological parameters of hair. In particular, NT-3 and NT-4, which are derived from a glial cell line, stimulate the formation of hairs characteristic of AGA under stress: with a smaller shaft diameter and reduced density.[151]

Glial cell-derived neurotrophic factor (GDNF) induces HF formation (mice).[152] The mechanism of action of the GDNF ligand family is mediated by its interaction with the glial cell-derived neurotrophic factor receptor alpha (GFRA) (mainly the GFRA1 isoform) and the activation of RET tyrosine kinase.[153] In RET-null cells, the neural cell adhesion molecule interacts directly with GDNF-GFRA1 and regulates intercellular communication.[154] On the other hand, the neural cell adhesion molecule mediates cell-cell and matrix adhesion, which is associated with DPC aggregation *in vivo*.[47] GDNF and NRTN regulate the HF cycle in mice, and blocking the Gfra1/Gfra2 genes enhances HF regression and disrupts the hair cycle.[155,156] GDNF producers are stem cell bulge cells with regenerative potential in terms of restoring the HF and skin by regulating hair formation and wound healing.[152]

BDNF is associated with depression and hair growth.[157] Hair loss in women is associated with low serum levels of BDNF (which is associated with psychiatric and neurodegenerative disorders, chronic stress, and depression).[158] In addition, higher cortisol levels and lower BDNF levels have been observed in patients with AGA.[151] However, a previous study reported high BDNF expression in supernatants obtained from DP at balding sites.[159] BDNF may also promote the transition from HF to catagen by modulating TNF-α/keratin 17-mediated apoptosis.[3] Thus, there are a number of growth factors and neurotrophic factors that may exert a stimulatory effect on hair growth and HF development by directly influencing the cellular microenvironment or HFSCs.

Clinical application of exosomes from different sources

Exos structure: Application of exosomes from different sources for HFSC activation

In addition to the internal content, an important aspect of the use of exosomes against AGA is the unique surface composition of these lipid-containing particles. The proteins Wnt3a and Wnt7b are expressed on the surface of exos and activate the Wnt cascade in the recipient cells. In addition, exosomes express membrane-associated Hedgehog signaling proteins. Interaction of exosomal surface proteins (macrophage exosomes) Wnt3a and Wnt7b with Frizzled4 and LRP5/6 receptors on DPCs leads to activation of the Wnt cascade, which regulates their proliferation, motility, hair shaft elongation, and the growth of HFs.[36] In addition, Wnt3a molecules, which activate Wnt signaling,[36] prevent inactivation of the Wnt cascade by dihydrotestosterone and suppress TGF-β signaling in AGA (Fig. 2).[6,11]

Exos derived from macrophages (MAC-Exos)

Perifollicular macrophages (MFs) activate epithelial stem cells of

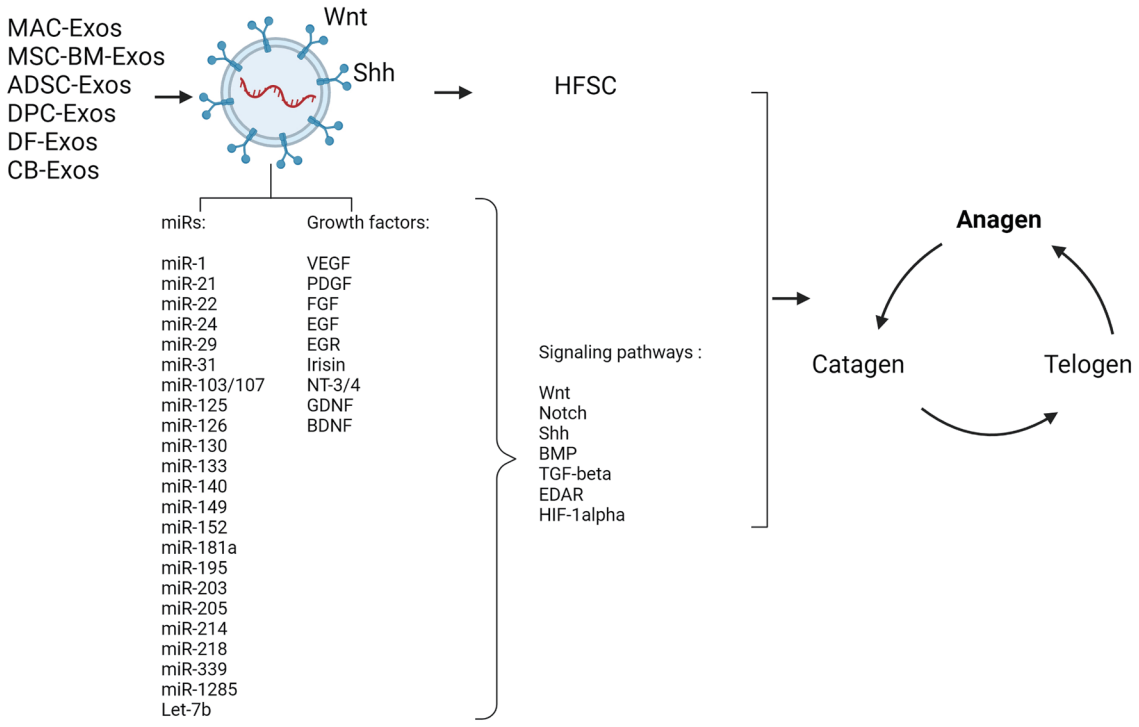


Fig. 2. The influence of microRNAs and growth factors contained in exosomes of various origins on the hair follicle cycle. ADSC, adipose-derived stem cell; BM, bone marrow; BDNF, brain-derived neurotrophic factor; CB, cord blood; DF, dermal fibroblast; DPC, dermal papillary cell; EGR, early growth response; EGF, epidermal growth factor; FGF, fibroblast growth factor; GDNF, glial cell line-derived neurotrophic factor; HFSC, hair follicle stem cell; MAC, macrophages; MSC, mesenchymal stem cell; NT, neurotrophin; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor.

the skin and regulate HF growth.[36] MFs produce TNF and trigger the AKT/β-catenin signaling cascade, activating HFSCs.[36]

There is evidence that MFs are present in the HF microenvironment and secrete Wnt10a, which induces Wnt signaling and increases *Axin2* and *Lef2* gene expression. MAC-Exos (from MF culture supernatants) express Wnt3a/Wnt7b molecules on the membrane, which enable exos to contact the cellular Frizzled and LRP5/6 receptors and stimulate the WNT cascade in HF-DPCs *in vitro* (Balb/c mouse model), resulting in thickening of the skin and an increase in HF.[36] The effect of MAC-Exos on DPCs was characterized by an anti-apoptotic effect (increased gene expression of *Bcl-2*) against a background of activation of Akt phosphorylation and induction of versican and *ALP* gene activity. MAC-Exos double the thickness of the human hair shaft by activating VEGF and KGF in DPCs.[36] The method of obtaining MFs is the least invasive compared to the isolation of MSCs from adipose tissue or BM and opens up the prospect that exos can be used in applied applications as hair growth promoters in AGA.

Bone marrow-derived exos

Preclinical studies on the secretome of BM-derived MSCs have shown that they could be used as stimulators for hair growth and regeneration. MSCs activated the proliferation of epidermal cells in mice (*in vivo*), inhibited MF infiltration, and reduced the production of reactive oxygen species (activation of matrix metalloproteinase and destruction of collagen tissue).[160] A study in which BM-MSCs were grown under hypoxic conditions and then injected into the scalp or papules of patients with alopecia resulted in improved hair growth.[161,162]

ExoCel and ExoFlo are promising new therapies that utilize the therapeutic potential of exosomes, as supported by a systematic review of preclinical/clinical data on exosomes.[163] ExoFlo is a drug based on exos derived from BM-MSCs, tested for sterility, and stored in facilities registered with the U.S. Food and Drug Administration that comply with Current Good Tissue Practice.[164] However, large-scale studies are needed for this class of drugs to establish standardized application protocols and test the feasibility of widespread use in clinical practice.

Exosomes from adipose tissue (ADSC-Exos)

Within the subcutaneous adipose tissue layer containing progenitor cells (hereinafter referred to as ASCs), intercellular interactions mediated by PDGF occur during the anagen phase.[134] ASCs can differentiate in the adipo- and osteo-direction via the expression of leptin or osteopontin, markers that are characteristic of DPCs at different stages of HF development.[134]

In the anagen phase, the thickness of the adipose tissue increases, and adipocytes begin to proliferate. The transition from catagen to telogen is characterized by a high production of BMP2 by adipocytes, which regulates the resting state in the niche, decreases in late telogen, and promotes the activation of HF-MSCs.[38] Anti-HC transformations inhibit adipogenesis; epithelial cells send signals that activate adipocyte expansion. The HFs absorb nutrients from the microvessels, which change during the hair growth cycle; anagen is associated with the induction of angiogenesis and the activation of bulge and matrix cells.[38] ADSCs control the HF cycle and are an essential part of the microenvironment.[6] The growth and development of the HF is related to the ADSCs that surround the DPCs and optimize the microenvironment of the HF.[165] ADSCs also influence HF morphogenesis by producing growth factors that

regulate growth, enhance DPC viability, and initiate HF regeneration under hypoxic conditions.[47]

Administration of condensed ADSC medium had a positive effect on hair growth.[6] ADSC-Exos are characterized by a spindle-shaped form and express CD9, CD81, and TSG101 molecules on the surface, inducing the Wnt cascade, ALP, and versican expression in DPCs. ADSC-Exos neutralize the effects of DHT (and DKK1) by activating pGSK-3β expression (Wnt cascade) and suppressing TGF-β, thereby restoring hair growth through anagen induction.[6,11] ADSC-exos highly express miR-122-5p, which downregulates miR-22 expression in DPCs.[11,20] In addition, ADSCs can transdifferentiate into DPC-type cells and induce hair growth.[134]

Supernatants from ADSC cultures exposed to hypoxia altered DPC signaling,[47] increased p-ERK/p-AKT phosphorylation and activation of ERK1/2 and AKT (MAPK) cascades,[47] and promoted DPC growth and HF formation by upregulating genes regulating proliferation, differentiation, and angiogenesis,[47] and reduced apoptosis.[166]

HIF-1α-mediated induction of ERK1/2 leads to the expression/secretion of MSC growth factors, particularly ADSC-derived (VEGF, bFGF, PDGF),[47] which stimulate HF growth. Activated HIF-1 binds to the HRE site with the nucleotide sequence ACGTG and forms the cyclic adenylate response element-binding protein HIF-1-p300/CBP, which initiates gene transcription. Genes containing one or more HREs are targeted and regulated by HIF-1α,[167] particularly the *BMP7* gene, inhibiting its repressive role in HF morphogenesis.[47]

Overexpression of the *HIF-1α* gene increased the expression of VEGF, bFGF, and PDGF in ADSCs. Hypoxia also promoted an increase in the expression of VEGFA, VEGFB, VEGFC, PDGFB, PDGFD, FGF2 (bFGF), IGFBP5, and IGF1R (Rap1, Ras, MAPK, PI3K-AKT, and HIF pathway genes). The transcription factor HIF-1α inhibited the promoter of the BMP family gene BMP7 and reduced its protein expression in cultured ADSCs,[47] which could also contribute to the transition of HF from the telogen to anagen stage.

Dermal papillary cell exosomes

Exos from isolated human DP exert stimulatory effects and prolong anagen time by inducing the expression of β-catenin and Shh (when administered to mice).[168,169] DPCs express α-SMA, laminin, fibronectin, and CD133.[170] DPC-Exos regulate the activity of epidermal cells, promote hair growth and regeneration, stimulate anagen HF, and induce proliferation and migration of ORS cells. In 3D-DPC-Exos cultures, cell proliferation of DPC and ORS cells (in human HF) was observed due to increased expression of growth factors (IGF-1, KGF, HGF).[171] Injection of human 3D/2D DPC-Exos spheres together with epidermal cells into mice enhanced HF neogenesis.[171] 4The induction of HF neogenesis by DPC-Exos was also confirmed in a mouse model with skin lesions. The effect of DPC-Exos on fibroblasts in mice and other mammals was characterized by abundant blood flow to the HF,[172–174] which activates hair growth via the Wnt/β-catenin cascade.

DPC-Exos-derived miR-22-5p was able to inhibit the proliferation of HFSC via its direct target gene *LEF1*.[87] In addition, miR-22-5p reduced the luciferase activity of FOXP1.[87] DPC-Exos-localized miR-218-5p activated the Wnt/β-catenin cascade and restored hair growth.[139] Similarly, has-miR-181a-3p expressed in DPC-Exos promoted cell proliferation and hair growth. Depending on the phase of HF development, different expression levels of miR-181 were observed, targeting the activation of the Wnt signaling pathway, proliferation of HFSCs, and HF growth.[90] In addition, sequencing revealed that DPC-Exos contain a number of functionally important miRs that regulate hair growth and development, including let-7f-5p and miR-22-5p as target regulators of genes involved in hair growth and differentiation, involved in the formation and differentiation of HF/microenvironmental cells (HFSCs, keratinocytes) and intercellular communication (*Dlx3, Foxn1, Hoxc13, Sostdc*), genes of the VEGF and Wnt signaling pathways (miR-1, miR-122), BMP (miR-21-5p), Runx (miR-378-3p, miR-145-5p), ERK (miR-592), and TGF (miR-106a-5p).[87]

In one study,[88] the targeting effect of DPC-Exos on HFSCs was demonstrated, which was reflected in significant expression levels of a large number of target genes (3,702). The strongest increase in gene expression was observed for the LEF1 gene, an important regulator of the HF life cycle.[88] DPCs express genes important for the morphogenesis of HF in the postnatal hair cycle (*versican,* SMA, SOX2, CTNB, and ALPL),[175] and produce exos containing miR-214, miR-218-5p, and miR-195-5p.[134] At the same time, heterogeneity of DPC subpopulations has been observed.[176]

Dermal fibroblast exosomes

Extracellular vesicles of stimulated human dermal fibroblasts contained Norrin, a specific activator of the *NDP* gene. Norrin is also secreted in DPC-stimulated vesicles/exos and activates HF development processes by acting ex vivo on cells of the microenvironment (keratinocytes). Norrin's specific receptor is Frizzled4 and is probably responsible for the activation of dermal fibroblasts and hair growth.[177]

Exos from human umbilical cord blood MSCs

Exos-MSCs from umbilical cord blood contain miR-181, which reduces burn-induced inflammation (rats).[169] In addition, exos from umbilical cord blood stimulated regenerative processes in the skin by activating the Wnt cascade and factors responsible for the growth of new blood vessels.[6]

Thus, exosomes from various sources could serve as potential effectors in the fight against AGA by inducing the growth and development of HFs. Despite significant progress in the study of exosomes and their components, there are still many unanswered questions regarding their future successful application in the clinic.

Conclusions

Studies on the functional potential of exosomes and their modulating properties on hair growth have been demonstrated in cell cultures and animal models. A feature of exosomal therapy is its low immunogenicity compared to cell therapy. Currently, many aspects of the effect of exos on HFs and HFSCs are still unclear, as the number of studies is insufficient and it is a relatively new direction in science. The most important unresolved problems in the use of exos in clinical practice include: the lack of investigation of the main basic processes that can be affected by exos from a molecular and genetic point of view; the safety of exosome treatment; and effective treatment methods with a precise description (protocol) of exos sources, methods of their isolation, content (components) of exosomes, storage, methods of administration, exact dosages, and frequency of repeated administration of exos or their individual components. However, even at this stage of development, the potential success of this scientific direction in the treatment of alopecia is assumed, which is supported by modern and comprehensive studies in humans.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Study concept and design (PI, NT), acquisition of data (NT, KY, OK), analysis and interpretation of data (NT, KY, OK), drafting of the manuscript (NT), critical revision of the manuscript for important intellectual content (PI, LL), administrative, technical, or material support (PI, LL), and study supervision (LL). All authors have made a significant contribution to this study and have approved the final manuscript.

References

[1] Rajendran RL, Gangadaran P, Kwack MH, Oh JM, Hong CM, Gopal A, *et al*. Engineered extracellular vesicle mimetics from macrophage promotes hair growth in mice and promotes human hair follicle growth. Exp Cell Res 2021;409(1):112887. doi:10.1016/j.yexcr.2021.112887, PMID:34678305.

[2] Panchaprateep R. Medical Treatment for Androgenetic Alopecia. Facial Plast Surg 2024;40(2):252–266. doi:10.1055/a-2196-4713, PMID:37871637.

[3] Yang M, Weng T, Zhang W, Zhang M, He X, Han C, *et al*. The Roles of Non-coding RNA in the Development and Regeneration of Hair Follicles: Current Status and Further Perspectives. Front Cell Dev Biol 2021;9:720879. doi:10.3389/fcell.2021.720879, PMID:34708037.

[4] Westgate GE, Grohmann D, Sáez Moya M. Hair Longevity-Evidence for a Multifactorial Holistic Approach to Managing Hair Aging Changes. J Clin Med 2025;14(6):1894. doi:10.3390/jcm14061894, PMID:40142702.

[5] Ntshingila S, Oputu O, Arowolo AT, Khumalo NP. Androgenetic alopecia: An update. JAAD Int 2023;13:150–158. doi:10.1016/j.jdin.2023.07.005, PMID:37823040.

[6] Tang X, Cao C, Liang Y, Han L, Tu B, Yu M, *et al*. Adipose-Derived Stem Cell Exosomes Antagonize the Inhibitory Effect of Dihydrotestosterone on Hair Follicle Growth by Activating Wnt/β-Catenin Pathway. Stem Cells Int 2023;2023:5548112. doi:10.1155/2023/5548112, PMID:37810630.

[7] Inui S, Itami S. Molecular basis of androgenetic alopecia: From androgen to paracrine mediators through dermal papilla. J Dermatol Sci 2011;61(1):1–6. doi:10.1016/j.jdermsci.2010.10.015, PMID:21167691.

[8] Thor D, Pagani A, Bukowiecki J, Houschyar KS, Kølle ST, Wyles SP, *et al*. A Novel Hair Restoration Technology Counteracts Androgenic Hair Loss and Promotes Hair Growth in A Blinded Clinical Trial. J Clin Med 2023;12(2):470. doi:10.3390/jcm12020470, PMID:36675398.

[9] York K, Meah N, Bhoyrul B, Sinclair R. A review of the treatment of male pattern hair loss. Expert Opin Pharmacother 2020;21(5):603–612. doi:10.1080/14656566.2020.1721463, PMID:32066284.

[10] Peera M, Rose L, Kaufman L, Zhang E, Alkhaifi M, Dulmage B. Hair loss: alopecia fears and realities for survivors of breast cancer-a narrative review. Ann Palliat Med 2024;13(5):1235–1245. doi:10.21037/apm-24-69, PMID:39129521.

[11] Liang Y, Tang X, Zhang X, Cao C, Yu M, Wan M. Adipose Mesenchymal Stromal Cell-Derived Exosomes Carrying MiR-122-5p Antagonize the Inhibitory Effect of Dihydrotestosterone on Hair Follicles by Targeting the TGF-β1/SMAD3 Signaling Pathway. Int J Mol Sci 2023;24(6):5703. doi:10.3390/ijms24065703, PMID:36982775.

[12] Lee JH, Choi S. Deciphering the molecular mechanisms of stem cell dynamics in hair follicle regeneration. Exp Mol Med 2024;56(1):110–117. doi:10.1038/s12276-023-01151-5, PMID:38182654.

[13] Bajoria PS, Dave PA, Rohit RK, Tibrewal C, Modi NS, Gandhi SK, *et al*. Comparing Current Therapeutic Modalities of Androgenic Alopecia: A Literature Review of Clinical Trials. Cureus 2023;15(7):e42768. doi:10.7759/cureus.42768, PMID:37663989.

[14] Seyed Jafari SM, Heidemeyer K, Hunger RE, de Viragh PA. Safety of Antiandrogens for the Treatment of Female Androgenetic Alopecia with Respect to Gynecologic Malignancies. J Clin Med 2024;13(11):3052. doi:10.3390/jcm13113052, PMID:38892763.

[15] Elariny AF, Ghozlan N, Wasief S, Moussa AE, Eldeeb ME. Evaluation of efficacy of follicular unit extraction versus follicular unit extraction with platelet rich plasma in treatment of cicatricial alopecia. J Cosmet Dermatol 2022;21(11):5931–5937. doi:10.1111/jocd.15213, PMID:35791055.

[16] Shimizu Y, Ntege EH, Sunami H. Current regenerative medicine-based approaches for skin regeneration: A review of literature and a report on clinical applications in Japan. Regen Ther 2022;21:73–80. doi:10.1016/j.reth.2022.05.008, PMID:35785041.

[17] Zhou Y, Seo J, Tu S, Nanmo A, Kageyama T, Fukuda J. Exosomes for hair growth and regeneration. J Biosci Bioeng 2024;137(1):1–8. doi:10.1016/j.jbiosc.2023.11.001, PMID:37996318.

[18] Ju Y, Hu Y, Yang P, Xie X, Fang B. Extracellular vesicle-loaded hydrogels for tissue repair and regeneration. Mater Today Bio 2023;18:100522. doi:10.1016/j.mtbio.2022.100522, PMID:36593913.

[19] Ersan M, Ozer E, Akin O, Tasli PN, Sahin F. Effectiveness of Exosome Treatment in Androgenetic Alopecia: Outcomes of a Prospective Study. Aesthetic Plast Surg 2024;48(21):4262–4271. doi:10.1007/s00266-024-04332-3, PMID:39174804.

[20] Li Y, Wang G, Wang Q, Zhang Y, Cui L, Huang X. Exosomes Secreted from Adipose-Derived Stem Cells Are a Potential Treatment Agent for Immune-Mediated Alopecia. J Immunol Res 2022;2022:7471246. doi:10.1155/2022/7471246, PMID:35155688.

[21] Yu A, Zhang Y, Zhong S, Yang Z, Xie M. Human umbilical cord mesenchymal stem cell-derived exosomes enhance follicular regeneration in androgenetic alopecia via activation of Wnt/β-catenin pathway. Stem Cell Res Ther 2025;16(1):418. doi:10.1186/s13287-025-04538-5, PMID:40751216.

[22] Ma C, Cheng M, Xiao T, Qi R, Gao X, Chen H, *et al*. miR-574-3p and miR-125a-5p in Adipose-Derived Mesenchymal Stem Cell Exosomes Synergistically Target TGF-β1/SMAD2 Signaling Pathway for the Treatment of Androgenic Alopecia. J Invest Dermatol 2025;145(11):2719–2735.e3. doi:10.1016/j.jid.2025.03.042, PMID:40306482.

[23] Devjani S, Ezemma O, Kelley KJ, Stratton E, Senna M. Androgenetic Alopecia: Therapy Update. Drugs 2023;83(8):701–715. doi:10.1007/s40265-023-01880-x, PMID:37166619.

[24] Gupta AK, Mays RR, Dotzert MS, Versteeg SG, Shear NH, Piguet V. Efficacy of non-surgical treatments for androgenetic alopecia: a systematic review and network meta-analysis. J Eur Acad Dermatol Venereol 2018;32(12):2112–2125. doi:10.1111/jdv.15081, PMID:29797431.

[25] Mohammadi P, Youssef KK, Abbasalizadeh S, Baharvand H, Aghdami N. Human Hair Reconstruction: Close, But Yet So Far. Stem Cells Dev 2016;25(23):1767–1779. doi:10.1089/scd.2016.0137, PMID:27649771.

[26] Hochfeld LM, Keller A, Anhalt T, Fricker N, Nöthen MM, Heilmann-Heimbach S, *et al*. Insights into Male Androgenetic Alopecia: Differential Gene Expression Profiling of Plucked Hair Follicles and Integration with Genetic Data. J Invest Dermatol 2019;139(1):235–238. doi:10.1016/j.jid.2018.06.182, PMID:30009830.

[27] Liu Q, Tang Y, Huang Y, Wang J, Yang K, Zhang Y, *et al*. Insights into male androgenetic alopecia using comparative transcriptome profiling: hypoxia-inducible factor-1 and Wnt/β-catenin signalling pathways. Br J Dermatol 2022;187(6):936–947. doi:10.1111/bjd.21783, PMID:35862273.

[28] Deng W, Hu T, Han L, Liu B, Tang X, Chen H, *et al*. miRNA microarray profiling in patients with androgenic alopecia and the effects of miR-133b on hair growth. Exp Mol Pathol 2021;118:104589. doi:10.1016/j.yexmp.2020.104589, PMID:33290799.

[29] Mohammadi P, Nilforoushzadeh MA, Youssef KK, Sharifi-Zarchi A, Moradi S, Khosravani P, *et al*. Defining microRNA signatures of hair follicular stem and progenitor cells in healthy and androgenic alopecia patients. J Dermatol Sci 2021;101(1):49–57. doi:10.1016/j.jdermsci.2020.11.002, PMID:33183906.

[30] Lin X, Zhu L, He J. Morphogenesis, Growth Cycle and Molecular

Regulation of Hair Follicles. Front Cell Dev Biol 2022;10:899095. doi:10.3389/fcell.2022.899095, PMID:35646909.
[31] Vatanashevanopakorn C, Sartyoungkul T. iPSC-based approach for human hair follicle regeneration. Front Cell Dev Biol 2023;11:1149050. doi:10.3389/fcell.2023.1149050, PMID:37325563.
[32] Tang X, Wang J, Chen J, Liu W, Qiao P, Quan H, *et al*. Epidermal stem cells: skin surveillance and clinical perspective. J Transl Med 2024;22(1):779. doi:10.1186/s12967-024-05600-1, PMID:39169334.
[33] Rishikaysh P, Dev K, Diaz D, Qureshi WM, Filip S, Mokry J. Signaling involved in hair follicle morphogenesis and development. Int J Mol Sci 2014;15(1):1647–1670. doi:10.3390/ijms15011647, PMID:24451143.
[34] Kiselev A, Park S. Immune niches for hair follicle development and homeostasis. Front Physiol 2024;15:1397067. doi:10.3389/fphys.2024.1397067, PMID:38711955.
[35] Lee SA, Li KN, Tumbar T. Stem cell-intrinsic mechanisms regulating adult hair follicle homeostasis. Exp Dermatol 2021;30(4):430–447. doi:10.1111/exd.14251, PMID:33278851.
[36] Rajendran RL, Gangadaran P, Seo CH, Kwack MH, Oh JM, Lee HW, *et al*. Macrophage-Derived Extracellular Vesicle Promotes Hair Growth. Cells 2020;9(4):856. doi:10.3390/cells9040856, PMID:32244824.
[37] Purba TS, Haslam IS, Poblet E, Jiménez F, Gandarillas A, Izeta A, *et al*. Human epithelial hair follicle stem cells and their progeny: current state of knowledge, the widening gap in translational research and future challenges. Bioessays 2014;36(5):513–525. doi:10.1002/bies.201300166, PMID:24665045.
[38] Gentile P, Garcovich S. Advances in Regenerative Stem Cell Therapy in Androgenic Alopecia and Hair Loss: Wnt pathway, Growth-Factor, and Mesenchymal Stem Cell Signaling Impact Analysis on Cell Growth and Hair Follicle Development. Cells 2019;8(5):466. doi:10.3390/cells8050466, PMID:31100937.
[39] Cuevas-Diaz Duran R, Martinez-Ledesma E, Garcia-Garcia M, Bajo Gauzin D, Sarro-Ramírez A, Gonzalez-Carrillo C, *et al*. The Biology and Genomics of Human Hair Follicles: A Focus on Androgenetic Alopecia. Int J Mol Sci 2024;25(5):2542. doi:10.3390/ijms25052542, PMID:38473791.
[40] Hu XM, Li ZX, Zhang DY, Yang YC, Fu SA, Zhang ZQ, *et al*. A systematic summary of survival and death signalling during the life of hair follicle stem cells. Stem Cell Res Ther 2021;12(1):453. doi:10.1186/s13287-021-02527-y, PMID:34380571.
[41] Zhang Y, Cui J, Cang Z, Pei J, Zhang X, Song B, *et al*. Hair follicle stem cells promote epidermal regeneration under expanded condition. Front Physiol 2024;15:1306011. doi:10.3389/fphys.2024.1306011, PMID:38455843.
[42] Lough DM, Yang M, Blum A, Reichensperger JD, Cosenza NM, Wetter N, *et al*. Transplantation of the LGR6+ epithelial stem cell into full-thickness cutaneous wounds results in enhanced healing, nascent hair follicle development, and augmentation of angiogenic analytes. Plast Reconstr Surg 2014;133(3):579–590. doi:10.1097/PRS.0000000000000075, PMID:24572851.
[43] Chacón-Martínez CA, Klose M, Niemann C, Glauche I, Wickström SA. Hair follicle stem cell cultures reveal self-organizing plasticity of stem cells and their progeny. EMBO J 2017;36(2):151–164. doi:10.15252/embj.201694902, PMID:27940653.
[44] Tanimura S, Tadokoro Y, Inomata K, Binh NT, Nishie W, Yamazaki S, *et al*. Hair follicle stem cells provide a functional niche for melanocyte stem cells. Cell Stem Cell 2011;8(2):177–187. doi:10.1016/j.stem.2010.11.029, PMID:21295274.
[45] Rompolas P, Mesa KR, Greco V. Spatial organization within a niche as a determinant of stem-cell fate. Nature 2013;502(7472):513–518. doi:10.1038/nature12602, PMID:24097351.
[46] Lee SH, Yoon J, Shin SH, Zahoor M, Kim HJ, Park PJ, *et al*. Valproic acid induces hair regeneration in murine model and activates alkaline phosphatase activity in human dermal papilla cells. PLoS One 2012;7(4):e34152. doi:10.1371/journal.pone.0034152, PMID:22506014.
[47] Wang Q, Zhou M, Zhang H, Hou Z, Liu D. Hypoxia Treatment of Adipose Mesenchymal Stem Cells Promotes the Growth of Dermal Papilla Cells via HIF-1α and ERK1/2 Signaling Pathways. Int J Mol Sci 2023;24(13):11198. doi:10.3390/ijms241311198, PMID:37446376.
[48] Yang Y, Li Y, Wang Y, Wu J, Yang G, Yang T, *et al*. Versican gene: regulation by the β-catenin signaling pathway plays a significant role in dermal papilla cell aggregative growth. J Dermatol Sci 2012;68(3):157–163. doi:10.1016/j.jdermsci.2012.09.011, PMID:23099107.
[49] Ji S, Zhu Z, Sun X, Fu X. Functional hair follicle regeneration: an updated review. Signal Transduct Target Ther 2021;6(1):66. doi:10.1038/s41392-020-00441-y, PMID:33594043.
[50] Zhang C, Wang D, Dowell R, Yi R. Single cell analysis of transcriptome and open chromatin reveals the dynamics of hair follicle stem cell aging. Front Aging 2023;4:1192149. doi:10.3389/fragi.2023.1192149, PMID:37465120.
[51] Li S, Chen J, Chen F, Wang C, Guo X, Wang C, *et al*. Liposomal honokiol promotes hair growth via activating Wnt3a/β-catenin signaling pathway and down regulating TGF-β1 in C57BL/6N mice. Biomed Pharmacother 2021;141:111793. doi:10.1016/j.biopha.2021.111793, PMID:34098216.
[52] Bai L, Sun H, Jiang W, Yang L, Liu G, Zhao X, *et al*. DNA methylation and histone acetylation are involved in Wnt10b expression during the secondary hair follicle cycle in Angora rabbits. J Anim Physiol Anim Nutr (Berl) 2021;105(3):599–609. doi:10.1111/jpn.13481, PMID:33404138.
[53] Hawkshaw NJ, Hardman JA, Alam M, Jimenez F, Paus R. Deciphering the molecular morphology of the human hair cycle: Wnt signalling during the telogen-anagen transformation. Br J Dermatol 2020;182(5):1184–1193. doi:10.1111/bjd.18356, PMID:31314901.
[54] Tsai SY, Sennett R, Rezza A, Clavel C, Grisanti L, Zemla R, *et al*. Wnt/β-catenin signaling in dermal condensates is required for hair follicle formation. Dev Biol 2014;385(2):179–188. doi:10.1016/j.ydbio.2013.11.023, PMID:24309208.
[55] Lien WH, Polak L, Lin M, Lay K, Zheng D, Fuchs E. In vivo transcriptional governance of hair follicle stem cells by canonical Wnt regulators. Nat Cell Biol 2014;16(2):179–190. doi:10.1038/ncb2903, PMID:24463605.
[56] Telerman SB, Rognoni E, Sequeira I, Pisco AO, Lichtenberger BM, Culley OJ, *et al*. Dermal Blimp1 Acts Downstream of Epidermal TGFβ and Wnt/β-Catenin to Regulate Hair Follicle Formation and Growth. J Invest Dermatol 2017;137(11):2270–2281. doi:10.1016/j.jid.2017.06.015, PMID:28668474.
[57] Zhu N, Lin E, Zhang H, Liu Y, Cao G, Fu C, *et al*. LncRNA H19 Overexpression Activates Wnt Signaling to Maintain the Hair Follicle Regeneration Potential of Dermal Papilla Cells. Front Genet 2020;11:694. doi:10.3389/fgene.2020.00694, PMID:32849769.
[58] Zhao B, Chen Y, Yang N, Chen Q, Bao Z, Liu M, *et al*. miR-218-5p regulates skin and hair follicle development through Wnt/β-catenin signaling pathway by targeting SFRP2. J Cell Physiol 2019;234(11):20329–20341. doi:10.1002/jcp.28633, PMID:30953362.
[59] Kwack MH, Ahn JS, Jang JH, Kim JC, Sung YK, Kim MK. SFRP2 augments Wnt/β-catenin signalling in cultured dermal papilla cells. Exp Dermatol 2016;25(10):813–815. doi:10.1111/exd.12993, PMID:26914690.
[60] Hamida OB, Kim MK, Kwack MH. The role of dexamethasone in mediating the contradictory effects of Wnt antagonists SFRP2 and SFRP3 on human hair follicle growth. Sci Rep 2023;13(1):16504. doi:10.1038/s41598-023-43688-5, PMID:37783752.
[61] Ali H, Zmuda JM, Cvejkus RK, Kershaw EE, Kuipers AL, Oczypok EA, *et al*. Wnt Pathway Inhibitor DKK1: A Potential Novel Biomarker for Adiposity. J Endocr Soc 2019;3(2):488–495. doi:10.1210/js.2018-00325, PMID:30746507.
[62] Ho CH, Sood T, Zito PM. Androgenetic Alopecia. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430924/.
[63] Papukashvili D, Rcheulishvili N, Liu C, Xie F, Tyagi D, He Y, *et al*. Perspectives on miRNAs Targeting DKK1 for Developing Hair Regeneration Therapy. Cells 2021;10(11):2957. doi:10.3390/cells10112957, PMID:34831180.
[64] Yan Q, Qi B, Zhang P, Jin Y, Cao K, Liu Y. Hair follicle stem cell proliferation and differentiation are achieved by miR-1285-3P through targeted regulation of NOTCH pathway. Prev Med 2023;173:107566. doi:10.1016/j.ypmed.2023.107566, PMID:37286091.
[65] Sakamoto K, Jin SP, Goel S, Jo JH, Voisin B, Kim D, *et al*. Disruption of the endopeptidase ADAM10-Notch signaling axis leads to skin dysbiosis and innate lymphoid cell-mediated hair follicle destruction. Immunity 2021;54(10):2321–2337.e10. doi:10.1016/j.immuni.2021.09.001, PMID:34582748.

[66] Morinaga H, Mohri Y, Grachtchouk M, Asakawa K, Matsumura H, Oshima M, *et al*. Obesity accelerates hair thinning by stem cell-centric converging mechanisms. Nature 2021;595(7866):266–271. doi:10.1038/s41586-021-03624-x, PMID:34163066.
[67] Sigafoos AN, Paradise BD, Fernandez-Zapico ME. Hedgehog/GLI Signaling Pathway: Transduction, Regulation, and Implications for Disease. Cancers (Basel) 2021;13(14):3410. doi:10.3390/cancers13143410, PMID:34298625.
[68] Lim CH, Sun Q, Ratti K, Lee SH, Zheng Y, Takeo M, *et al*. Hedgehog stimulates hair follicle neogenesis by creating inductive dermis during murine skin wound healing. Nat Commun 2018;9(1):4903. doi:10.1038/s41467-018-07142-9, PMID:30464171.
[69] Zhang X, Lei T, Chen P, Wang L, Wang J, Wang D, *et al*. Stem Cells from Human Exfoliated Deciduous teeth Promote Hair Regeneration in Mouse. Cell Transplant 2021;30:9636897211042927. doi:10.1177/09636897211042927, PMID:34633878.
[70] Monsivais D, Nagashima T, Prunskaite-Hyyryläinen R, Nozawa K, Shimada K, Tang S, *et al*. Endometrial receptivity and implantation require uterine BMP signaling through an ACVR2A-SMAD1/SMAD5 axis. Nat Commun 2021;12(1):3386. doi:10.1038/s41467-021-23571-5, PMID:34099644.
[71] Infarinato NR, Stewart KS, Yang Y, Gomez NC, Pasolli HA, Hidalgo L, *et al*. BMP signaling: at the gate between activated melanocyte stem cells and differentiation. Genes Dev 2020;34(23-24):1713–1734. doi:10.1101/gad.340281.120, PMID:33184221.
[72] Olsen OE, Hella H, Elsaadi S, Jacobi C, Martinez-Hackert E, Holien T. Activins as Dual Specificity TGF-β Family Molecules: SMAD-Activation via Activin- and BMP-Type 1 Receptors. Biomolecules 2020;10(4):519. doi:10.3390/biom10040519, PMID:32235336.
[73] Diao X, Yao L, Wang X, Li S, Qin J, Yang L, *et al*. Hair Follicle Development and Cashmere Traits in Albas Goat Kids. Animals (Basel) 2023;13(4):617. doi:10.3390/ani13040617, PMID:36830404.
[74] Plikus MV, Guerrero-Juarez CF, Ito M, Li YR, Dedhia PH, Zheng Y, *et al*. Regeneration of fat cells from myofibroblasts during wound healing. Science 2017;355(6326):748–752. doi:10.1126/science.aai8792, PMID:28059714.
[75] Chen P, Miao Y, Zhang F, Huang J, Chen Y, Fan Z, *et al*. Nanoscale microenvironment engineering based on layer-by-layer self-assembly to regulate hair follicle stem cell fate for regenerative medicine. Theranostics 2020;10(25):11673–11689. doi:10.7150/thno.48723, PMID:33052240.
[76] Wu J, Yu L, Liu Y, Xiao B, Ye X, Zhao H, *et al*. Hypoxia regulates adipose mesenchymal stem cells proliferation, migration, and nucleus pulposus-like differentiation by regulating endoplasmic reticulum stress via the HIF-1α pathway. J Orthop Surg Res 2023;18(1):339. doi:10.1186/s13018-023-03818-1, PMID:37158945.
[77] Agrawal R, Dale TP, Al-Zubaidi MA, Benny Malgulwar P, Forsyth NR, Kulshreshtha R. Pluripotent and Multipotent Stem Cells Display Distinct Hypoxic miRNA Expression Profiles. PLoS One 2016;11(10):e0164976. doi:10.1371/journal.pone.0164976, PMID:27783707.
[78] Schumacker PT. Hypoxia-inducible factor-1 (HIF-1). Crit Care Med 2005;33(12 Suppl):S423–S425. doi:10.1097/01.ccm.0000191716.38566.e0, PMID:16340411.
[79] Pagani A, Aitzetmüller MM, Brett EA, König V, Wenny R, Thor D, *et al*. Skin Rejuvenation through HIF-1α Modulation. Plast Reconstr Surg 2018;141(4):600e–607e. doi:10.1097/PRS.0000000000004256, PMID:29596193.
[80] Bukowiecki J, Pförringer D, Thor D, Duscher D, Brett E. HIF-1α Stimulators Function Equally to Leading Hair Loss Agents in Enhancing Dermal Papilla Growth. Skin Pharmacol Physiol 2020;33(6):309–316. doi:10.1159/000512123, PMID:33326985.
[81] Ye J, Tang X, Long Y, Chu Z, Zhou Q, Lin B. The effect of hypoxia on the proliferation capacity of dermal papilla cell by regulating lactate dehydrogenase. J Cosmet Dermatol 2021;20(2):684–690. doi:10.1111/jocd.13578, PMID:32599679.
[82] Zheng M, Jang Y, Choi N, Kim DY, Han TW, Yeo JH, *et al*. Hypoxia improves hair inductivity of dermal papilla cells via nuclear NADPH oxidase 4-mediated reactive oxygen species generation'. Br J Dermatol 2019;181(3):523–534. doi:10.1111/bjd.17706, PMID:30703252.
[83] Seo J, Yan L, Kageyama T, Nanmo A, Chun YS, Fukuda J. Hypoxia inducible factor-1α promotes trichogenic gene expression in human dermal papilla cells. Sci Rep 2023;13(1):1478. doi:10.1038/s41598-023-28837-0, PMID:36707659.
[84] Suhara T, Hishiki T, Kasahara M, Hayakawa N, Oyaizu T, Nakanishi T, *et al*. Inhibition of the oxygen sensor PHD2 in the liver improves survival in lactic acidosis by activating the Cori cycle. Proc Natl Acad Sci U S A 2015;112(37):11642–11647. doi:10.1073/pnas.1515872112, PMID:26324945.
[85] Han QF, Li WJ, Hu KS, Gao J, Zhai WL, Yang JH, *et al*. Exosome biogenesis: machinery, regulation, and therapeutic implications in cancer. Mol Cancer 2022;21(1):207. doi:10.1186/s12943-022-01671-0, PMID:36320056.
[86] Cheng M, Ma C, Chen HD, Wu Y, Xu XG. The Roles of Exosomes in Regulating Hair Follicle Growth. Clin Cosmet Investig Dermatol 2024;17:1603–1612. doi:10.2147/CCID.S465963, PMID:38984321.
[87] Yan H, Gao Y, Ding Q, Liu J, Li Y, Jin M, *et al*. Exosomal Micro RNAs Derived from Dermal Papilla Cells Mediate Hair Follicle Stem Cell Proliferation and Differentiation. Int J Biol Sci 2019;15(7):1368–1382. doi:10.7150/ijbs.33233, PMID:31337968.
[88] Li J, Zhao B, Yao S, Dai Y, Zhang X, Yang N, *et al*. Dermal PapillaCell-Derived Exosomes Regulate Hair Follicle Stem Cell Proliferation via LEF1. Int J Mol Sci 2023;24(4):3961. doi:10.3390/ijms24043961, PMID:36835374.
[89] Li J, Zhao B, Dai Y, Zhang X, Chen Y, Wu X. Exosomes Derived from Dermal Papilla Cells Mediate Hair Follicle Stem Cell Proliferation through the Wnt3a/β-Catenin Signaling Pathway. Oxid Med Cell Longev 2022;2022:9042345. doi:10.1155/2022/9042345, PMID:36388171.
[90] Zhao B, Li J, Zhang X, Dai Y, Yang N, Bao Z, *et al*. Exosomal miRNA-181a-5p from the cells of the hair follicle dermal papilla promotes the hair follicle growth and development via the Wnt/β-catenin signaling pathway. Int J Biol Macromol 2022;207:110–120. doi:10.1016/j.ijbiomac.2022.02.177, PMID:35248611.
[91] Ogawa M, Udono M, Teruya K, Uehara N, Katakura Y. Exosomes Derived from Fisetin-Treated Keratinocytes Mediate Hair Growth Promotion. Nutrients 2021;13(6):2087. doi:10.3390/nu13062087, PMID:34207142.
[92] Krefft-Trzciniecka K, Cisoń H, Pakiet A, Nowicka D, Szepietowski JC. Enhancing Quality of Life and Sexual Functioning in Female Androgenetic Alopecia: Therapeutic Potential of Hair Follicle-Derived Stem Cells. Healthcare (Basel) 2024;12(6):608. doi:10.3390/healthcare12060608, PMID:38540572.
[93] Krefft-Trzciniecka K, Piętowska Z, Pakiet A, Nowicka D, Szepietowski JC. Short-Term Clinical Assessment of Treating Female Androgenetic Alopecia with Autologous Stem Cells Derived from Human Hair Follicles. Biomedicines 2024;12(1):153. doi:10.3390/biomedicines12010153, PMID:38255258.
[94] Wu J, Yang Q, Wu S, Yuan R, Zhao X, Li Y, *et al*. Adipose-Derived Stem Cell Exosomes Promoted Hair Regeneration. Tissue Eng Regen Med 2021;18(4):685–691. doi:10.1007/s13770-021-00347-y, PMID:34173219.
[95] Xiong J, Liu Z, Jia L, Sun Y, Guo R, Xi T, *et al*. Bioinspired engineering ADSC nanovesicles thermosensitive hydrogel enhance autophagy of dermal papilla cells for androgenetic alopecia treatment. Bioact Mater 2024;36:112–125. doi:10.1016/j.bioactmat.2024.02.023, PMID:38440324.
[96] Shin H, Won CH, Chung WK, Park BS. Up-to-date Clinical Trials of Hair Regeneration Using Conditioned Media of Adipose-Derived Stem Cells in Male and Female Pattern Hair Loss. Curr Stem Cell Res Ther 2017;12(7):524–530. doi:10.2174/1574888X12666170504120244, PMID:28474542.
[97] Won CH, Park GH, Wu X, Tran TN, Park KY, Park BS, *et al*. The Basic Mechanism of Hair Growth Stimulation by Adipose-derived Stem Cells and Their Secretory Factors. Curr Stem Cell Res Ther 2017;12(7):535–543. doi:10.2174/1574888X12666170829161058, PMID:28875863.
[98] Fukuoka H, Narita K, Suga H. Hair Regeneration Therapy: Application of Adipose-Derived Stem Cells. Curr Stem Cell Res Ther 2017;12(7):531–534. doi:10.2174/1574888X12666170522114307, PMID:28530535.
[99] Legiawati L, Suseno LS, Sitohang IBS, Yusharyahya SN, Pawitan JA, Liem IK, *et al*. Combination of adipose-derived stem cell conditioned media and minoxidil for hair regrowth in male androgenetic alopecia: a randomized, double-blind clinical trial. Stem Cell Res Ther

2023;14(1):210. doi:10.1186/s13287-023-03440-2, PMID:37605227.
[100] Ramdasi S, Tiwari SK. Human Mesenchymal Stem Cell-Derived Conditioned Media for Hair Regeneration Applications. J Stem Cells 2016;11(4):201–211. PMID:28296872.
[101] Ni J, Ye D, Zeng W, Ma S, Wang Z, Kuang Y, *et al*. Promotion of hair growth by a conditioned medium from human umbilical cord mesenchymal stem cells cultivated in a 3D scaffold of gelatin sponge. Eur J Med Res 2024;29(1):270. doi:10.1186/s40001-024-01830-7, PMID:38704575.
[102] Kamali-Dolat Abadi M, Yousefi G, Dehghani F, Alizadeh AA, Jangholi A, Moadab MA, *et al*. The Effect of Mesenchymal Stem Cells Derived-Conditioned Media in Combination with Oral Anti-Androgenic Drugs on Male Pattern Baldness: An Animal Study. Cell J 2023;25(11):790–800. doi:10.22074/cellj.2023.2008138.1377, PMID:38071411.
[103] Chen H, Yamaguchi S, Wang Y, Kaminogo K, Sakai K, Hibi H. Cytoprotective role of human dental pulp stem cell-conditioned medium in chemotherapy-induced alopecia. Stem Cell Res Ther 2024;15(1):84. doi:10.1186/s13287-024-03695-3, PMID:38500206.
[104] Munir J, Yoon JK, Ryu S. Therapeutic miRNA-Enriched Extracellular Vesicles: Current Approaches and Future Prospects. Cells 2020;9(10):2271. doi:10.3390/cells9102271, PMID:33050562.
[105] Horsburgh S, Fullard N, Roger M, Degnan A, Todryk S, Przyborski S, *et al*. MicroRNAs in the skin: role in development, homoeostasis and regeneration. Clin Sci (Lond) 2017;131(15):1923–1940. doi:10.1042/CS20170039, PMID:28705953.
[106] Yan H, Jin M, Li Y, Gao Y, Ding Q, Wang X, *et al*. miR-1 Regulates Differentiation and Proliferation of Goat Hair Follicle Stem Cells by Targeting IGF1R and LEF1 Genes. DNA Cell Biol 2022;41(2):190–201. doi:10.1089/dna.2021.0288, PMID:35007429.
[107] Yuan S, Zhang P, Wen L, Jia S, Wu Y, Zhang Z, *et al*. miR-22 promotes stem cell traits via activating Wnt/β-catenin signaling in cutaneous squamous cell carcinoma. Oncogene 2021;40(39):5799–5813. doi:10.1038/s41388-021-01973-5, PMID:34345013.
[108] Cai B, Li M, Zheng Y, Yin Y, Jin F, Li X, *et al*. EZH2-mediated inhibition of microRNA-22 promotes differentiation of hair follicle stem cells by elevating STK40 expression. Aging (Albany NY) 2020;12(13):12726–12739. doi:10.18632/aging.103165, PMID:32657761.
[109] Amelio I, Lena AM, Bonanno E, Melino G, Candi E. miR-24 affects hair follicle morphogenesis targeting Tcf-3. Cell Death Dis 2013;4(11):e922. doi:10.1038/cddis.2013.426, PMID:24232098.
[110] Jiang Y, Liu H, Zou Q, Li S, Ding X. miR-29a-5p Inhibits Prenatal Hair Placode Formation Through Targeting EDAR by ceRNA Regulatory Network. Front Cell Dev Biol 2022;10:902026. doi:10.3389/fcell.2022.902026, PMID:35646897.
[111] Ge M, Liu C, Li L, Lan M, Yu Y, Gu L, *et al*. miR-29a/b1 Inhibits Hair Follicle Stem Cell Lineage Progression by Spatiotemporally Suppressing WNT and BMP Signaling. Cell Rep 2019;29(8):2489–2504.e4. doi:10.1016/j.celrep.2019.10.062, PMID:31747615.
[112] Mardaryev AN, Ahmed MI, Vlahov NV, Fessing MY, Gill JH, Sharov AA, *et al*. Micro-RNA-31 controls hair cycle-associated changes in gene expression programs of the skin and hair follicle. FASEB J 2010;24(10):3869–3881. doi:10.1096/fj.10-160663, PMID:20522784.
[113] Kim BK, Yoon SK. Hairless Up-Regulates Tgf-β2 Expression via Down-Regulation of miR-31 in the Skin of "Hairpoor" (HrHp) Mice. J Cell Physiol 2015;230(9):2075–2085. doi:10.1002/jcp.24935, PMID:25639665.
[114] Chen X, Zhong L, Li X, Liu W, Zhao Y, Li J. Down-regulation of microRNA-31-5p inhibits proliferation and invasion of osteosarcoma cells through Wnt/β-catenin signaling pathway by enhancing AXIN1. Exp Mol Pathol 2019;108:32–41. doi:10.1016/j.yexmp.2019.03.001, PMID:30844369.
[115] Todosenko N, Khlusov I, Yurova K, Khaziakhmatova O, Litvinova L. Signal Pathways and microRNAs in Osteosarcoma Growth and the Dual Role of Mesenchymal Stem Cells in Oncogenesis. Int J Mol Sci 2023;24(10):8993. doi:10.3390/ijms24108993, PMID:37240338.
[116] Lv C, Li F, Li X, Tian Y, Zhang Y, Sheng X, *et al*. MiR-31 promotes mammary stem cell expansion and breast tumorigenesis by suppressing Wnt signaling antagonists. Nat Commun 2017;8(1):1036. doi:10.1038/s41467-017-01059-5, PMID:29051494.
[117] Tian Y, Ma X, Lv C, Sheng X, Li X, Zhao R, *et al*. Stress responsive miR-31 is a major modulator of mouse intestinal stem cells during regeneration and tumorigenesis. Elife 2017;6:e29538. doi:10.7554/eLife.29538, PMID:28870287.
[118] Feng Y, Wang J, Ma J, Zhang L, Chu C, Hu H, *et al*. miR-31-5p promotes proliferation and inhibits apoptosis of goat hair follicle stem cells by targeting RASA1/MAP3K1 pathway. Exp Cell Res 2021;398(2):112441. doi:10.1016/j.yexcr.2020.112441, PMID:33338478.
[119] Luan L, Shi J, Yu Z, Andl T. The major miR-31 target genes STK40 and LATS2 and their implications in the regulation of keratinocyte growth and hair differentiation. Exp Dermatol 2017;26(6):497–504. doi:10.1111/exd.13355, PMID:28419554.
[120] Yu Y, Zhang X, Liu F, Zhu P, Zhang L, Peng Y, *et al*. A stress-induced miR-31-CLOCK-ERK pathway is a key driver and therapeutic target for skin aging. Nat Aging 2021;1(9):795–809. doi:10.1038/s43587-021-00094-8, PMID:37117623.
[121] Zhang ZC, Liu JX, Shao ZW, Pu FF, Wang BC, Wu Q, *et al*. In vitro effect of microRNA-107 targeting Dkk-1 by regulation of Wnt/β-catenin signaling pathway in osteosarcoma. Medicine (Baltimore) 2017;96(27):e7245. doi:10.1097/MD.0000000000007245, PMID:28682874.
[122] Liu J, Wu M, Feng G, Li R, Wang Y, Jiao J. Downregulation of LINC00707 promotes osteogenic differentiation of human bone marrow-derived mesenchymal stem cells by regulating DKK1 via targeting miR-103a-3p. Int J Mol Med 2020;46(3):1029–1038. doi:10.3892/ijmm.2020.4672, PMID:32705245.
[123] Chen HY, Lang YD, Lin HN, Liu YR, Liao CC, Nana AW, *et al*. miR-103/107 prolong Wnt/β-catenin signaling and colorectal cancer stemness by targeting Axin2. Sci Rep 2019;9(1):9687. doi:10.1038/s41598-019-41053-z, PMID:31273221.
[124] Wang S, Kobeissi A, Dong Y, Kaplan N, Yang W, He C, *et al*. MicroRNAs-103/107 Regulate Autophagy in the Epidermis. J Invest Dermatol 2018;138(7):1481–1490. doi:10.1016/j.jid.2018.02.002, PMID:29452119.
[125] Goodarzi HR, Abbasi A, Saffari M, Fazelzadeh Haghighi M, Tabei MB, Noori Daloii MR. Differential expression analysis of balding and nonbalding dermal papilla microRNAs in male pattern baldness with a microRNA amplification profiling method. Br J Dermatol 2012;166(5):1010–1016. doi:10.1111/j.1365-2133.2011.10675.x, PMID:21967250.
[126] Wu Z, Hai E, Di Z, Ma R, Shang F, Wang M, *et al*. Chi-miR-130b-3p regulates Inner Mongolia cashmere goat skin hair follicles in fetuses by targeting Wnt family member 10A. G3 (Bethesda) 2021;11(1):jkaa023. doi:10.1093/g3journal/jkaa023, PMID:33561234.
[127] Liao Y, Jia X, Ren Y, Deji Z, Gesang Y, Ning N, *et al*. Suppressive role of microRNA-130b-3p in ferroptosis in melanoma cells correlates with DKK1 inhibition and Nrf2-HO-1 pathway activation. Hum Cell 2021;34(5):1532–1544. doi:10.1007/s13577-021-00557-5, PMID:34117611.
[128] He J, Wei C, Huang X, Zhang G, Mao J, Li X, *et al*. MiR-23b and miR-133 Cotarget TGFβ2/NOTCH1 in Sheep Dermal Fibroblasts, Affecting Hair Follicle Development. Cells 2024;13(6):557. doi:10.3390/cells13060557, PMID:38534401.
[129] Cai B, Li M, Zheng Y, Yin Y, Jin F, Li X, *et al*. MicroRNA-149-Mediated MAPK1/ERK2 Suppression Attenuates Hair Follicle Stem Cell Differentiation. Hum Gene Ther 2022;33(11-12):625–637. doi:10.1089/hum.2021.065, PMID:35171714.
[130] Xu Y, Chen B, George SK, Liu B. Downregulation of MicroRNA-152 contributes to high expression of DKK1 in multiple myeloma. RNA Biol 2015;12(12):1314–1322. doi:10.1080/15476286.2015.1094600, PMID:26400224.
[131] Mancini M, Saintigny G, Mahé C, Annicchiarico-Petruzzelli M, Melino G, Candi E. MicroRNA-152 and -181a participate in human dermal fibroblasts senescence acting on cell adhesion and remodeling of the extra-cellular matrix. Aging (Albany NY) 2012;4(11):843–853. doi:10.18632/aging.100508, PMID:23238588.
[132] He M, Lv X, Mwacharo JM, Li Y, Wang S, Sun W. MicroRNA-181a Targets GNAI2 and Affects the Proliferation and Induction Ability of Dermal Papilla Cells: The Potential Involvement of the Wnt/β-Catenin Signaling Pathway. Int J Mol Sci 2024;25(14):7950. doi:10.3390/ijms25147950, PMID:39063192.
[133] Zhu N, Huang K, Liu Y, Zhang H, Lin E, Zeng Y, *et al*. miR-195-5p Reg-

ulates Hair Follicle Inductivity of Dermal Papilla Cells by Suppressing Wnt/β-Catenin Activation. Biomed Res Int 2018;2018:4924356. doi:10.1155/2018/4924356, PMID:29850524.
[134] Kazi T, Nagata A, Nakagawa T, Matsuzaki T, Inui S. Dermal Papilla Cell-Derived Extracellular Vesicles Increase Hair Inductive Gene Expression in Adipose Stem Cells via β-Catenin Activation. Cells 2022;11(2):202. doi:10.3390/cells11020202, PMID:35053317.
[135] Ahmed MI, Alam M, Emelianov VU, Poterlowicz K, Patel A, Sharov AA, *et al*. MicroRNA-214 controls skin and hair follicle development by modulating the activity of the Wnt pathway. J Cell Biol 2014;207(4):549–567. doi:10.1083/jcb.201404001, PMID:25422376.
[136] Luo Z, Dou J, Xie F, Lu J, Han Q, Zhou X, *et al*. miR-203a-3p promotes loureirin A-induced hair follicle stem cells differentiation by targeting Smad1. Anat Rec (Hoboken) 2021;304(3):531–540. doi:10.1002/ar.24480, PMID:32589363.
[137] Xia ZL, Wang Y, Sun QD, Du XF. MiR-203 is involved in osteoporosis by regulating DKK1 and inhibiting osteogenic differentiation of MSCs. Eur Rev Med Pharmacol Sci 2018;22(16):5098–5105. doi:10.26355/eurrev_201808_15703, PMID:30178828.
[138] Warshauer E, Samuelov L, Sarig O, Vodo D, Bindereif A, Kanaan M, *et al*. RBM28, a protein deficient in ANE syndrome, regulates hair follicle growth via miR-203 and p63. Exp Dermatol 2015;24(8):618–622. doi:10.1111/exd.12737, PMID:25939713.
[139] Hu S, Li Z, Lutz H, Huang K, Su T, Cores J, *et al*. Dermal exosomes containing miR-218-5p promote hair regeneration by regulating β-catenin signaling. Sci Adv 2020;6(30):eaba1685. doi:10.1126/sciadv.aba1685, PMID:32832660.
[140] Li X, Wu Y, Xie F, Zhang F, Zhang S, Zhou J, *et al*. miR-339-5p negatively regulates loureirin A-induced hair follicle stem cell differentiation by targeting DLX5. Mol Med Rep 2018;18(2):1279–1286. doi:10.3892/mmr.2018.9110, PMID:29901112.
[141] Zhou L, Wang H, Jing J, Yu L, Wu X, Lu Z. Regulation of hair follicle development by exosomes derived from dermal papilla cells. Biochem Biophys Res Commun 2018;500(2):325–332. doi:10.1016/j.bbrc.2018.04.067, PMID:29654758.
[142] Tomita Y, Akiyama M, Shimizu H. PDGF isoforms induce and maintain anagen phase of murine hair follicles. J Dermatol Sci 2006;43(2):105–115. doi:10.1016/j.jdermsci.2006.03.012, PMID:16725313.
[143] Cao L, Tian T, Huang Y, Tao S, Zhu X, Yang M, *et al*. Neural progenitor cell-derived nanovesicles promote hair follicle growth via miR-100. J Nanobiotechnology 2021;19(1):20. doi:10.1186/s12951-020-00757-5, PMID:33430889.
[144] Aguirre GA, González-Guerra JL, Espinosa L, Castilla-Cortazar I. Insulin-Like Growth Factor 1 in the Cardiovascular System. Rev Physiol Biochem Pharmacol 2018;175:1–45. doi:10.1007/112_2017_8, PMID:29294200.
[145] Castela M, Linay F, Roy E, Moguelet P, Xu J, Holzenberger M, *et al*. Igf1r signalling acts on the anagen-to-catagen transition in the hair cycle. Exp Dermatol 2017;26(9):785–791. doi:10.1111/exd.13287, PMID:28094870.
[146] Xia Y, Chen J, Ding J, Zhang J, Chen H. IGF1- and BM-MSC-incorporating collagen-chitosan scaffolds promote wound healing and hair follicle regeneration. Am J Transl Res 2020;12(10):6264–6276. PMID:33194028.
[147] Li K, Sun Y, Liu S, Zhou Y, Qu Q, Wang G, *et al*. The AR/miR-221/IGF-1 pathway mediates the pathogenesis of androgenetic alopecia. Int J Biol Sci 2023;19(11):3307–3323. doi:10.7150/ijbs.80481, PMID:37496996.
[148] He Y, Liu X, Qu Q, Chen J, Fan Z, Zhu D, *et al*. Overexpression of miR-122 promotes apoptosis of dermal papilla cells by directly targeting IGF1R in androgenetic alopecia. Cell Biol Int 2022;46(2):185–191. doi:10.1002/cbin.11723, PMID:34747545.
[149] Xia Y, You XE, Chen H, Yan YJ, He YC, Ding SZ. Epidermal growth factor promotes mesenchymal stem cell-mediated wound healing and hair follicle regeneration. Int J Clin Exp Pathol 2017;10(7):7390–7400. PMID:31966581.
[150] Kim Y, Lee JM, Jang YN, Park AY, Kim SY, Kim BJ, *et al*. Irisin promotes hair growth and hair cycle transition by activating the GSK-3β/β-catenin pathway. Exp Dermatol 2024;33(8):e15155. doi:10.1111/exd.15155, PMID:39133009.
[151] Cheng Y, Lv LJ, Cui Y, Han XM, Zhang Y, Hu CX. Psychological stress impact neurotrophic factor levels in patients with androgenetic alopecia and correlated with disease progression. World J Psychiatry 2024;14(10):1437–1447. doi:10.5498/wjp.v14.i10.1437, PMID:39474391.
[152] Lisse TS, Sharma M, Vishlaghi N, Pullagura SR, Braun RE. GDNF promotes hair formation and cutaneous wound healing by targeting bulge stem cells. NPJ Regen Med 2020;5:13. doi:10.1038/s41536-020-0098-z, PMID:32566252.
[153] Mulligan LM. GDNF and the RET Receptor in Cancer: New Insights and Therapeutic Potential. Front Physiol 2018;9:1873. doi:10.3389/fphys.2018.01873, PMID:30666215.
[154] Soret R, Schneider S, Bernas G, Christophers B, Souchkova O, Charrier B, *et al*. Glial Cell-Derived Neurotrophic Factor Induces Enteric Neurogenesis and Improves Colon Structure and Function in Mouse Models of Hirschsprung Disease. Gastroenterology 2020;159(5):1824–1838.e17. doi:10.1053/j.gastro.2020.07.018, PMID:32687927.
[155] Botchkareva NV, Botchkarev VA, Welker P, Airaksinen M, Roth W, Suvanto P, *et al*. New roles for glial cell line-derived neurotrophic factor and neurturin: involvement in hair cycle control. Am J Pathol 2000;156(3):1041–1053. doi:10.1016/S0002-9440(10)64972-3, PMID:10702420.
[156] Vishlaghi N, Rieger S, McGaughey V, Lisse TS. GDNF neurotrophic factor signalling determines the fate of dermal fibroblasts in wound-induced hair neogenesis and skin regeneration. Exp Dermatol 2022;31(4):577–581. doi:10.1111/exd.14526, PMID:35020233.
[157] Ren SY, Zhang YN, Wang MJ, Wen BR, Xia CY, Li X, *et al*. Hair growth predicts a depression-like phenotype in rats as a mirror of stress traceability. Neurochem Int 2021;148:105110. doi:10.1016/j.neuint.2021.105110, PMID:34166749.
[158] Mohamed NE, Soltan MR, Galal SA, El Sayed HS, Hassan HM, Khatery BH. Female Pattern Hair Loss and Negative Psychological Impact: Possible Role of Brain-derived Neurotrophic Factor (BDNF). Dermatol Pract Concept 2023;13(3):e2023139. doi:10.5826/dpc.1303a139, PMID:37557155.
[159] Panchaprateep R, Korkij W, Asawanonda P. Brain-derived nerve factor and neurotrophins in androgenetic alopecia. Br J Dermatol 2011;165(5):997–1002. doi:10.1111/j.1365-2133.2011.10514.x, PMID:21729031.
[160] Xu P, Xin Y, Zhang Z, Zou X, Xue K, Zhang H, *et al*. Extracellular vesicles from adipose-derived stem cells ameliorate ultraviolet B-induced skin photoaging by attenuating reactive oxygen species production and inflammation. Stem Cell Res Ther 2020;11(1):264. doi:10.1186/s13287-020-01777-6, PMID:32611371.
[161] Fukuoka H, Suga H, Narita K, Watanabe R, Shintani S. The Latest Advance in Hair Regeneration Therapy Using Proteins Secreted by Adipose-Derived Stem Cells. Am J Cosmet Surg 2012;29(4):273–282. doi:10.5992/AJCS-D-12-00015.1.
[162] Shimizu Y, Ntege EH, Sunami H, Inoue Y. Regenerative medicine strategies for hair growth and regeneration: A narrative review of literature. Regen Ther 2022;21:527–539. doi:10.1016/j.reth.2022.10.005, PMID:36382136.
[163] Gupta AK, Wang T, Rapaport JA. Systematic review of exosome treatment in hair restoration: Preliminary evidence, safety, and future directions. J Cosmet Dermatol 2023;22(9):2424–2433. doi:10.1111/jocd.15869, PMID:37381168.
[164] Sengupta V, Sengupta S, Lazo A, Woods P, Nolan A, Bremer N. Exosomes Derived from Bone Marrow Mesenchymal Stem Cells as Treatment for Severe COVID-19. Stem Cells Dev 2020;29(12):747–754. doi:10.1089/scd.2020.0080, PMID:32380908.
[165] Jin SE, Sung JH. Hair regeneration using adipose-derived stem cells. Histol Histopathol 2016;31(3):249–256. doi:10.14670/HH-11-686, PMID:26536569.
[166] Kwon OS, Han JH, Yoo HG, Chung JH, Cho KH, Eun HC, *et al*. Human hair growth enhancement in vitro by green tea epigallocatechin-3-gallate (EGCG). Phytomedicine 2007;14(7-8):551–555. doi:10.1016/j.phymed.2006.09.009, PMID:17092697.
[167] Dyson HJ, Wright PE. Role of Intrinsic Protein Disorder in the Function and Interactions of the Transcriptional Coactivators CREB-binding Protein (CBP) and p300. J Biol Chem 2016;291(13):6714–6722. doi:10.1074/jbc.R115.692020, PMID:26851278.

[168] Liu F, Liu S, Luo X, Fan Z, Huang S, Deng F, *et al*. Combatting ageing in dermal papilla cells and promoting hair follicle regeneration using exosomes from human hair follicle dermal sheath cup cells. Exp Dermatol 2024;33(1):e14948. doi:10.1111/exd.14948, PMID:37950506.
[169] Carrasco E, Soto-Heredero G, Mittelbrunn M. The Role of Extracellular Vesicles in Cutaneous Remodeling and Hair Follicle Dynamics. Int J Mol Sci 2019;20(11):2758. doi:10.3390/ijms20112758, PMID:31195626.
[170] Zhang P, Kling RE, Ravuri SK, Kokai LE, Rubin JP, Chai JK, *et al*. A review of adipocyte lineage cells and dermal papilla cells in hair follicle regeneration. J Tissue Eng 2014;5:2041731414556850. doi:10.1177/2041731414556850, PMID:25383178.
[171] Kwack MH, Seo CH, Gangadaran P, Ahn BC, Kim MK, Kim JC, *et al*. Exosomes derived from human dermal papilla cells promote hair growth in cultured human hair follicles and augment the hair-inductive capacity of cultured dermal papilla spheres. Exp Dermatol 2019;28(7):854–857. doi:10.1111/exd.13927, PMID:30924959.
[172] Shang Y, Li M, Zhang L, Han C, Shen K, Wang K, *et al*. Exosomes derived from mouse vibrissa dermal papilla cells promote hair follicle regeneration during wound healing by activating Wnt/β-catenin signaling pathway. J Nanobiotechnology 2024;22(1):425. doi:10.1186/s12951-024-02689-w, PMID:39030543.
[173] Liu P, Tan Q, Jiang Y, Lü Q. [Wound-induced hair follicle neogenesis: a new perspective on hair follicles regeneration in adult mammals]. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi 2020;34(3):393–398. doi:10.7507/1002-1892.201905102, PMID:32174089.
[174] Xue Y, Lim CH, Plikus MV, Ito M, Cotsarelis G, Garza LA. Wound-Induced Hair Neogenesis Model. J Invest Dermatol 2022;142(10):2565–2569. doi:10.1016/j.jid.2022.07.013, PMID:36153062.
[175] Kazi T, Niibe I, Nishikawa A, Matsuzaki T. Optimal stimulation toward the dermal papilla lineage can be promoted by combined use of osteogenic and adipogenic inducers. FEBS Open Bio 2020;10(2):197–210. doi:10.1002/2211-5463.12763, PMID:31730301.
[176] O'Brien K, Breyne K, Ughetto S, Laurent LC, Breakefield XO. RNA delivery by extracellular vesicles in mammalian cells and its applications. Nat Rev Mol Cell Biol 2020;21(10):585–606. doi:10.1038/s41580-020-0251-y, PMID:32457507.
[177] le Riche A, Aberdam E, Marchand L, Frank E, Jahoda C, Petit I, *et al*. Extracellular Vesicles from Activated Dermal Fibroblasts Stimulate Hair Follicle Growth Through Dermal Papilla-Secreted Norrin. Stem Cells 2019;37(9):1166–1175. doi:10.1002/stem.3043, PMID:31237401.