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REVIEW ARTICLE

AN OVERVIEW OF QUIESCENT HAIR FOLLICLE STEM CELL RE-ACTIVATION FOR ANDROGENETIC ALOPECIA TREATMENT: A COMPREHENSIVE REVIEW

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ABSTRACT

Hair follicle stem cells (HFSCs) are undifferentiated, self-renew and multipotent cells in skin. Androgenetic Alopecia (AGA) is affecting 85% of males and 40% of females throughout the world. Its exact cause is unknown Androgens play a pivotal role in AGA etiology, but it is associated with other diseases, such as; hyper-androgenemia, hypothyroidism, prostate cancer, nutritional deficiencies, autoimmune diseases and even COVID-19. Multiple treatments have been considered for androgenetic alopecia, but, it was not satisfactory results. In individuals with AGA, hair follicle stem cells in bulge remain but are quiescent and it has been suggested that this may make AGA reversible. The activation of these cells through re-activation of signaling pathways such as wnt/β-catenin pathway may be the most effective treatment strategy for AGA. Five known signaling pathways which control HFSCs functions, are; wnt/β-catenin, sonic hedgehog (shh), notch, bone morphogenesis protein(BMP) and apoptosis signaling pathways. The Wnt pathway plays an important role in hair growth and regulates HFSC expression during the telogen-anagen phase transition, Shh pathway induces quiescent HFSCs to be activated and initiate to proliferate, Notch signaling plays a vital role in the activation, proliferation, differentiation of HFSCs and metabolite generation, then determines the fate of HFSCs and BMP is involved in HFSCs differentiation. The most recent attempt to treat AGA is to activate quiescent HFSCs in bulge using signaling pathways such as wnt/β-catenin. The golden goal of all research is to gain a deeper understanding of disease pathomechanisms to encourage the development of more effective treatments with greater specificity and less or zero adverse effects. This is ambitious but achievable dream.

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INTRODUCTION

Hair follicle stem cells (HFSCs) alike other stem cells (SCs), are undifferentiated, self-renew and pluripotent cells that to be resident in dermis adjacent epidermal cells. These cells maintain proliferation potency for all over life (1-3). Hair shaft emerge of a hair follicle while 2-6 hair shaft grow out of each hair follicle. Hair follicle(HF) functions including: thermoregulation, physical protection, sensory input, and decorative purposes for social interactions (4). A healthy human scalp has 120000 follicles (5). Androgenetic alopecia (AGA) is the most commonhair loss, affecting 85% of males and 40%of females, all around the world (6). Several factors, such as genetics, hormones, and systemic diseases are main leading cause of AGA(6). By the way, its exact cause is unknown. AGA epidemiological factors are different and depend on age and race. Based on earlier prevalence data,up 30% of white men will have AGA by the age of 30 years, up to 50% by 50 years, and 80% by 70 years (7-10). Chinese, Japanese, and African American people are less affected than Caucasians(11). Hair growth can be disrupted by HFSCs niche pathology, e.g. dysfunction of dermal papilla cells in androgenetic alopecia (12). Although, androgens play a pivotal role in AGA etiology, but it is associated with other diseases, such as; hyper-androgenemia (13), hypothyroidism (14), prostate cancer(15), nutritional deficiencies (16), autoimmune diseases (17) and even COVID-19(6).

Indeed, Genetic polymorphism including androgen receptor (AR), 7p21, 20P11, and 2Q35 susceptibility genes on the X chromosome, cigarette smoking, alcohol intake, eating habits such as: high consumption of meat and insufficient fruits and vegetables, sleep disturbance, bacterial and viral infections, infection SARS-CoV-2 (COVID-19), Cancers e.g. prostate cancer, thyroid cancer, and metabolic diseases and of course, psychological disorders such as; Depression, anxiety, obsessive–compulsive disorder, and loss of confidence are high risk factors for AGA(6). At present, treatments include drug and non-drug therapy. The current pharmacological treatment for AGA includes androgen metabolism modulators. Other treatment strategies are nutrient therapy, natural products, low-level light therapy and hair transplantation surgery. The use of Wnt activators and SFRP1 antagonism is the latest therapeutic strategy to treat hair loss, especially in AGA(18). Multiple treatments have been considered for AGA, but it was not satisfactory results. However, efforts are still ongoing. In this paper, as much as possible, we collected and updated all findings on AGA pathophysiology and its therapeutic strategies that have been applied in clinical level. Local microenvironment or niche of HFSCs is a complex signaling network of biomolecules such as; cytokines, growth factors and other stimulators around them that regulate HFSCs activities. Control of HFSCs either physiological or pathological states is done by a variety of signaling pathways such as wnt/β-catenin signaling pathway and so on which will be explained further. In the first part of the review, we

focused on reactivating signaling pathways of HFSCs to regenerate hair follicles and subsequently regrow hair. In the second part, various treatment strategies for AGA are described. First of all, we take a look at the physiology of hair growth.

DISCUSSION

Hair cycle: Naturally, HFs from outgrowth to downfall hairs, undergo three main stages (1, 19-25):

A) anagen, hair growth phase
B) catagen, regressive phase (stop hair growth)
C) telogen, resting phase (hair loss)

Each stage of hair cycle continues 2-10 years, 2-4 weeks and 2-3 month, respectively (21). Hair follicles along with sebaceous and sweat glands are skin appendages that with extracellular matrix, fibroblasts and vascular endothelial cells make up the connective tissue of the dermis. Skin is made of two layers, which are from surface to depth; epidermis and dermis. In the same way, dermis is composed three layer, which are: papillary dermis, reticular dermis and hypodermis. Hair follicles originate from the hypodermis (Figure 1). It is estimates that humans have 5 million hair follicles with two types of hair (1, 26):

a. Terminal hair that is long, thick and pigmented
b. Villus hair that is short, thin and without pigment

Hair follicles are made up of three parts;

1. Outer root sheath (ORS), the upper part of hair follicle which connected to epidermis (deep purple)
2. Inner root sheath (IRS), the middle part of hair follicle which is located between the hair shaft in the center and the outer root sheath (ORS) peripherally (light purple)
3. Hair shaft (HS), which is made by differentiating IRS.

Each hair follicle produces 2-6 hair shafts. In human, hair follicles are formed by epithelial and mesenchymal cells interaction(21). At the end of each hair follicle, there is a bulb consist of dermal papilla region in the center of which are dermal papilla cells (DPCs).

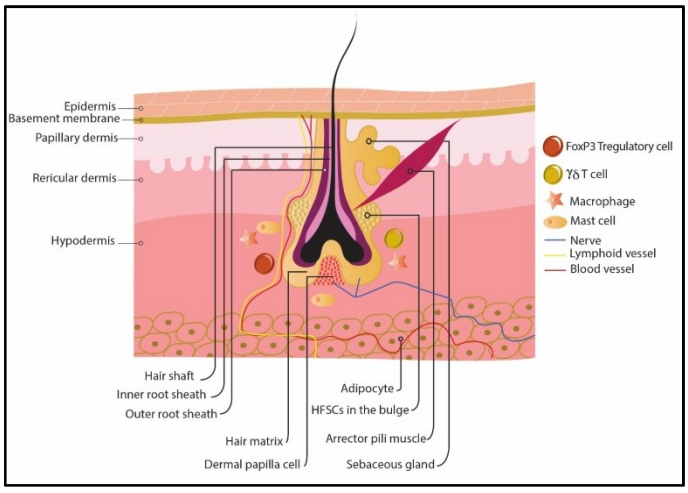

Figure 1. Hair follicle structure

These cells are undifferentiated and strongly proliferating which are necessary for hair follicles formation. Hair growth cycle and regeneration are mainly controlled by these cells (27, 28). Interaction between HFSCs and DPCs play crucial role in hair cycle regulation (29-31). Hair as nail and sebaceous gland is one of skin appendages which is made up by epithelial- mesenchymal interaction. Epithelial-mesenchymal interaction is inevitable not only for embryonic HF morphogenesis but also for postnatal hair cycling (32). Keratinocytes from epidermis and fibroblasts from dermis provide the basis for the aforementioned interaction. Wnt/β-catenin signaling may be required for mentioned interaction(33). In the embryonic period, the stages of hair follicle development are; placode, hair germ, hair peg, hair follicle, respectively (19).See more Figure 2. For postnatal follicular epithelial-mesenchymal interaction, although DP cells provide signaling ligands, such as TGF-β2 and FGF-7(34) to activate HFSCs for a new hair cycle, signals from epithelial cells are also required for proper anagen entry (35). HFSCs are located in the special of ORS called the bulge. The bulge is located adjacent the arrectorpili muscle into the HF epithelium below the sebaceous gland and encapsulated by immune privilege area (36). HFSCs are first identified as slow-cycling label-retaining cells located in the bulge epithelium (12) and today, those are called bulge stem cells which are relatively quiescent stem cells. These cells immigrate downward dermal papilla region where to form secondary hair germ stem cells.

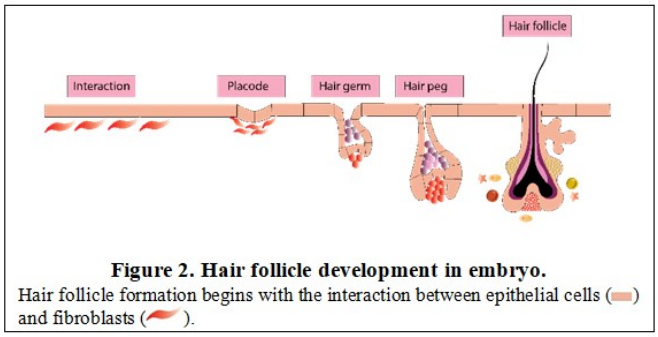

Figure 2. Hair follicle development in embryo.
Hair follicle formation begins with the interaction between epithelial cells ( ) and fibroblasts ( ).

Recent cells are more active than bulge stem cells. Secondary hair germ stem cells are seen only in telogen phase. These cells are activated, proliferated and differentiated, not only cause the formation of hair follicle and sebaceous gland, but also immigrate to the epidermis and involve in epithelium regeneration (1, 26). Some researchers believe that bulge stem cells are separate from secondary hair germ stem cells (37, 38). By the way, HFs regeneration from telogen to anagen is done by the coordinated activation of these two cell populations: primed HFSCs in the secondary hair germ are first activated, followed by the activation of quiescent HFSCs in the bulge later (39). In anagen, HFSCs give rise to hair germs, then the transient amplifying cells in the matrix of the new follicle proliferate rapidly to form a new hair filament (39). In catagen, hair follicle stem cells are maintained in the bulge and in the transition from telogen to anagen, the signals from the DP stimulate the hair germ and quiescent bulge stem cells to become activated (37).

Taken together, HFSCs include (4, 40-43):

a- Epithelial stem cells of the bulge with slow-cycle
b- Epithelial progenitors in the secondary hair germ with fast-cycle
c- Dermal papilla cells in dermal papilla region of bulb
d- Melanocyte stem cells

HFSCs functions are regulated by intra and extra-follicular signals. Currently, the known intra-follicular signals are all proteins and receptors which stimulate cytoplasmic signaling pathways, such as (44, 45):

1. Wnt/β catenin pathway
2. Sonic hedgehog (shh) pathway
3. Notch pathway
4. Bone morphogenetic proteins (BMP) pathway
5. Apoptotic pathway
6. phosphoinositol 3 kinase/AK strain transforming(PI3K/AKT) pathway

Extra-follicular signals have been known including:

1. Intradermal adipocytes (46, 47)
2. Dermal fibroblasts (48, 49)
3. Blood vessels (50, 51)
4. Lymphatic vessels (52, 53)
5. Peripheral nerves (54, 55)

Some of these mediators are positive regulator, such as; wnt proteins (56) and growth factors such as fibroblast growth factor(FGF), platelet derived growth factor (PDGF) (47) and so on, that promote hair growth. Likewise, other mediators are negative regulators, such as; BMP which prevents hair growth (57). Hair growth cycle can be deregulated by paracrine factors from the follicle itself and/or from the surrounding dermal tissue, or by endocrine factors leading to hair loss (37, 40).

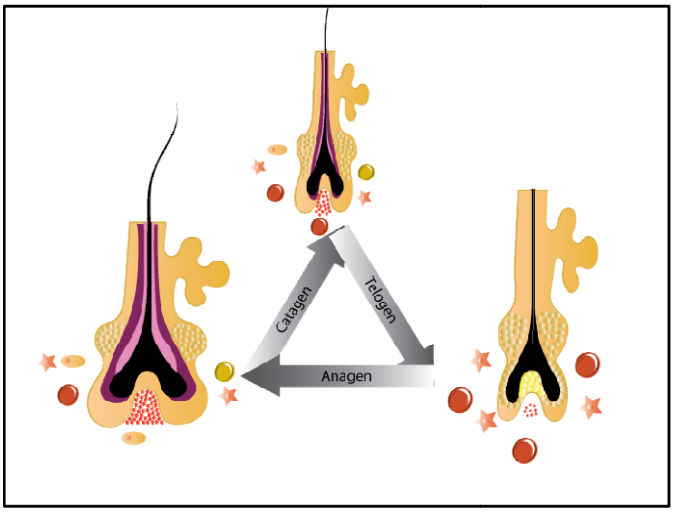

Figure 3. HFSCs in each stage of the hair cycle

Some of these mediators are positive regulator, such as; wnt proteins (56) and growth factors such as fibroblast growth factor(FGF), platelet derived growth factor (PDGF) (47) and so on, that promote hair growth. Likewise, other mediators are negative regulators, such as; BMP which prevents hair growth(57). Hair growth cycle can be deregulated by paracrine factors from the follicle itself and/or from the surrounding dermal tissue, or by endocrine factors leading to hair loss (37, 40).

Hair follicles associated immune cells

What is the importance of Immune responses, immune cells and their cytokines in hair cycle? It is known thatcytokines and hair follicles associated immune cells delete pathogens, prevent from immune dysregulation and maintain tissue homeostasis(4).It has been shown that T cells and macrophages(MQs) are the major effectors in hair follicles regeneration (58, 59). The immune cells, including macrophages, mast cells, and γδT cells and regulatory T (Treg) cells regulate the activity of HFSCs(36, 59). see more figure 1.In mice, mast cells are involved in the transition telogen to anagen as well as anagen to catagen (60). Histamine and serotonin secreted by mast cells promote the proliferation of keratinocytes and also, mast cells contribute hair loss in AGA (61). When skin is injured e.g. by hair plucking, HFs release chemokines such as CCL2 that recruit MQs (62). Then MQs are activated by the apoptosis signal-regulating kinase 1(ASK1). Activated MQs release cytokines such as tumor necrosis factor-α(TNF-α). This cytokine activates HFSCs by inducing AKT-dependent β-catenin accumulation (63). After that, HFSCs proliferate and differentiate to promote premature anagen entry (64). MQs are divided into two main cell populations; M1 and M2 phenotypes (65). M2 phenotype is responsible for tissue regeneration, then these cellsstimulate hair regeneration via paracrine secretion of Insulin growth factor(IGF) and hepatocyte growth factor(HGF) (66). With the production of new hair shaft, injured skin is repaired (32). Regulatory T cells(Treg cells) are in close contact with HFSCs and can increase the proliferation and differentiation of HFSCs following hair plucking(59). Treg cells express high level of Notch ligand family member called Jagged 1 (Jag 1) which facilitate HFSCs function and then promote HF regeneration and subsequent hair re-growth (59, 67). γδT cells are seen in outer root sheath of HFs. Activated γδT cells function include; 1) stimulation of epidermal stem cell proliferation to accelerate wound healing and 2)HFSC activation for hair regrowth (68).

Hair follicle stem cells: The main hair stem cells are: hair follicle stem cells (HFSCs) in bluge and dermal papilla cells (DPCs) in dermal papilla region. But the other stem cells within HFs are alsoinvolved in tissue homeostasis and damage repair, which include; keratinocyte progenitors, melanocyte progenitors, nestin-expressing stem cells, skin-derived precursor cells (SKPs) located in the dermal papilla region and stem cells in sebaceous and sweat gland (44, 69-71). As mentioned before, HFSCs are multipotent and capable to regenerate HFs and consequently hair growth through reaction with DPCs (1). HFSCs originate from neuroectoderm and have been shown to be capable of differentiating into nerve cells, glia cells, smoot muscle cells, skeletal muscle cells, cardiac cells and melanocytes (72). The term 'HFSCs' was first used in 1990s, which is first identified in the bulge epithelium as label-retaining cells (40). These cells are often silent. But, at the end of telogen, few of these cells are activated by receiving signals from activators such as secretory factors of DPCs and then the anagen phase is started (73). At present, CK15 is the best marker to identify human HFSCs (74). Integrin β-1, CD34, CK19, CD200, pleckstrin homology-like domain family 1(PHLDA1) also called T cell death associated gene 51 (TDAG51) and finally nuclear factor of T cell 1 (NFATC1) are other specific markers. PHLDA1 can prevent apoptosis (44). HFSCs have other markers such as: CD71, CD146, connexin 43, SCA-1, Bcrp1 and P75NTR (75). The main function of HFSCs is to maintance homeostasis of HFs, skin wound healing, renewal and reestablishment of hair follicles (44, 76). The origin of DPCs may be dermal fibroblasts. In fact, DPCs are formed by epithelial -mesenchymal interaction in the embryonic stage. As mentioned above, after birth, DPCs are located in dermal papilla region of each hair follicle. DPCs are the main responsible for hair formation. These cells proliferate and differentiate and then develop hair shaft, inner root sheath and outer root sheath, from inside to outside(see more Figure1). In mouse, the most important markers of DPCs are sex determining region Y-box 2 (SOX2) and CD133 (77). In vitro, DPCs can differentiate to several types of cells such as; chondrocyte, blood cells, smooth muscle cells, fibroblast, osteoblast, adipocyte and neuron or glia (78). Among dermal papilla cells, there are other stem cells called skin-derived progenitors(SKPs) that are capable to differentiating into the cells mentioned above (79). DPCs play pivotal roles in hair formation, growth, and cycling (80).

HFSC signaling pathways: Local microenvironment or niche of HFSCs is a complex signaling network of biomolecules such as; cytokines, growth factors and other stimulators around them that regulate HFSCs activities. Control of HFSCs either physiological or pathological states is done by a variety of signaling pathways.The regulation of survival and death signaling pathways plays a role in the quiescence, activation, differentiation and metabolism of HFSCs which is essential for skin homeostasis, hair regeneration and hair growth (44, 81, 82).

Five known signaling pathways which control HFSCs functions (25, 83) are;

1. Wnt/β-catenin signaling pathway
2. Sonic hedgehog (Shh) signaling pathway
3. NOTCH signaling pathway
4. Bone morphogenetic protein (BMP) signaling pathway
5. Apoptotic pathway

The first four pathways involve in HFSCs survival and the last pathway leads to HFSCs death.

Molecular mechanism of Wnt/β-catenin signaling pathway

Wnt family proteins are secretory factors that have been found in all tissues. So far, 19 members of this family protein have been identified in human and mice which are separated from each other by

numbering such as; wnt1, wnt2. Each of the subgroups are named with small letters e.g. wnt1a or wnt1b and so on. Wnt comes from Wingless-related integration site (25). For the first time, int oncogenic protein called int1was found in mouse breast cancer. But later, a protein similar to int1 in drosophila was identified. Initially, the name of this protein was changed to int/wingless and then to wnt (84, 85). Wnt proteins, are a family of highly conserved proteins that regulate multiple functions (84) including; cell-cell interaction in lung development, homeostasis, regeneration following injury(86), development and adult tissue homeostasis (87), self-renewing stem cells or stem cells control (88), tissue regeneration after injury (89), hematopoiesis (90), cellular proliferation and differentiation (91) and motility (92). Of course, it has been said that wnt proteins act to maintain the undifferentiated state of stem cells, while other growth factors instruct the cells to proliferate. These other factors include FGF and EGF, signaling through tyrosine kinase pathways (88). The diverse roles of wnt signaling has been revealedin HFs development (44). In physiological state, HFSCs in bulge are silent. But, in telogen phase, extracellular proteins wnt increase and bind to their receptor named Frizzled onthe surface of HFSCs. lipoprotein receptorrelated protein or Lrp5/6 receptors are co-receptors for wnt proteins (Look at Figure 4). By binding wnt to Frizzled and Lrp, cytoplasmic protein Dv1 (Disheveled) attaches to Frizzled and Lrp cytoplasmic tail.

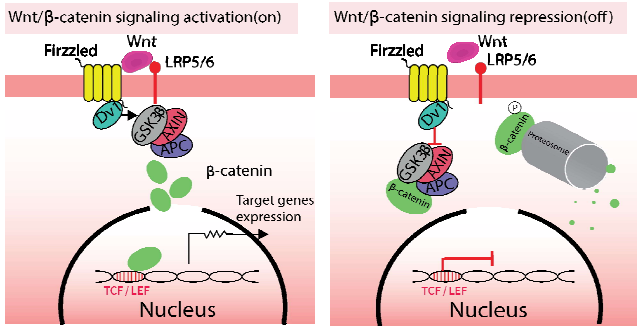

Figure 4. wnt/β-catenin signaling pathway

a. In the Wnt/β-catenin signaling ON (activation), By binding wnt to Frizzled and Lrp, cytoplasmic protein Dv1 attaches to Frizzled and Lrp cytoplasmic tail. Then,the inhibitory complex of β-catenin containg Axin, APC,and GSCK3, by disconnecting from Dv1, releases β-catenin. Then, β-catenin is translocated to the nucleus and binds to transcription factors of TCF/LEF family to promote the expression of target genes.
b. In the Wnt/β-catenin signaling OFF (repression), Dv1 protein joins the inhibitory complex and a multiprotein complex is formed with APC, Axin, GSK3 and Dv1, which can target and phosphorylate β-catenin. After that, β-cateninis ubiquitinated and degraded by proteosomes. The T-shaped lines indicate inhibitory interactions involved in this pathway, and the solid arrows indicate activating interactions. Abbreviations: Lrp5/6; LDL receptor-related proteins 5 and 6, Dv1; Disheveled 1, APC; tumor suppressor Adenomatous Polyposis Coli, GSK3β: glycogen synthesis kinase 3β, TCF/LEF; T cell factor/Lymphoid Enhancer Factor.

As a result, the inhibitory complex of β-catenin is suppressed. The component of this inhibitory complex are; Axin, APC, Dv1 and GSCK3. By disconnecting Dv1 from complex andconnecting it to wnt receptor, the inhibitory effect of this complex has been removed and then β-catenin is released. Subsequently, the cytoplasmic concentration ofβ-catenin increases. Then, β-catenin is translocated to the nucleus and binds to transcription factors of TCF/LEF family to promote the expression of target genes, such as Axin2, LEF1and Lgr5. By expression genes, HFSCs activated and the telogen phase turns into anagen (25, 88). Inanagen phase, β-catenin is overregulated in HFSCs. But, in catagen and telogen phases, β-catenin is downregulated. In these stages, repression of wnt signaling is triggered (Figure 3.). In the absence of a Wnt signal, Wnt inhibitors (*e.g.*, sFRP1, Dkk1, Dkk3 or Wif) bind to Frizzled/Lrp. Then Dv1 protein joins the inhibitory complex and a multiprotein complex is formed with APC, Axin, GSK3 and Dv1, which can target and phosphorylate β-catenin. After that, β-cateninis ubiquitinated and degraded by proteosomes. By reducing β-catenin, TCF/LEF genes expression are downregulated. HFSCs are inactivated and hair regeneration and regrowth is prevented. Recent events are seen physiologically in catagen and telogen. But, if the breakdown of β-catenin is not restored, hair lossbecomes permanent (25, 93, 94). Wnt7 andwnt10b functions as a major activator, play a key role in wnt/β-catenin signaling in HFSCs. Hence, they involve in hair growth. In addition, Wnt10b is an activator that regulates HFSC expression during the telogen-anagen phase transition(95, 96). See more Figure 4.

Molecular mechanism of Shh signaling pathway: Shh signaling pathway plays crucial role in tissue development, homeostasis and regeneration. It regulates the morphogenesis of various organs during embryogenesis (97, 98). Shh signaling in like manner to wnt/β-catenin pathway helpsquiescent HFSCs to proliferate and regulate dermal factors topromote HFSCs activation (38). Shh similar to wnt factorsareextracellular protein in multiple tissues, including HF tissue which are bound to their receptors called Patched(PTCH),during the transition from telogen to anagen. As a result, the inhibitory effect of PTCH on Smoothened (Smo) is removed. Smo is a G protein-coupled receptor (GPCR)-like protein. Subsequently, Smo is translocated to the cell membrane of HFSCs and Gli proteins areseparated from suppressor of fused homologue (sufu) proteins and then Gli proteins are translocatedinto the nucleus, leading to the transcription of target genes e.g. Ptch and Gli1. Quiescent HFSCs are activated and initiate to proliferate (99, 100). See more Figure 5.

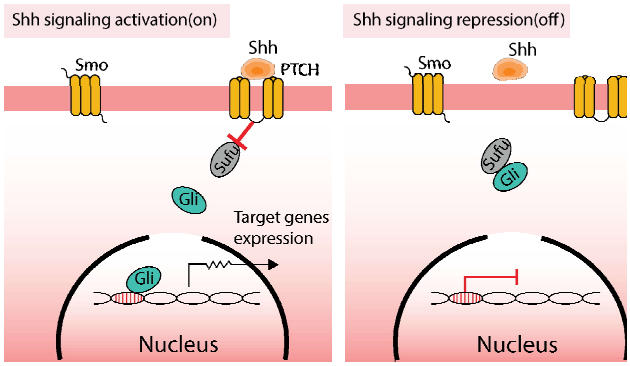

Figure 5. Shh signaling pathway

a. with Shh-PTCH binding, the inhibitory effect of PTCH on Smoothened(Smo) is removed. Gli proteins are separated from sufu and then Gli proteins are translocated into the nucleus, leading to target gene expression.
b. in the repression state, Gli protein are inhibited by sufu andremain in the cytoplasm.

The T-shaped lines indicate inhibitory interactions involved in this pathway, and the solid arrows indicate activating interactions. Abbreviations; Shh: Sonic hedgehog, Smo: Smoothened, PTCH: Patched, Sufu: suppressor of fused homologue proteins, Gli: glioma-associated oncogene.

Molecular mechanism of Notch signaling pathway: The Notch receptor family is a type I single transmembrane receptor protein family with four members in mammalian including; in mice and humans (101). These surface receptors play a key role in the proliferation and differentiation of various skin cellsspecial during the development of mammalian embryos (102, 103). Many studies have demonstrated a significant relationship between Notch signaling and hair health and hair-related diseases (104). Notch signaling plays a vital role in the activation, proliferation, differentiation of HFSCs and metabolite generation (44).The Notch family has four receptors (Notch 1,2,3,4) with five ligands such as:

Delta like-1,3,4 (Dll 1,3,4) , Jagged 1 and Jagged 2(105).

After the cell-cell interaction, Notch receptors bind to their ligands on the adjacent cell. As a result, a conformational change occurs in Notch receptor that expose the recognition site for cleavage by ADAM and γ-secretase, leading to the release of the active Notch intracellular domain (NICD). Subsequently, NICD is translocated to the nucleus, leading to the formation of a complex, the DNA-binding protein CSL (CBF1/RBPjκ/Su(H)/lag-1)/additional coactivators (Co-A)/mastermind (MAM), which induces the transcription of target genes (44, 101, 106). See more Figure 6.

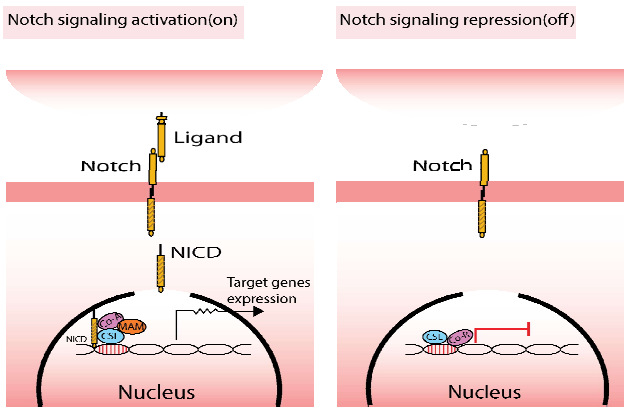

Figure 6. Notch signaling pathway

a. After binding Notch receptors to their ligands on the adjacent cell, Notch receptors are cleaved and NICDomains are released and then translocateto the nucleusfor target expression.
b. In the repression state, Notch receptors remain on the cell surface.

The T-shaped lines indicate inhibitory interactions involved in this pathway, and the solid arrows indicate activating interactions. Abbreviations; NICD: Notch intracellular domain, CSL: CBF1/ RBPjκ/Su(H)/lag-1, Co-A: co-activator, Co-R: co-receptor, MAM: mastermind.

Molecular mechanism of TGF-β/BMP signaling pathway: In 1970, a physician named Marshall Urist utilized the term bone morphogenetic protein (BMP) after demonstrating that these proteins play a crucial role in osteogenesis(107). Yet, more than 20 BMPs have been identified (108). BMPs are members of TGF-β superfamily. The TGF-β superfamily plays an important role in the embryogenesis, homeostasis, bone and cartilage formation, and dysfunction of the TGF-β signaling pathways are associated with many human diseases, such as fibrosis, cancer and immune disorders (107). Among BMPs, only BMP2 and BMP4 are associated with hair follicles (109). BMPs promote self-regulated proliferation and differentiation of HFSCs (110).

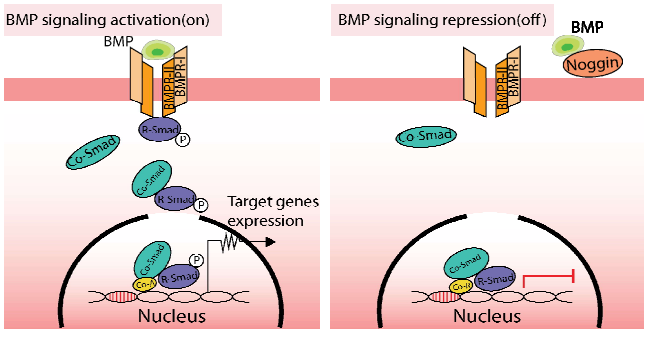

Figure 7. BMP signaling pathway

a. With binding BMP to its receptors, R-smad is phosphorylated and binds to Co-smad. Then, both as a transcription factors with coactivators (Co-A) are translocated to the nucleusfor target genes expression.
b. The association of R-smad/Co-smad complex with coreptors (Co-R) inhibits of the expression of the target genes. In this case, Noggin prevents BMP from binding to its receptors.

The expression of BMPs are opposite to wnt/β-catenin in different phases of the hair growth cycle. BMPs are highly expressed in catagen or regressive phase but, wnt/β-catenin proteins in anagen or proliferative phase of the hair growth cycle. It indicates that BMP and Wnt/β-catenin signals cooperatively regulate the balance between HFSCs and epidermal regeneration (111). BMPs bind to transmembrane heterodimeric receptor complex formed by BMPR I and BMPR II (112). After being released from its inhibitor called Noggin, BMP binds to its membrane receptor complex and causes cytoplasmic protein R-smad to be phosphorylated. Then phosphorylated R-smad connects to transcription factor Co-smad. R-smad/Co-smad complex is able to cross the nuclear membrane, bind to the promotor and leading to the expression of target genes. As a result, HFSCs will be turned off. See more Figure 7. The T-shaped lines indicate inhibitory interactions involved in this pathway, and the solid arrows indicate activating interactions. Abbreviations; BMPR I/II: Bone morphogenetic protein receptor I/II, smad: suppressor of mothers against decapentaplegic, R-smad: receptor-activated smad, Co-A: co-activators, Co-R: co-receptors.

Molecular mechanism of Apoptotic signaling pathway: B-cell lymphoma-2(BCL-2) family is divided into twomain groups based on their function (1) anti-apoptotic proteins (BCL-2, BCL-X_L, BCL-W, MCL-1, BFL-1/A1), and (2) pro-apoptotic proteins (BAD, BID, BIK, BIM, BMF, HRK, NOXA, PUMA, etc.). pro-apoptotic proteins such as; BAX and BAK are also per-formers (113). Bcl-2 family members are Ced-9 homologues. They control cell death primarily by regulating mitochondrial outer membrane permeability(MOMP) that leads to the release of intermembrane proteins, the subsequent caspase activation and apoptosis (113). BCL-2family proteins regulate programmed cell death. Among them, Bcl-2 and Bcl-xL inhibit cell death. In contrast, there are members (Bax, Bak, Bid, and Bad) that promote cell death (114). The balance between pro-apoptotic and anti-apoptotic members of Bcl-2 family leads to maintaining homeostasis in HFSCs of the bulge. In catagen, inner root sheath, matrix and outer root sheath keratinocytes undergo apoptosis with the activation of pro-apoptotic proteins, while bulge HFSCs survive by anti-apoptotic proteins and continue to self-renew and replace differentiated or/and destroyed cells (115).

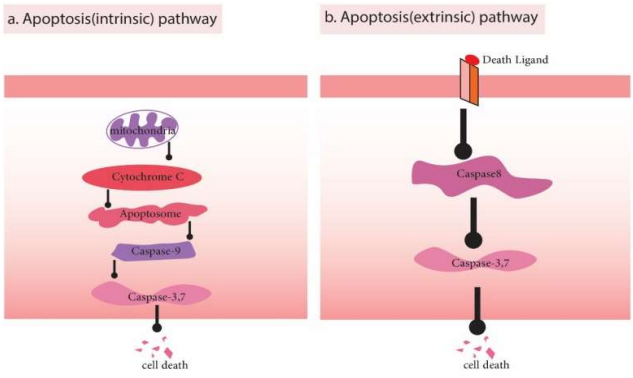

Figure 8. Apoptosis signaling pathway

a. In intrinsic pathway with the release of cytochrome C, caspase 9 is finally activated. Then, with the activation of caspases 3 and 7, cell death occurs.
b. In extrinsic pathway, with death ligand-receptor binding, caspase 8 is activated. After that, with the activation of caspases 3 and 7, cell death also occurs.

Apoptosis or cell death programmed mediates in two known pathways: intrinsic and extrinsic pathway. Intrinsic pathwayactivated by intercellular stresses such as; radical oxidative species (ROS) and DNA damage, while extrinsic pathway initiated by Fas-Fas ligand interaction (116). In both pathways, with the activation of caspases and the formation of caspase3/7 complex, DNA damage and apoptosis occur. See more Figure 8. A study revealed that a miR-149-5p inhibitor can suppress the proliferation and trigger the apoptosis of HFSCs, while miR-149-5p can upregulate the expression of Bcl-2 and downregulate caspase 3, as well as induce anti-apoptotic responses in

HFSCs (116). Hence, it is suggested that microRNAs are involved in the regulation of apoptosis in HFSCs and contribute the survival of these cells. See more Figure 8. The solid arrows indicate activating interactions. PI3K-Akt Pathway is an intracellular signal transduction pathway that promotes metabolism, proliferation, cell survival, growth and angiogenesis in response to extracellular signals (117). When HFSCs injury, by binding the ligand to the receptor, PI3K is activated which activates AKT. The recent downstream transcription factor is a serine/threonine kinase that is also known as protein kinase B. Then, AKT phosphorylates FOXO, GSK3 and mTOR. Then, FOXO and GSK3 are inhibited but, mTOR is activated. As a result, apoptosis and glycogen synthesis are inhibited, but by activating the processes of cell growth and proliferation, hair follicles are regenerated (118, 119). See more Figure 9.

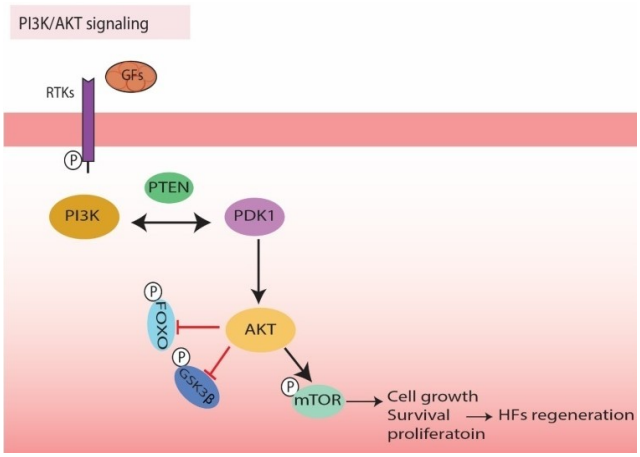

Figure 9. PI3K/AKT signaling pathway

When HFSCs injury, by binding the ligand to the receptor, PI3K is activated which activates AKT through PDK1. AKT phosphorylates FOXO, GSK3 and mTOR. Then, FOXO and GSK3 are inhibited but, mTOR is activated. By activating the processes of cell growth and proliferation, hair follicles are regenerated. The T-shaped lines indicate inhibitory interactions involved in this pathway, and the solid arrows indicate activating interactions. Abbreviations; Akt: Ak strain transforming, mTOR: mammalian target of rapamycin, GFs: growth factors, GSK3: glycogen synthesis kinase 3, FOXO: Fork-head box O, PTEN: Phosphatase and TENs in homolog deleted on chromosome 10. PDK1:3-Phosphoinositide-dependent kinase 1, PI3K: Phosphoinositide 3-Kinase, RTK: Receptor tyrosine kinase, HFs: Hair Follicles.

The Wnt pathway plays an important role in hair growth and regulates HFSC expression during the telogen-anagen phase transition, Shh pathway induces quiescent HFSCs to be activated and initiate to proliferate, Notch signaling plays a vital role in the activation, proliferation, differentiation of HFSCs and metabolite generation, then determines the fate of HFSCs and BMP is involved in HFSCs differentiation. Many evidences propose that more than one of these pathways is active in HFSCs, either at the same time or in different periods (112, 120). Then, there is a crosstalk between signaling pathways, thus, the interactions between them are complex and the balance between signaling pathways is vital to the development of HFSCs.

Hair loss regeneration: from dream to reality: AGA is a diffuse and non-scaring alopecia, induced by genetic and hormonal factors. It is characterized by the progressive miniaturization of hairfollicles, with the transformation of terminal hair into villus hair (121). A number of genes determine the predisposition for androgenetic alopecia in a polygenic fashion Multiple genes associated with the progression of AGA, including IGF-1,DKK-1, and TGF β1(122). It is believed that the action mechanism of PRP in hair growth may be include that Activated PRP induce the proliferation of dermal papilla (DP) cells by activating extracellular signal-related kinase (ERK) and protein kinase B (Akt, an anti-apoptotic signaling molecule) signaling (123-125). EGF and PDGF in PRP upregulate the ERK pathway, leading to the increased transcription of genes involved in cellular proliferation and differentiation. Thus, activated PRP affect hair cycling by prolonging anagen phase and preventing apoptosis and the catagen phase.

Hair loss classification: A reduction in the number of hair strands , hair thinning or both is called hair loss (126). see more table 1. It can be classified as: scarring and non-scaring are seen rare (127-129)and more respectively. Non-scarring alopecia includes: Alopecia Areata, Anagen effluvium, Androgenetic alopecia, Telogen effluvium, Tinea capitis, Trichorrhexis nodosa Trichotillomania, Patchy hair loss and diffuse hair loss alone or associate with patchy type, see more Table 2.

Table 1. Alopecia classification in terms of etiology

Hormonal type	Non-hormonal type
Androgenetic Alopecia	- senescent alopecia
	- circatricial alopecia
	- alopecia areata
	- traction alopecia

Androgenetic Alopecia pathogenesis: The factors involve in HFs disorder include hormonal and non-hormonal. Androgens are main players in hair growth or loss. Non-hormonal factors are medication (138), microbial inflammation (139), trauma(140), malnutrition(16), aging(141)and vitamin deficiency (142). Hormonal hair loss is occurred by androgens, Thyroid hormones and glucocorticoids. All three type hormones have several functional roles on healthy human skin such as; hair growth, proliferation and differentiation of sebaceous glands and wound healing(143, 144). But, in AGA, dihydrotestosterone (DHT) , as a master androgen, is involved in the reduction of anagen phase, increasing of hair follicles number in catagen and telogen phases and so delaying the telogen-to-anagen transition (143). Androgenetic alopecia is morphologically characterized by transformation of thick and pigmented terminal scalp hair into short (122). Androgens are an important regulator for hair growth with paradoxical effects on HFs in different body regions. Androgens can stimulate the transformation of small villus HFs into large terminal HFs after puberty, such as beard, pubic hair and axillary hair (145, 146). On the contrary, in the scalp of individuals with androgenetic alopecia, androgens inhibit hair growth and lead to hair loss (147). Serum high level of androgens in females can lead to hirsutism with excessive male pattern hair growth(148). These opposing effects of androgens on human hair growth have long been a mystery (149, 150). Androgens act through the intracellular androgen receptor. In HFs, androgen receptors are mainly expressed by DP (151, 152). In contrast, keratinocytes do not express androgen receptors or show androgen receptor-dependent signaling activation, hence it has been suggested that keratinocytes may not be the primary responding cells in HFs (153, 154). Dihydrotestosterone (DHT) is produced from testosterone by 5-α-reductase. type I and II are two forms of this enzyme. Type I is primarily produced in skin and liver and then is transferred to the prostate by blood circulation. Type II is mainly made in the prostate. Both of these enzymes convert testosterone to dihydrotestosterone. Then DHT is attached to androgenetic receptors (ARs) on cells including dermal papilla cells of hair follicles. Subsequently, these cells are stimulated and trigger to produce Transforming growth factor-1(TGF-1). TGF-1 is a catagen inducer in hair cycle. Therefore, TGF-1, as a negative regulator, causes hair loss by inducing apoptosis (155-158). In androgenetic alopecia, all of these events, just happen in HFs of scalp not in other regions of body. Can decreased DHT production or inhibition of 5-α-reductase activity or preventing from DHT attachment to androgen receptors on DPCs and or inhibition of TGF-1 production in scalp HFs be suitable strategies for AGA treatments?

Dermal papilla cells regulate hair growth. The same cells are attacked by 5-α-reductase.

DPcells in the balding area exhibit higher activity of type II 5-alpha-reductase, an enzyme that are normally highly expressed in the

prostate. This enzyme converts testosterone into dihydrotestosterone via 5α-reductase (159). Local sustained dihydrotestosterone stimulation to DP compromises its functions, leading to deteriorating hair growth, shortened anagen and prolonged telogen (150).

Hair loss treatments: Quality of life may decrease in patients with AGA and they may be depressed (160). Hence, it needs to be treated. At present, treatments include drug and non-drug therapy. The current pharmacological treatment for AGA includes androgen metabolism modulators, such as:

1. Finasteride, dutasteride (oral) and minoxidil (topical) as a 5-alpha reductase inhibitor
2. Flutamide as an antiandrogen agent(1)
3. Spironolactone for female androgenetic alopecia

Othertreatment strategiesare nutrient therapy, natural products, low-level light therapy and hair transplantation surgery. The use ofWnt activators and SFRP1 antagonism is the latest therapeutic strategy to treat hair loss, especially in AGA (18).

The current research methods for AGA treatment are all type of cell transplant including:

1. Dermal papilla cells (with or without epidermal components)
2. Embryonic dermal cells
3. Hair follicle stem cells in bulge

In addition, platelet- rich plasma(PRP) and nano-molecoles are also technics which have been used for AGA treatment in trial or clinical. Reactivating of quiescent stem cells in bulge is the last research field for AGA treatment.

Of course, immunotherapy is used to treat some types of hair loss including (161);

1. Alopecia Areata
2. Alopecia Totalis
3. Alopecia Universalis

In recent treatment model, three chemicals are used which are: Diphencyprone (DPCP), Dinitrochlorobenzene (DNCB) and/or Squaric acid dibutyl ester (SADBE).

Drug therapy for AGA: Finasteride (1 mg/day), dutasteride (0.5 mg/day), both of them are orally and topical minoxidil as a 5-alpha reductase inhibitors have been approved by Food and Drug Administration (FDA) of USA. Finasteride inhibits Type II 5α-reductase. Dutasteride (as a dual inhibitor) inhibits both Type I and II 5α-reductase (159). But, due to side effects and short shelf life of these drugs, researchers have been attempted to producemore effective drugs. Recently, Chinese made a capsule consist of 2,3,5,4'-tetrahydroxystilbene, 2-o-β-D-glucoside, Chlorogenic acid, Emodin, Ferulic acid, Isoimperatorin, Paeoniflorin. These compounds are prepared from plants (122).

PRP mechanism of action in the treatment of AGA: Platelets in PRP become activated when injected into the scalp and release multiple growth factors, which promote hair growth. These growth factors play a role in fibroblast activation, collagen synthesis, stimulation of the extracellularmatrix, and overexpression of endogenous growth factors (123).

Growth factors that are released by activated platelets in PRP including (124);

- Platelet-derived growth factor (PDGF), after binding to its receptor in the dermal papilla cells, leads to the activation of hair germ(47).
- Transforming growth factor beta (TGF-β), as a BMP inhibitor, it activates HFSCs and enters the anagen phase (162).
- vascular endothelial growth factor (VEGF), increase in anagen phase and in outer root sheath keratinocytes of hair follicles strongly induced perifollicular vascularization, resulting in accelerated hair regrowth after hair loss and in increased size of hair follicles and hair shafts (163).
- epidermal growth factor (EGF), is essential for the initiation of hair growth and prevents entry into the catagen phase(164).
- insulin like growth factor-1(IGF-1),induce and prolong the anagen phase of the hair growth cycle (165).

It is suggestedthat mentioned growth factors promote cell proliferation, differentiation, angiogenesis, chemotaxis and neovascularization that is essential for hair regrowth (166). Although, PRP mechanism of action is not still completely cleared, but it is reported that activated platelet induce to proliferate dermal papilla calls. It is mediated by extracellular signal-related kinase (ERK) pathway and protein kinase B signaling(124). Platelet growth factors such as FGF and PDGF increase ERK signaling activity and promote to the upregulated transcription of genes involved in DPCs proliferation and differentiation(125). Hence, with proliferating and differentiating of DPCs take parts in hair regrowth. It has been reported that PRP can increase the number and thickness of hair (167). Taken together, PRP effects on hair growth cycle include hair follicles vascularization, prolong the anagen phase, inhibition of apoptosis in the catagen phase and acceleration of telogen- anagen transition (167, 168). Despite these reports, there is still no complete and definitive treatment with PRP for all patients having AGA.

Nutrient therapy and natural products for AGA treatment: The factors involved in hair follicle disorders include; poor nutrition, medication, vitamin deficiency, aging, hormone changes and inflammation (143). At present, approved drugs at clinical and natural products in traditional stages are used for treatment or at least for reducing the risk of AGA. Natural products consist of carotenoids, polyphenol (169-171). Polyphenols include flavonoids, procyanidins, phenolic acid and stilbenes and also flavonoids contain visnadin, hesperidin and baicalin which have been studied for hair regrowth in AGA(172)and these compounds are thought to reduce the risk of AGA(173). Natural products are found in various fruits, vegetables and nuts. A great deal trials are done till these products have been alternated drug approved by FDA, precisely because of their side effects or long term use. Serenoa repens; an extract from the berries of the saw palmetto palm tree, Panax ginseng C.A. Mey. ;a plant in traditional Chinese medicine, Malus pumila Mill. cultivar Annurca (Annurca apple) a native plant in south ofItaly, Allium sativum L. (garlic); a type of vegetable that is widely used in food all over the world, Caffeine from Coffea arabica L.; is a xanthine (purine) alkaloid, found inGuarana, yerba mate, Cacao and tea, Rosmarinus o_cinalis L.; is a common evergreen, aromatic shrub**,** Capsicum annuum L.(pepper**)**; originate in southern America are among these compounds (143). Serenoa repens are promoted hair growth by the inhibition of 5α-reductase, HF vascularization and improvement of anagen phase(174, 175). Red ginseng oil upregulates Wnt/β-catenin and Shh/Gli-pathways-mediated expression of genes such as β-catenin, Lef-1, sonic hedgehog, Cyclin D1, Cyclin E and also downregulates TGF-β and enhances anti-apoptotic protein Bcl-2 expression (176, 177). As a result, Red ginseng oil may promote hair growth. Annurca apple consist of oligomeric procyanidin such as procyanidin B2 that improves skin quality and hair growth as well as to enhance hair density, weight and content of hair keratin (173, 178), Garlic may involve in hair growth by protecting keratinocytes (179). Caffeine in tea and coffee with downregulating TGF-β2 and upregulating IGF-1 in male and female increases hair shaft elongation, prolonging anagen phase and hair matrix keratinocyte proliferation. By the way, it has been reported that female HFs demonstrate a higher sensitivity to caffeine than male HFs(180, 181). Rosemary leaf extract improves hair growth by preventing 5α-reductase activity(182). Finally, pepper rich in flavonoids, phenolic

acid derivatives, vitamin C and E, pro vitamin A and minerals such as: Fe^{2+}, Mg^{2+}, Ca^{2+} and etc. strongly increases IGF-I production in HFs and promoting hair growth(183).

Wnt activators and SFRP1 antagonismfor AGA treatment: Due to the importance of wnt/β-catenin signaling in the activation of HFSCs, much attention has been paid to the use of wnt activators or wnt inhibitor antagonists. Although, the use of these activators or antagonists was raised in the treatment of neurodegenerative disorders such as; Alzheimer's disease, Parkinson's disease and Bipolar disease and also osteoporosis and vitiligo(184), but, over activation of wnt/ β-catenin signaling pathway leads to stomach, colon, liver, ovaries and breast cancer (185, 186). Known physiological activators of wnt/ β-catenin signaling are the lypoglycoproteins of the Wnt family (19 seen in humans), cell surface receptors of the Frizzled family (FZD, 10 found in humans) and LRP5/6 co-receptors**(**187**).**The most important physiological inhibitor of wnt/ β-catenin signaling is Glycogen synthase kinase-3β (GSK3β). This kinasealso called tau phosphorylating kinase, is a proline-directed serine/threonine kinase which was originally identified due to its role in glycogen metabolism (188). The most known artificial activators of wnt/ β-catenin signaling are GSK3B inhibitors. These compounds include Lithium chloride(189)or peptide synthesis(190). In general, the inhibition of GSK3βincludes (191):

1. A staurosporine analogue as a modest inhibitor of GSK-3β
2. A series of 3-indolyl-4-indazolylmaleimides
3. Maleimides 18 and 22**(**poor to high potency for GSK-3β inhibition)

In recent years, the use of wnt activators or secreted Frizzled-related protein 1(SFRP1) antagonism are raised in the treatment of AGA(192). SFRP1 itself is a secreted antagonist of wnt signaling.
Indirubins are natural products obtained from edible mollusks which are effective in inhibitingGSK3β(193). Among them, we can mention 6-bromo-indirubin-3$'$-oxime(6BIO) and indirubin-5-nitro-3$'$-oxime(INO) which can activate wnt/ β-catenin signaling together with lithium chloride(194). It is believed that the mentioned products are able to effective in hair regeneration by proliferation and differentiation of HFSCs (195).

CONCLUSION

Activating of quiescent HFSCs through activation of wnt/β-catenin signaling pathway may be one of the current hopes in definitive treatment of AGA. HFSCs are potentially able to generate new hair follicle. Our study groupsupposes that hair loss can be overcome byusing wnt/β-catenin signaling activators. Its results will be published in the future.

REFERENCES

1. Balañá ME, Charreau HE, Leirós GJ. Epidermal stem cells and skin tissue engineering in hair follicle regeneration. *World journal of stem cells.* 2015;7(4):711.
2. Blanpain C, Lowry WE, Geoghegan A, Polak L, Fuchs E. Self-renewal, multipotency, and the existence of two cell populations within an epithelial stem cell niche. *Cell.* 2004;118(5):635-48.
3. Oshima H, Rochat A, Kedzia C, Kobayashi K, Barrandon Y. Morphogenesis and renewal of hair follicles from adult multipotent stem cells. *Cell.* 2001;104(2):233-45.
4. Waleed R, Sarthak S, Jeff B. Immune modulation of hair follicle regeneration. *NPJ Regenerative Medicine.* 2020;5(1).
5. Rutnin S, Chanprapaph K, Pakornphadungsit K, Leerunyakul K, Visessiri Y, Srisont S, et al. Variation of hair follicle counts among different scalp areas: a quantitative histopathological study. *Skin Appendage Disorders.* 2022;8(1):24-30.
6. Chen S, Xie X, Zhang G, Zhang Y. Comorbidities in Androgenetic Alopecia: A Comprehensive Review. *Dermatology and Therapy.* 2022;12(10):2233-47.
7. Lolli F, Pallotti F, Rossi A, Fortuna MC, Caro G, Lenzi A, et al. Androgenetic alopecia: a review. *Endocrine.* 2017;57:9-17.
8. Hamilton JB. Patterned loss of hair in man: types and incidence. *Annals of the New York Academy of Sciences.* 1951;53(3):708-28.
9. Yip L, Zaloumis S, Irwin D, Severi G, Hopper J, Giles G, et al. Gene-wide association study between the aromatase gene (CYP19A1) and female pattern hair loss. *British Journal of Dermatology.* 2009;161(2):289-94.
10. Severi G, Sinclair R, Hopper J, English D, McCredie M, Boyle P, et al. Androgenetic alopecia in men aged 40–69 years: prevalence and risk factors. *British journal of dermatology.* 2003;149(6):1207-13.
11. Otberg N, Finner AM, Shapiro J. Androgenetic alopecia. Endocrinology and metabolism clinics of North America. 2007;36(2):379-98.
12. Tumbar T, Guasch G, Greco V, Blanpain C, Lowry WE, Rendl M, et al. Defining the epithelial stem cell niche in skin. *Science.* 2004;303(5656):359-63.
13. Özcan D. Pediatric androgenetic alopecia: a retrospective review of clinical characteristics, hormonal assays and metabolic syndrome risk factors in 23 patients. *Anais Brasileiros de Dermatologia.* 2022;97:166-72.
14. Sarkar P, Chakraborti K, Mondal S, Ghoshal L, Bandyopadhyay D. Association of metabolic syndrome with early-onset androgenetic alopecia: a case-control study. *Iranian Journal of Dermatology.* 2022;25(2):106-10.
15. Giles GG, Severi G, Sinclair R, English DR, McCredie MR, Johnson W, et al. Androgenetic alopecia and prostate cancer: findings from an Australian case-control study. *Cancer Epidemiology Biomarkers & Prevention.* 2002;11(6):549-53.
16. Guo EL, Katta R. Diet and hair loss: effects of nutrient deficiency and supplement use. *Dermatology Practical & Conceptual.* 2017;7(1):1.
17. Porwal MH, Salter A, Patel D, Obeidat AZ. Alopecia in multiple sclerosis patients treated with disease modifying therapies. Journal of central nervous system disease. 2022;14:117957 35221109674.
18. Wall D, Meah N, Fagan N, York K, Sinclair R. Advances in hair growth. Faculty Reviews. 2022;11.
19. Duverger O, Morasso MI, editors. To grow or not to grow: hair morphogenesis and human genetic hair disorders. *Seminars in cell & developmental biology;* 2014: Elsevier.
20. Burg D, Yamamoto M, Namekata M, Haklani J, Koike K, Halasz M. Promotion of anagen, increased hair density and reduction of hair fall in a clinical setting following identification of FGF5-inhibiting compounds via a novel 2-stage process. *Clinical, Cosmetic and Investigational Dermatology.* 2017:71-85.
21. Müller-Röver S, Foitzik K, Paus R, Handjiski B, van der Veen C, Eichmüller S, et al. A comprehensive guide for the accurate classification of murine hair follicles in distinct hair cycle stages. *Journal of Investigative Dermatology.* 2001;117(1):3-15.
22. Foitzik K, Langan EA, Paus R. Prolactin and the skin: a dermatological perspective on an ancient pleiotropic peptide hormone. *Journal of Investigative Dermatology.* 2009; 129(5):1071-87.
23. Oh JW, Kloepper J, Langan EA, Kim Y, Yeo J, Kim MJ, et al. A guide to studying human hair follicle cycling in vivo. *Journal of Investigative Dermatology.* 2016;136(1):34-44.
24. Lee J, Tumbar T, editors. Hairy tale of signaling in hair follicle development and cycling. *Seminars in Cell & Developmental Biology;* 2012: Elsevier.
25. Zarei R, Saeedi M, Hosseinzade A. Re-activation of Wnt/β-catenin Signaling Pathway in Hair Follicle Stem Cells in Treatment of Androgenetic Alopecia. *Journal of Mazandaran University of Medical Sciences.* 2022;32(215):189-200.
26. Buffoli B, Rinaldi F, Labanca M, Sorbellini E, Trink A, Guanziroli E, et al. The human hair: from anatomy to physiology. *International Journal of Dermatology.*

2014;53(3):331-41.
27. Bejaoui M, Oliva AK, Ke MS, Ferdousi F, Isoda H. 3D Spheroid Human Dermal Papilla Cell as an Effective Model for the Screening of Hair Growth Promoting Compounds: Examples of Minoxidil and 3, 4, 5-Tri-O-caffeoylquinic acid (TCQA). Cells. 2022;11(13):2093.
28. Paus R, Cotsarelis G. The biology of hair follicles. New England journal of medicine. 1999;341(7):491-7.
29. Ji S, Zhu Z, Sun X, Fu X. Functional hair follicle regeneration: an updated review. *Signal Transduction and Targeted Therapy.* 2021;6(1):66.
30. Ren X, Xia W, Xu P, Shen H, Dai X, Liu M, et al. Lgr4 deletion delays the hair cycle and inhibits the activation of hair follicle stem cells. *Journal of Investigative Dermatology.* 2020;140(9):1706-12. e4.
31. Houschyar KS, Borrelli MR, Tapking C, Popp D, Puladi B, Ooms M, et al. Molecular mechanisms of hair growth and regeneration: current understanding and novel paradigms. *Dermatology.* 2020;236(4):271-80.
32. Chen C-L, Huang W-Y, Wang EHC, Tai K-Y, Lin S-J. Functional complexity of hair follicle stem cell niche and therapeutic targeting of niche dysfunction for hair regeneration. *Journal of biomedical science.* 2020;27:1-11.
33. Andl T, Reddy ST, Gaddapara T, Millar SE. WNT signals are required for the initiation of hair follicle development. *Developmental cell.* 2002;2(5):643-53.
34. Oshimori N, Fuchs E. The harmonies played by TGF-β in stem cell biology. Cell stem cell. 2012;11(6):751-64.
35. Myung PS, Takeo M, Ito M, Atit RP. Epithelial Wnt ligand secretion is required for adult hair follicle growth and regeneration. *Journal of Investigative Dermatology.* 2013;133(1):31-41.
36. Castellana D, Paus R, Perez-Moreno M. Macrophages contribute to the cyclic activation of adult hair follicle stem cells. PLoS biology. 2014;12(12):e1002002.
37. Greco V, Chen T, Rendl M, Schober M, Pasolli HA, Stokes N, et al. A two-step mechanism for stem cell activation during hair regeneration. Cell stem cell. 2009;4(2):155-69.
38. Hsu Y-C, Li L, Fuchs E. Transit-amplifying cells orchestrate stem cell activity and tissue regeneration. Cell. 2014;157(4):935-49.
39. Hsu Y-C, Pasolli HA, Fuchs E. Dynamics between stem cells, niche, and progeny in the hair follicle. Cell. 2011;144(1):92-105.
40. Cotsarelis G, Sun T-T, Lavker RM. Label-retaining cells reside in the bulge area of pilosebaceous unit: Implications for follicular stem cells, hair cycle, and skin carcinogenesis. Cell. 1990;61:1329-37.
41. Rahmani W, Abbasi S, Hagner A, Raharjo E, Kumar R, Hotta A, et al. Hair follicle dermal stem cells regenerate the dermal sheath, repopulate the dermal papilla, and modulate hair type. Developmental cell. 2014;31(5):543-58.
42. Biernaskie J, Paris M, Morozova O, Fagan BM, Marra M, Pevny L, et al. SKPs derive from hair follicle precursors and exhibit properties of adult dermal stem cells. Cell stem cell. 2009;5(6):610-23.
43. Nishimura EK, Jordan SA, Oshima H, Yoshida H, Osawa M, Moriyama M, et al. Dominant role of the niche in melanocyte stem-cell fate determination. Nature. 2002;416(6883):854-60.
44. Hu X-M, Li Z-X, Zhang D-Y, Yang Y-C, Fu S-a, Zhang Z-Q, et al. A systematic summary of survival and death signalling during the life of hair follicle stem cells. *Stem Cell Research & Therapy.* 2021;12(1):1-29.
45. Clevers H, Loh KM, Nusse R. An integral program for tissue renewal and regeneration: Wnt signaling and stem cell control. science. 2014;346(6205):1248012.
46. Chen J, Fan Z-X, Zhu D-C, Guo Y-L, Ye K, Dai D, et al. Emerging Role of Dermal White Adipose Tissue in Modulating Hair Follicle Development During Aging. *Frontiers in Cell and Developmental Biology.* 2021:2639.
47. Festa E, Fretz J, Berry R, Schmidt B, Rodeheffer M, Horowitz M, et al. Adipocyte lineage cells contribute to the skin stem cell niche to drive hair cycling. Cell. 2011;146(5):761-71.
48. Xu K, Yu E, Wu M, Wei P, Yin J. Cells, growth factors and biomaterials used in tissue engineering for hair follicles regeneration. *Regenerative Therapy.* 2022;21:596-610.
49. Plikus MV, Mayer JA, de La Cruz D, Baker RE, Maini PK, Maxson R, et al. Cyclic dermal BMP signalling regulates stem cell activation during hair regeneration. Nature. 2008; 451(7176):340-4.
50. Xiao Y, Woo W-M, Nagao K, Li W, Terunuma A, Mukouyama Y-s, et al. Perivascular hair follicle stem cells associate with a venule annulus. *Journal of Investigative Dermatology.* 2013;133(10):2324-31.
51. Mecklenburg L, Tobin DJ, Müller-Röver S, Handjiski B, Wendt G, Peters EM, et al. Active hair growth (anagen) is associated with angiogenesis. *Journal of Investigative Dermatology.* 2000;114(5):909-16.
52. Peña-Jimenez D, Fontenete S, Megias D, Fustero-Torre C, Graña-Castro O, Castellana D, et al. Lymphatic vessels interact dynamically with the hair follicle stem cell niche during skin regeneration in vivo. *The EMBO Journal.* 2019;38(19):e101688.
53. Gur-Cohen S, Yang H, Baksh SC, Miao Y, Levorse J, Kataru RP, et al. Stem cell–driven lymphatic remodeling coordinates tissue regeneration. Science. 2019;366(6470):1218-25.
54. Beigom Hejazian L, Akbarnejad Z, Moghani Ghoroghi F, Esmaeilzade B, Chaibakhsh S. Augmenting Peripheral Nerve Regeneration Using Hair Follicle Stem Cells in Rats. *Basic and Clinical Neuroscience.* 2022;13(1).
55. Brownell I, Guevara E, Bai CB, Loomis CA, Joyner AL. Nerve-derived sonic hedgehog defines a niche for hair follicle stem cells capable of becoming epidermal stem cells. *Cell stem cell.* 2011;8(5):552-65.
56. Kishimoto J, Burgeson RE, Morgan BA. Wnt signaling maintains the hair-inducing activity of the dermal papilla. *Genes & development.* 2000;14(10):1181-5.
57. Chen C-C, Chuong CM. Multi-layered environmental regulation on the homeostasis of stem cells: the saga of hair growth and alopecia. *Journal of dermatological science.* 2012;66(1):3-11.
58. Rompolas P, Mesa KR, Greco V. Spatial organization within a niche as a determinant of stem-cell fate. Nature. 2013;502(7472):513-8.
59. Ali N, Zirak B, Rodriguez RS, Pauli ML, Truong H-A, Lai K, et al. Regulatory T cells in skin facilitate epithelial stem cell differentiation. Cell. 2017;169(6):1119-29. e11.
60. Paus R, Maurer M, Slominski A, Czarnetzki BM. Mast cell involvement in murine hair growth. *Developmental biology.* 1994;163(1):230-40.
61. Hobo A, Harada K, Maeda T, Uchiyama M, Irisawa R, Yamazaki M, et al. IL-17-positive mast cell infiltration in the lesional skin of lichen planopilaris: Possible role of mast cells in inducing inflammation and dermal fibrosis in cicatricial alopecia. *Experimental dermatology.* 2020;29(3):273-7.
62. Chen C-C, Wang L, Plikus MV, Jiang TX, Murray PJ, Ramos R, et al. Organ-level quorum sensing directs regeneration in hair stem cell populations. Cell. 2015;161(2):277-90.
63. Wang X, Chen H, Tian R, Zhang Y, Drutskaya MS, Wang C, et al. Macrophages induce AKT/β-catenin-dependent Lgr5+ stem cell activation and hair follicle regeneration through TNF. Nature communications. 2017;8(1):14091.
64. Wu YF, Wang SH, Wu PS, Fan SMY, Chiu HY, Tsai TH, et al. Enhancing hair follicle regeneration by nonablative fractional laser: assessment of irradiation parameters and tissue response. Lasers in surgery and medicine. 2015;47(4):331-41.
65. Wang C, Ma C, Gong L, Guo Y, Fu K, Zhang Y, et al. Macrophage polarization and its role in liver disease. Frontiers in immunology. 2021;12:5381.
66. Chu S-Y, Chou C-H, Huang H-D, Yen M-H, Hong H-C, Chao P-H, et al. Mechanical stretch induces hair regeneration through the alternative activation of macrophages. *Nature*

communications. 2019;10(1):1524.
67. Li J, Tan J, Martino MM, Lui KO. Regulatory T-cells: potential regulator of tissue repair and regeneration. *Frontiers in immunology.* 2018;9:585.
68. Cruz MS, Diamond A, Russell A, Jameson JM. Human αβ and γδ T cells in skin immunity and disease. *Frontiers in immunology.* 2018;9:1304.
69. Toma JG, Akhavan M, Fernandes KJ, Barnabé-Heider F, Sadikot A, Kaplan DR, et al. Isolation of multipotent adult stem cells from the dermis of mammalian skin. *Nature cell biology.* 2001;3(9):778-84.
70. Amoh Y, Li L, Campillo R, Kawahara K, Katsuoka K, Penman S, et al. Implanted hair follicle stem cells form Schwann cells that support repair of severed peripheral nerves. *Proceedings of the National Academy of Sciences.* 2005;102(49):17734-8.
71. Nagel S, Rohr F, Weber C, Kier J, Siemers F, Kruse C, et al. Multipotent nestin-positive stem cells reside in the stroma of human eccrine and apocrine sweat glands and can be propagated robustly in vitro. PloS one. 2013;8(10):e78365.
72. Fuchs E. Scratching the surface of skin development. *Nature.* 2007;445(7130):834-42.
73. Paus R, Foitzik K. In search of the "hair cycle clock": a guided tour. Differentiation. 2004;72(9-10):489-511.
74. Inoue K, Aoi N, Sato T, Yamauchi Y, Suga H, Eto H, et al. Differential expression of stem-cell-associated markers in human hair follicle epithelial cells. Laboratory Investigation. 2009;89(8):844-56.
75. Mii S, Amoh Y, Katsuoka K, Hoffman RM. Comparison of nestin-expressing multipotent stem cells in the tongue fungiform papilla and vibrissa hair follicle. *Journal of cellular biochemistry.* 2014;115(6):1070-6.
76. Li KN, Jain P, He CH, Eun FC, Kang S, Tumbar T. Skin vasculature and hair follicle cross-talking associated with stem cell activation and tissue homeostasis. Elife. 2019;8:e45977.
77. Driskell RR, Clavel C, Rendl M, Watt FM. Hair follicle dermal papilla cells at a glance. *Journal of cell science.* 2011; 124(8):1179-82.
78. Jahoda CA, Whitehouse CJ, Reynolds AJ, Hole N. Hair follicle dermal cells differentiate into adipogenic and osteogenic lineages. *Experimental dermatology.* 2003;12(6):849-59.
79. Lako M, Armstrong L, Cairns PM, Harris S, Hole N, Jahoda CA. Hair follicle dermal cells repopulate the mouse haematopoietic system. *Journal of Cell Science*. 2002;115(20):3967-74.
80. Madaan A, Verma R, Singh AT, Jaggi M. Review of hair follicle dermal papilla cells as in vitro screening model for hair growth. *International Journal of Cosmetic Science*. 2018;40(5):429-50.
81. Aran S, Zahri S, Asadi A, Khaksar F, Abdolmaleki A. Hair follicle stem cells differentiation into bone cells on collagen scaffold. *Cell and Tissue Banking*. 2020;21:181-8.
82. Kanno H. Regenerative therapy for neuronal diseases with transplantation of somatic stem cells. *World journal of stem cells.* 2013;5(4):163.
83. González-Fernández C, González P, Rodríguez FJ. New insights into Wnt signaling alterations in amyotrophic lateral sclerosis: a potential therapeutic target? *Neural Regeneration Research.* 2020;15(9):1580.
84. Qiu W, Lei M, Zhou L, Bai X, Lai X, Yu Y, et al. Hair follicle stem cell proliferation, Akt and Wnt signaling activation in TPA-induced hair regeneration. *Histochemistry and cell biology.* 2017;147:749-58.
85. Patel S, Alam A, Pant R, Chattopadhyay S. Wnt signaling and its significance within the tumor microenvironment: novel therapeutic insights. *Frontiers in immunology.* 2019;10:2872.
86. Aros CJ, Pantoja CJ, Gomperts BN. Wnt signaling in lung development, regeneration, and disease progression. *Communications biology*. 2021;4(1):601.
87. Steinhart Z, Angers S. Wnt signaling in development and tissue homeostasis. *Development.* 2018;145(11):dev146589.
88. Nusse R. Wnt signaling and stem cell control. *Cell research.* 2008;18(5):523-7.
89. Zhou Y, Jin J, Feng M, Zhu D. Wnt signaling in inflammation in tissue repair and regeneration. *Current Protein and Peptide Science.* 2019;20(8):829-43.
90. Richter J, Traver D, Willert K. The role of Wnt signaling in hematopoietic stem cell development. *Critical reviews in biochemistry and molecular biology.* 2017;52(4):414-24.
91. Teo J-L, Kahn M. The Wnt signaling pathway in cellular proliferation and differentiation: a tale of two coactivators. *Advanced drug delivery reviews.* 2010;62(12):1149-55.
92. Koch S, Acebron SP, Herbst J, Hatiboglu G, Niehrs C. Post-transcriptional Wnt signaling governs epididymal sperm maturation. *Cell.* 2015;163(5):1225-36.
93. Huelsken J, Vogel R, Erdmann B, Cotsarelis G, Birchmeier W. β-Catenin controls hair follicle morphogenesis and stem cell differentiation in the skin. *Cell.* 2001;105(4):533-45.
94. Driskell RR, Lichtenberger BM, Hoste E, Kretzschmar K, Simons BD, Charalambous M, et al. Distinct fibroblast lineages determine dermal architecture in skin development and repair. *Nature.* 2013;504(7479):277-81.
95. Wu P, Zhang Y, Xing Y, Xu W, Guo H, Deng F, et al. Correction to: The balance of Bmp6 and Wnt10b regulates the telogen-anagen transition of hair follicles. *Cell Communication and Signaling.* 2020;18(1):4.
96. Shin DW. The Molecular Mechanism of Natural Products Activating Wnt/β-Catenin Signaling Pathway for Improving Hair Loss. Life. 2022;12(11):1856.
97. Abe Y, Tanaka N. Roles of the hedgehog signaling pathway in epidermal and hair follicle development, homeostasis, and cancer. *Journal of developmental biology.* 2017;5(4):12.
98. Ingham PW, McMahon AP. Hedgehog signaling in animal development: paradigms and principles. Genes & development. 2001;15(23):3059-87.
99. Carballo GB, Honorato JR, de Lopes GPF, Spohr TCLdSe. A highlight on Sonic hedgehog pathway. *Cell Communication and Signaling.* 2018;16:1-15.
100. Jeng K-S, Chang C-F, Lin S-S. Sonic hedgehog signaling in organogenesis, tumors, and tumor microenvironments. I*nternational Journal of Molecular Sciences.* 2020;21(3):758.
101. Wang X, Liu Y, He J, Wang J, Chen X, Yang R. Regulation of signaling pathways in hair follicle stem cells. Burns & Trauma. 2022;10.
102. Aubin-Houzelstein G. Notch signaling and the developing hair follicle. Notch Signaling in Embryology and Cancer. 2012:142-60.
103. Nusse R, Clevers H. Wnt/β-catenin signaling, disease, and emerging therapeutic modalities. Cell. 2017;169(6):985-99.
104. Blanpain C, Fuchs E. Epidermal stem cells of the skin. Annu Rev Cell Dev Biol. 2006;22:339-73.
105. Artavanis-Tsakonas S, Rand MD, Lake RJ. Notch signaling: cell fate control and signal integration in development. Science. 1999;284(5415):770-6.
106. Wu J, Li W, Guo L, Zhao L, Sun S, Li H. The crosstalk between the Notch, Wnt, and SHH signaling pathways in regulating the proliferation and regeneration of sensory progenitor cells in the mouse cochlea. Cell and Tissue Research. 2021;386:281-96.
107. Aluganti Narasimhulu C, Singla DK. The role of bone morphogenetic protein 7 (BMP-7) in inflammation in heart diseases. Cells. 2020;9(2):280.
108. Mazerbourg S, Hsueh AJ. Genomic analyses facilitate identification of receptors and signalling pathways for growth differentiation factor 9 and related orphan bone morphogenetic protein/growth differentiation factor ligands. *Human reproduction update.* 2006;12(4):373-83.
109. Hansdah K, Singh N, Bouzid A, Priyadarshi S, Ray CS, Desai A, et al. Evaluation of the Genetic Association and mRNA Expression of the COL1A1, BMP2, and BMP4 Genes in the Development of Otosclerosis. *Genetic Testing and Molecular Biomarkers*. 2020;24(6):343-51.
110. Adam RC, Yang H, Ge Y, Lien W-H, Wang P, Zhao Y, et al. Temporal layering of signaling effectors drives chromatin remodeling during hair follicle stem cell lineage progression.

Cell stem cell. 2018;22(3):398-413. e7.
111. Fuchs E, Tumbar T, Guasch G. Socializing with the neighbors: stem cells and their niche. Cell. 2004;116(6):769-78.
112. Rishikaysh P, Dev K, Diaz D, Qureshi WMS, Filip S, Mokry J. Signaling involved in hair follicle morphogenesis and development. *International Journal of Molecular Sciences.* 2014;15(1):1647-70.
113. Kale J, Osterlund EJ, Andrews DW. BCL-2 family proteins: changing partners in the dance towards death. *Cell Death & Differentiation.* 2018; 25(1):65-80.
114. Youle RJ, Strasser A. The BCL-2 protein family: opposing activities that mediate cell death. *Nature reviews Molecular cell biology.* 2008;9(1):47-59.
115. Sotiropoulou PA, Candi A, Mascré G, De Clercq S, Youssef KK, Lapouge G, et al. Bcl-2 and accelerated DNA repair mediates resistance of hair follicle bulge stem cells to DNA-damage-induced cell death. *Nature cell biology.* 2010;12(6):572-82.
116. Wang J, Qu J, Li Y, Feng Y, Ma J, Zhang L, et al. miR-149-5p regulates goat hair follicle stem cell proliferation and apoptosis by targeting the CMTM3/AR axis during superior-quality brush hair formation. *Frontiers in Genetics.* 2020;11:529757.
117. Chen Y, Fan Z, Wang X, Mo M, Zeng SB, Xu R-H, et al. PI3K/Akt signaling pathway is essential for de novo hair follicle regeneration. Stem Cell Research & Therapy. 2020;11(1):1-10.
118. Cheon HI, Bae S, Ahn KJ. Flavonoid silibinin increases hair-inductive property via Akt and Wnt/β-catenin signaling activation in 3-dimensional-spheroid cultured human dermal papilla cells. 2019.
119. Yamane M, Seo J, Zhou Y, Asaba T, Tu S, Nanmo A, et al. Effects of the PI3K/Akt signaling pathway on the hair inductivity of human dermal papilla cells in hair beads. *Journal of Bioscience and Bioengineering.* 2022;134(1):55-61.
120. Massagué J, Chen Y-G. Controlling TGF-β signaling. *Genes & development.* 2000;14(6):627-44.
121. Dinh QQ, Sinclair R. Female pattern hair loss: current treatment concepts. *Clinical interventions in aging.* 2007; 2(2):189-99.
122. Dhurat R, Sharma A, Rudnicka L, Kroumpouzos G, Kassir M, Galadari H, et al. 5-Alpha reductase inhibitors in androgenetic alopecia: Shifting paradigms, current concepts, comparative efficacy, and safety. *Dermatologic therapy.* 2020;33(3):e13379.
123. Stevens J, Khetarpal S. Platelet-rich plasma for androgenetic alopecia: a review of the literature and proposed treatment protocol. *International Journal of Women's Dermatology.* 2019;5(1):46-51.
124. Alves R, Grimalt R. A review of platelet-rich plasma: history, biology, mechanism of action, and classification. *Skin appendage disorders.* 2018;4(1):18-24.
125. Li ZJ, Choi HI, Choi DK, Sohn KC, Im M, Seo YJ, et al. Autologous platelet-rich plasma: a potential therapeutic tool for promoting hair growth. *Dermatologic Surgery.* 2012; 38(7pt1):1040-6.
126. Choi BY. Targeting Wnt/β-catenin pathway for developing therapies for hair loss. *International journal of molecular sciences.* 2020; 21(14):4915.
127. Salhab O, Khayat L, Alaaeddine N. Stem cell secretome as a mechanism for restoring hair loss due to stress, particularly alopecia areata: narrative review. *Journal of Biomedical Science.* 2022; 29(1):1-11.
128. Seetharam KA. Alopecia areata: An update. *Indian journal of dermatology, venereology and leprology*. 2013;79:563.
129. Phillips TG, Slomiany WP, Robert Allison I. Hair loss: common causes and treatment. *American family physician.* 2017; 96(6):371-8.
130. Abd El Fattah NMM, Mokadem A, Abd El Fattah SM, Ghonemy SM. Brief Treatment Modalities of Alopecia Areata. *The Egyptian Journal of Hospital Medicine.* 2022;89(2):6127-31.
131. Gentile P. Hair Loss and Telogen Effluvium Related to COVID-19: The Potential Implication of Adipose-Derived Mesenchymal Stem Cells and Platelet-Rich Plasma as Regenerative Strategies. *International Journal of Molecular Sciences.* 2022;23(16):9116.
132. 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.
133. Rebora A. Telogen effluvium: a comprehensive review. Clinical, cosmetic and investigational dermatology. 2019:583-90.
134. Degreef H. Clinical forms of dermatophytosis (ringworm infection). Mycopathologia. 2008;166:257-65.
135. Olusoji EB, Adesina MA, Kanmodi KK. Trichotillomania: hair pulling disorder. *World News of Natural Sciences.* 2018(20):208-14.
136. Purvis C, Tjiattas-Saleski L. Patchy Hair Loss. *Osteopathic Family Physician.* 2019;11(5):36-9.
137. Trüeb RM, Dias MFRG. Alopecia areata: a comprehensive review of pathogenesis and management. *Clinical reviews in allergy & immunology.* 2018;54:68-87.
138. Meznerics FA, Illés K, Dembrovszky F, Fehervari P, Kemeny LV, Kovacs KD, et al. Platelet-Rich Plasma in Alopecia Areata—A Steroid-Free Treatment Modality: A Systematic *Review and Meta-Analysis of Randomized Clinical Trials.* Biomedicines. 2022;10(8):1829.
139. Yang Y, Qu L, Mijakovic I, Wei Y. Advances in the human skin microbiota and its roles in cutaneous diseases. *Microbial Cell Factories.* 2022;21(1):176.
140. Xu L, Liu KX, Senna MM. A practical approach to the diagnosis and management of hair loss in children and adolescents. *Frontiers in medicine.* 2017;4:112.
141. Williams R, Pawlus AD, Thornton MJ. Getting under the skin of hair aging: the impact of the hair follicle environment. *Experimental Dermatology.* 2020;29(7):588-97.
142. Almohanna HM, Ahmed AA, Tsatalis JP, Tosti A. The role of vitamins and minerals in hair loss: a review. *Dermatology and therapy.* 2019;9(1):51-70.
143. Bassino E, Gasparri F, Munaron L. Protective role of nutritional plants containing flavonoids in hair follicle disruption: A review. *International Journal of Molecular Sciences.* 2020;21(2):523.
144. Price VH, editor Androgenetic alopecia in women. *Journal of Investigative Dermatology Symposium Proceedings;* 2003: Elsevier.
145. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Archives of disease in childhood.* 1969;44(235):291.
146. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Archives of disease in childhood.* 1970;45(239):13-23.
147. Nyholt DR, Gillespie NA, Heath AC, Martin NG. Genetic basis of male pattern baldness. *Journal of Investigative Dermatology.* 2003;121(6):1561-4.
148. Azziz R. The evaluation and management of hirsutism. Obstetrics & Gynecology. 2003;101(5):995-1007.
149. Thornton M, Laing I, Hamada K, Messenger A, Randall V. Differences in testosterone metabolism by beard and scalp hair follicle dermal papilla cells. *Clinical endocrinology.* 1993;39(6):633-9.
150. Randall VA, Hibberts NA, Thornton MJ, Hamada K, Merrick AE, Kato S, et al. The hair follicle: a paradoxical androgen target organ. *Hormone Research in Paediatrics.* 2000;54(5-6):243-50.
151. Hibberts N, Howell A, Randall V. Balding hair follicle dermal papilla cells contain higher levels of androgen receptors than those from non-balding scalp. *Journal of Endocrinology.* 1998;156:59-65.
152. Ando Y, Yamaguchi Y, Hamada K, Yoshikawa K, Itami S. Expression of mRNA for androgen receptor, 5α-reductase and 17β-hydroxysteroid dehydrogenase in human dermal papilla cells. *British journal of dermatology.* 1999;141(5):840-5.
153. Choudhry R, Hodgins M, Van der Kwast T, Brinkmann A,

Boersma W. Localization of androgen receptors in human skin by immunohistochemistry: implications for the hormonal regulation of hair growth, sebaceous glands and sweat glands. *Journal of Endocrinology.* 1992;133(3):467-NP.
154. Lai J-J, Chang P, Lai K-P, Chen L, Chang C. The role of androgen and androgen receptor in skin-related disorders. *Archives of dermatological research.* 2012;304:499-510.
155. Sawaya ME, Price VH. Different levels of 5α-reductase type I and II, aromatase, and androgen receptor in hair follicles of women and men with androgenetic alopecia. *Journal of Investigative Dermatology.* 1997;109(3):296-300.
156. Inui S, Fukuzato Y, Nakajima T, Yoshikawa K, Itami S. Androgen-inducible TGF-β1 from balding dermal papilla cells inhibits epithelial cell growth: a clue to understanding paradoxical effects of androgen on human hair growth. *The FASEB journal*. 2002;16(14):1967-9.
157. Inui S, Itami S. Molecular basis of androgenetic alopecia: from androgen to paracrine mediators through dermal papilla. *Journal of Dermatological Science.* 2011;61(1):1-6.
158. Hibino T, Nishiyama T. Role of TGF-β2 in the human hair cycle. Journal of dermatological science. 2004;35(1):9-18.
159. Marks LS. 5α-reductase: history and clinical importance. *Reviews in urology.* 2004; 6(Suppl 9):S11.
160. Talavera-Adame D, Newman D, Newman N. Conventional and novel stem cell based therapies for androgenic alopecia. *Stem Cells and Cloning: Advances and Applications.* 2017:11-9.
161. Zerbinati N, Esposito C, D'Este E, Calligaro A, Valsecchi R. Topical immunotherapy of alopecia areata: a large retrospective study. *Dermatology and Therapy.* 2018;8:101-10.
162. Oshimori N, Fuchs E. Paracrine TGF-β signaling counterbalances BMP-mediated repression in hair follicle stem cell activation. *Cell stem cell.* 2012;10(1):63-75.
163. Yano K, Brown LF, Detmar M. Control of hair growth and follicle size by VEGF-mediated angiogenesis. The Journal of clinical investigation. 2001;107(4):409-17.
164. Mak KK, Chan SY. Epidermal growth factor as a biologic switch in hair growth cycle. *Journal of Biological Chemistry.* 2003;278(28):26120-6.
165. Alves R, Grimalt R. Randomized placebo-controlled, double-blind, half-head study to assess the efficacy of platelet-rich plasma on the treatment of androgenetic alopecia. *Dermatologic surgery.* 2016;42(4):491-7.
166. Kim DH, Je YJ, Kim CD, Lee YH, Seo YJ, Lee JH, et al. Can platelet-rich plasma be used for skin rejuvenation? Evaluation of effects of platelet-rich plasma on human dermal fibroblast. *Annals of dermatology.* 2011;23(4):424-31.
167. Giordano S, Romeo M, Lankinen P. Platelet-rich plasma for androgenetic alopecia: Does it work? Evidence from meta analysis. *Journal of cosmetic dermatology.* 2017;16(3):374-81.
168. Borowiecka JM, Dalewski B, Pałka Ł. Effectiveness of Platelet-Rich Plasma in the Treatment of Androgenic Alopecia Compared to Placebo and Topical Minoxidil: A Systematic Review. *Scientia Pharmaceutica.* 2022;91(1):4.
169. Fortes C, Mastroeni S, Mannooranparampil T, Abeni D, Panebianco A. Mediterranean diet: fresh herbs and fresh vegetables decrease the risk of Androgenetic Alopecia in males. *Archives of Dermatological Research.* 2018;310:71-6.
170. Bassino E, Antoniotti S, Gasparri F, Munaron L. Effects of flavonoid derivatives on human microvascular endothelial cells. *Natural product research.* 2016;30(24):2831-4.
171. Bai L, Guo S, Liu Q, Cui X, Zhang X, Zhang L, et al. Characterization of nine polyphenols in fruits of Malus pumila Mill by high-performance liquid chromatography. *journal of food and drug analysis.* 2016;24(2):293-8.
172. Roy R, Thakur M, Dixit V. Effect of citrullus colocynthis. On hair growth in albino rats. *Pharmaceutical biology.* 2007;45(10):739-44.
173. Lee YI, Ham S, Lee SG, Jung I, Suk J, Yoo J, et al. An Exploratory In Vivo Study on the Effect of Annurca Apple Extract on Hair Growth in Mice. *Current Issues in Molecular Biology.* 2022;44(12):6280-9.
174. Murugusundram S. Serenoa repens: does it have any role in the management of androgenetic alopecia? *Journal of cutaneous and aesthetic surgery.* 2009;2(1):31.
175. Bassino E, Gasparri F, Munaron L. Serenoa repens and N-acetyl glucosamine/milk proteins complex differentially affect the paracrine communication between endothelial and follicle dermal papilla cells. *Journal of Cellular Physiology.* 2019;234(5):7320-9.
176. Bak M-J, Hong S-G, Lee J-W, Jeong W-S. Red ginseng marc oil inhibits iNOS and COX-2 via NFκB and p38 pathways in LPS-stimulated RAW 264.7 macrophages. *Molecules.* 2012; 17(12):13769-86.
177. Truong V-L, Bak MJ, Lee C, Jun M, Jeong W-S. Hair regenerative mechanisms of red ginseng oil and its major components in the testosterone-induced delay of anagen entry in C57BL/6 mice. Molecules. 2017;22(9):1505.
178. Badolati N, Sommella E, Riccio G, Salviati E, Heintz D, Bottone S, et al. Annurca apple polyphenols ignite keratin production in hair follicles by inhibiting the pentose phosphate pathway and amino acid oxidation. *Nutrients.* 2018;10(10):1406.
179. Jung E, Jung F, Mrowietz C, Kiesewetter H, Pindur G, Wenzel E. Influence of garlic powder on cutaneous microcirculation. A randomized placebo-controlled double-blind cross-over study in apparently healthy subjects. *Arzneimittel-forschung.* 1991;41(6):626-30.
180. Dhurat R, Chitallia J, May TW, Jayaraaman AM, Madhukara J, Anandan S, et al. An open-label randomized multicenter study assessing the noninferiority of a caffeine-based topical liquid 0.2% versus minoxidil 5% solution in male androgenetic alopecia. *Skin pharmacology and physiology.* 2017;30(6):298-305.
181. Saewan N. Effect of coffee berry extract on anti-aging for skin and hair—In vitro approach. Cosmetics. 2022;9(3):66.
182. Padule K, Shinde S, Chitlange S, Giram P, Nagore D. The Advancement of Herbal-Based Nanomedicine for Hair. Cosmetics. 2022;9(6):118.
183. Rastegar H, Ahmadi Ashtiani H, Aghaei M, Ehsani A, Barikbin B. Combination of herbal extracts and platelet-rich plasma induced dermal papilla cell proliferation: involvement of ERK and A kt pathways. *Journal of cosmetic dermatology.* 2013;12(2):116-22.
184. Bonnet C, Brahmbhatt A, Deng SX, Zheng JJ. Wnt signaling activation: Targets and therapeutic opportunities for stem cell therapy and regenerative medicine. *RSC chemical biology.* 2021;2(4):1144-57.
185. Ahmed K, Shaw HV, Koval A, Katanaev VL. A second WNT for old drugs: drug repositioning against WNT-dependent cancers. *Cancers.* 2016;8(7):66.
186. Elmadbouh OH, Pandol SJ, Edderkaoui M. Glycogen Synthase Kinase 3β: A True Foe in Pancreatic Cancer. *International Journal of Molecular Sciences.* 2022;23(22):14133.
187. MacDonald BT, Tamai K, He X. Wnt/β-catenin signaling: components, mechanisms, and diseases. *Developmental cell.* 2009;17(1):9-26.
188. Yang J, Yang H, Wang L, Zhou P. Glycogen Synthase Kinase 3β (GSK3β) Regulates Myogenic Differentiation in Skeletal Muscle Satellite Cells of Sheep. *Animals.* 2022;12(20):2789.
189. Zhang J, He L, Yang Z, Li L, Cai W. Lithium chloride promotes proliferation of neural stem cells in vitro, possibly by triggering the Wnt signaling pathway. *Animal cells and systems.* 2019;23(1):32-41.
190. Licht-Murava A, Paz R, Vaks L, Avrahami L, Plotkin B, Eisenstein M, et al. A unique type of GSK-3 inhibitor brings new opportunities to the clinic. *Science Signaling.* 2016; 9(454):ra110-ra.
191. Kozikowski AP, Gaisina IN, Petukhov PA, Sridhar J, King LT, Blond SY, et al. Highly Potent and Specific GSK-3β Inhibitors That Block Tau Phosphorylation and Decrease α-Synuclein Protein Expression in a Cellular Model of Parkinson's Disease. *ChemMedChem: Chemistry Enabling Drug Discovery.*

2006;1(2):256-66.
192. Vañó-Galván S, Camacho F. New treatments for hair loss. Actas Dermo-Sifiliográficas (English Edition). 2017;108(3):221-8.
193. Sklirou AD, Gaboriaud-Kolar N, Papassideri I, Skaltsounis A-L, Trougakos IP. 6-bromo-indirubin-3′-oxime (6BIO), a Glycogen synthase kinase-3β inhibitor, activates cytoprotective cellular modules and suppresses cellular senescence-mediated biomolecular damage in human fibroblasts. *Scientific Reports.* 2017;7(1):1-13.
194. Kamelamela N, Zalesne M, Morimoto J, Robbat A, Wolfe BE. Indigo-and indirubin-producing strains of Proteus and Psychrobacter are associated with purple rind defect in a surface-ripened cheese. *Food microbiology.* 2018;76:543-52.
195. Blagodatski A, Klimenko A, Jia L, Katanaev VL. Small molecule Wnt pathway modulators from natural sources: history, state of the art and perspectives. Cells. 2020;9(3):589.

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