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Hair Biology and Androgenetic Alopecia

Diagnosis, Neogenesis, and Management

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KEYWORDS
• Hair follicle • Hair cycle • Stem cell niches • Diagnostic tests • Androgenetic alopecia
• FDA-approved and novel therapy

KEY POINTS
- Hair development, cycling, and androgenetic alopecia are believed to be significantly triggered by molecular and cellular stem cell activity.
- Typical normal hair characteristics define lanugo, vellus, intermediate, and terminal hairs.
- Complete personal, family history, diagnostic tests, and clinical presentations determine the type of alopecia and therapeutic alternatives.
- The precise etiology for the development of male and female pattern baldness, including telogen effluvium, are unknown, which is a challenge for directed therapies.
- A knowledge of medications approved by the Food and Drug Administration (FDA) and novel approaches that can provide safe and effective stand-alone or combined remedies in conjunction with surgical procedures.

INTRODUCTION

Scalp hair normally serves various physiologic roles that include protection against excessive exposure to ultraviolet radiation [1] and cold temperatures, as well as defining an individual's social, sexual, and health well-being [2]. The occurrence of androgenetic alopecia (AGA) in previously vibrant healthy individuals can produce devastating psychological impacts as thinning, shortening, or loss of hair progressively advances. Because male pattern hair loss (MPHL) and female pattern hair loss (FPHL) affect more than 50% of men and nearly 50% of women [3] by 50 years of age, concerned individuals often seek treatment advice from primary care physicians, dermatologists, or cosmetic surgeons. Physicians must be well-informed to recommend to their patients safe and effective therapies and avoidance of "miracle" cures. Fundamentals for hair loss counseling and management include a sophisticated understanding of the development, regulation, and dysregulation of hair follicles in both normal and diseased conditions.

Previous extensive investigations of hair development in both invertebrates [4] and in mice [5] have added clarity to the morphologic and cyclical transformations. Schofield [6,7] first proposed the term,

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"niches," in hematopoietic tissues to describe slow cycling stem cells in specialized domains. Stem cells within similar domains have also been observed within human hair follicles and were found to leave their niches and evolve into rapidly dividing transit-amplifying to dynamically proliferate and commit to terminal differentiation.

MPHL, FPHL, and telogen effluvium (shedding) are believed to be affected by molecular and cellular disturbances during hair cycle regulation initiated by a variety of triggers; that is, hormones, stresses, drugs, metabolic and nutritional deficiencies, immunologic alterations, and diets. In general, the mechanism of action of these damaging factors is not fully understood or controllable. As investigators continue to identify more putative mediators and attempt to regulate the complex cross-communications within the stem cell hierarchy, new innovative therapeutic approaches may be possible to stimulate more effectively hair growth in MPHL/FPHL conditions, enhance follicular growth after transplantation, and treat other acquired diseased conditions.

The purpose of this article was to provide current information on the biology, potential stem cell–based pathophysiology, diagnostic tests, clinical presentation, Food and Drug Administration (FDA)-approved approaches, and novel non–FDA-approved treatments for patterned hair loss.

HAIR DEVELOPMENT

Hair follicles are organized into many heterogeneous cell types in stem cell habitats that interface with each other in a hierarchical manner during embryonic and postnatal cycling (Fig. 1). In a review by Schmidt-Ulrich and Paus [8], de novo initiation of follicle development in mice embryos was contingent on reciprocal cross-talk between single layered primitive epidermal cells (*placodes*) and dermal mesenchymal cells (*condensates*) regulated through canonical Wingless (Wnt) and Hedgehog (Hh) pathways via β-catenin transcription factors, receptors, ligands, and adhesion molecules. The undifferentiated *placode* cells (Stage 1) are transformed into *primary germ center* [9] *(Stage 2)*, composed of a population of quiescent histone label retaining cells (LRCs) with specified stem cell markers, such as Sox9 proteins. As epithelial hair germ cells plunge downward forming the hair peg and the outer root sheath (ORS), a trail of Sox9 LRC cells congregates into another niche, called the bulge (Stage 3–5). These specialized bulge LCR Sox9 stem cells are located subjacent to the ORS and positioned between the sebaceous gland units and opposite to the point of insertion of the arrector pili muscle. Progeny of the LRC Sox9-derived bulge stem cells are a requirement for formation of the sebaceous gland lineage and the later described hair germ, both of which promote cyclic phases of postnatal follicles

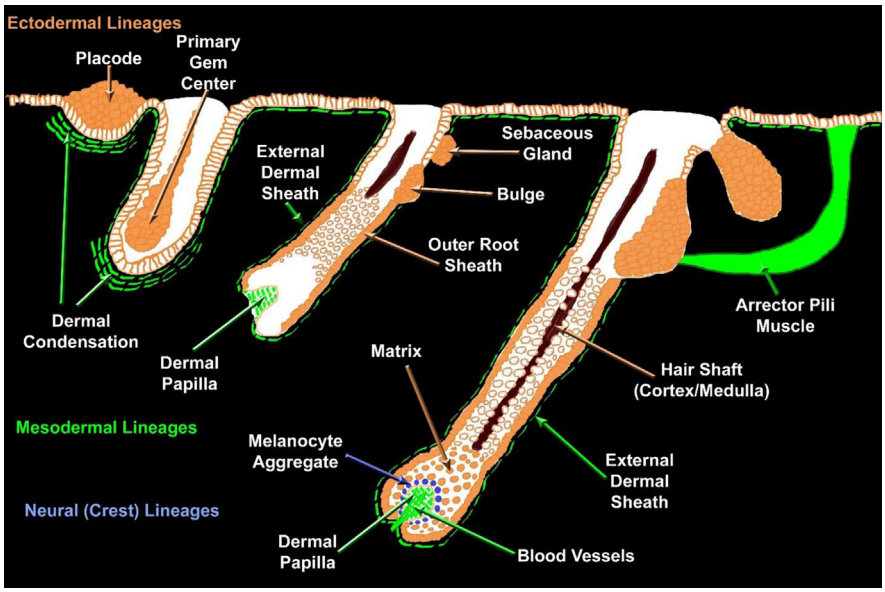

FIG. 1 Schematic representation of hair follicle morphogenesis during nascent development by germ stem cells and their niches from Stage 0 to Stage 8.

in the nude mice model. As the LRC Sox9 stem cells travel downward toward the proximal bulb, a highly proliferative, transit-amplifying Sox9 progeny, called matrix cell [10], gathers just above the bulb, and will play a leading role in the eventual formation of the inner root sheath, cortex, and medulla of the nascent hair (Stages 6–8) via a cascade of signals [11]. In developmental waves [12], melanocytes arrive to populate the central core of the hair shaft and external root sheath, accompanied by migrating hematopoietic cells and neurotrophin-induced nerve cells that form capillary loops and nerve innervations located around the mesenchymal-derived dermal papilla.

As mentioned previously, once epithelial *placodes* have formed in Stage 1, cues from *placode cells* induce the assemblage of mesenchymal *condensate cells* [13], which release their own molecular message of signals and transcriptional factors to facilitate the downward migration of epithelial cells (Stage 2). The mesenchymal stem cells in the dermal *condensates* also begin their own journey downward during Stages 3 to 5, external to the advancing epithelial columns, and eventually form into the *dermal sheath* and proximal *dermal papilla* at the base of the nascent follicular bulb. The dermal sheath stem cells have been considered a cellular reservoir for dermal papilla cells and can regenerate a new dermal papilla after its loss. The dermal papilla stem cells participate in epithelial-mesenchymal cross-talk through their unique gene signature molecules with the surrounding epithelial cells of the matrix, ORS to induce de novo follicle development during Stages 6 to 8 with cycling and stimulated hair growth [14].

HAIR CYCLING

Normal cycling hair follicles undergo complete loss and regeneration of the inferior nonpermanent portion of the terminal hair and are driven by niche epidermal and dermal stem cells in an asynchronous manner through stages of *anagen* growth phase (2–6 years), transitioning through brief *catagen* shrinking phase (3–4 weeks), and ending in quiescent miniaturized *telogen* phase (3–4 months) (Fig. 2). Recently, an additional phase, called *exogen*, was recognized when the passively retained hair shaft is actively shed from the telogen follicle.

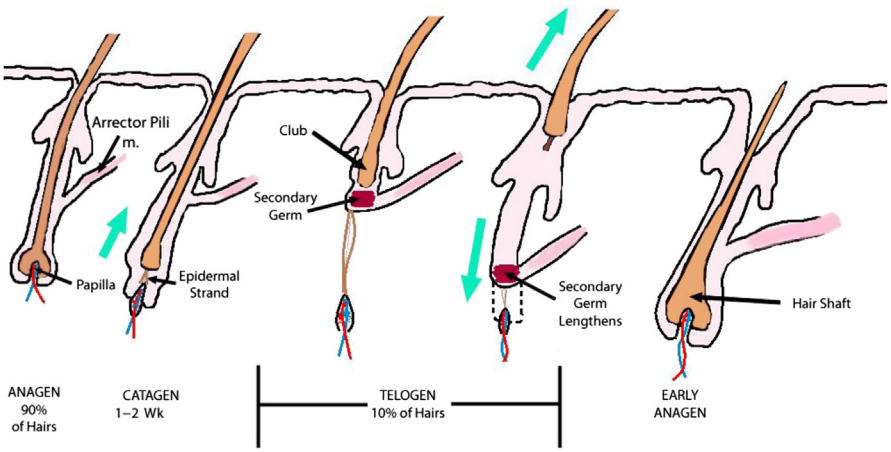

FIG. 2 Schematic representation of normal mature follicle cycling from anagen growth, catagen regression, and telogen resting phases. Legend for DVD. PRP has emerged as a novel new treatment that might have a beneficial role in hair regrowth. It is proposed that the stimulatory growth factors released from the α-granules in platelets may act on the stem cells in the bulge and dermal papillae areas of follicles and promoting neovascularization. The safety and efficiency for its salutary results are increasingly being investigated through investigational research board studies with a larger cohort of subjects who have male and female androgenetic hair loss. Current investigational protocols are under way to evaluate the effects of differing concentrations of PRP, number and intervals of treatment sessions, and the additive benefits of combined usage with fat, cosmeceutical growth factors, and low-level light therapy. This DVD demonstrates one method that is under study to validate the safety and effectiveness of PRP for the treatment of MPHL.

Anagen phase is characterized by actively dividing cells in the bulb above and around the dermal papilla and epidermal-derived matrix to form elements of the hair shaft. Catagen phase is believed to be initiated by apoptotic signals released from exhausted matrix cells that trigger inhibitory transcriptional pathways from the dermal papilla. These inhibitory signaling molecules activate the catagen-telogen hair germ, located above the matrix-bulb, to direct the sequential loss of the lower follicle, leaving a thin epithelial strand, called the fibrous streamer [15]. Telogen phase is marked by a complete interruption between the nonpermanent and permanent portions of the follicle that has retracted to form the club hair demarcated at the level of the bulge and arrector pili attachments. The cretinized dermal papilla, releasing inhibitory signaling molecules to suppress bulge and hair germ activities, has translocated itself distally in the lower dermis [16,17]. After a short telogen period, the 3 stem cell niches (hair germ, dermal papilla, and bulge) are believed to coordinate cellular stimulation or inhibition to recapitulate an entire new lower follicle and shaft [18,19]. Toward the end of telogen, regulating molecular mechanisms [16] remain unclear, but most likely involve the bursting of hair germ cellular activity to fuel the initial stages of telogen-anagen regeneration. The bulge niche appears to act more as the engine that maintains progression of the hair cycle and is the reservoir of long-term stem cells.

STEM CELL DYSFUNCTION IN ALOPECIA

Elegant studies [20–23] from global gene expression patterns, unique cell-surface marker CD200, intermediate filament protein KRT15, and transcriptional profiles of Wnt inhibitors WIFI and DKK3, have suggested that overrepresented keratinocyte stem cells, isolated from bulge niches in human scalp anagen follicles, represented the progeny of the slow cycling ORS-LRCs. In human bulge-ORS cells, CD34 expression was low or absent but was most highly expressed and confined to cells in the sub-bulge region of the ORS of the anagen hair follicle. These cells underwent apoptosis at the end of anagen and were considered to be a bulge-derived progenitor population [24].

Garza and his group [25] reported that KRT15, ITGA6, and CD200 expressions in stem cell bulge populations in AGA anagen bald and hair (nonbald) scalp were maintained at normal levels, but CD34 progenitor cells in the sub-bulge region were significantly diminished. Because the hair germ cells and matrix cells arose from bulge and sub-bulge cells at the end of catagen and were believed to be immediately responsible for the formation of the new lower hair follicle at anagen, any loss of progenitor cells in the sub-bulge region might lead to miniaturized or loss of anagen follicles and eventually baldness. Other investigators [26] similarly postulated that miniaturization in AGA might result from diminished conversion of hair follicle bulge stem cells to progenitor cells. Further investigations are needed to determine whether the loss of these cells represents a primary or secondary event in AGA.

NORMAL HAIR DEMOGRAPHICS

The total number of anagen scalp hair follicles in an adult is estimated between 100,000 and 250,000, but the number varies depending on the individual's ethnicity, hair color, age, and sex. Because the average scalp area is approximately 500 cm^2, the calculated normal density averages approximately 200 hairs/cm^2. The typical growth rate of anagen hair averages between 0.3 and 0.3 mm/d, whereas the typical shed rate averages 50 to 100 hairs per day. In clinical practice, a distinction is made among lanugo, vellus, and intermediate and terminal hairs, based on differences in their shaft diameters, lengths, pigmentations, and depths (Table 1).

TABLE 1
Typical Hair Characteristics

Type	Shaft Diameter	Medullated/Pigmentation	Length	Depth
Lanugo	<30 μm	Nonmedullated/poorly pigmented	<0.5 cm	Upper dermis
Vellus	<30 μm	Nonmedullated/poorly pigmented	<2.0 cm	Upper-mid dermis
Intermediate	30–50 μm	Medullated/pigmented	>2.0 cm	Mid-deep dermis
Terminal	>50–100 μm	Medullated/pigmented	>2.0 cm	Deep dermis/subcutaneous fat

DIAGNOSTIC TEST FOR ANDROGENETIC ALOPECIA

For the diagnosis of AGA, a complete personal (medications, treatments, concomitant diseases) and family history are required to guide the clinical examination. A description of hair loss, age of onset, acute or chronic duration, focal or diffuse distribution, associated symptoms, and the evolutionary course are important to diagnose AGA or *telogen effluvium*. More laboratory tests might be necessary to confirm findings in individual cases. In women, a first-line blood test, such as a complete blood count, erythrocyte sedimentation rate, serum ferritin, thyroid profile, and complete hormonal panel is recommended. In men, it might not be necessary to obtain first-line blood test for MPHL, unless diffuse FPHL, is suspected.

Several clinical tests might be carried out when faced with a diagnostic dilemma. A Pull Test, performed by grasping 50 to 70 hairs, might be useful in delineating active areas of alopecia. In male or female AGA, for example, the removal of more than 6 hairs in the frontal-crown scalp indicates a "positive" Pull Test, whereas a "negative" Pull Test is usually 0 to 3 hairs in the occiput. If positive diffusely, including the occipital scalp, a diagnosis of telogen effluvium should be considered. Other more sophisticated tests, such as phototrichography, dermatoscopy, and dynamic growth rates after shaving procedures, might provide additional diagnostic information for improved treatment plans.

ANDROGENETIC ALOPECIA

AGA represents a general term for hair loss that typically acquires the characteristic MPHL or FPHL. In MPHL, AGA is mediated principally by the conversion of testosterone to dihydrotestosterone by the enzyme *5α-reductase type II* and presence of androgen receptors in the dermal papilla in genetically susceptible hair follicles [27]. In FPHL, the evidence for an androgen-dependent trait is present in some cases, but other nonandrogenic environmental pathways may play more prominent roles. Although MPHL and FPHL share common histopathological findings but different clinical presentations, current genome-wide association studies suggest their etiologies may not necessarily be the same [28].

MALE PATTERN HAIR LOSS AND TREATMENT

MPHL is believed to be due to a polygenic mode of inheritance [29] and is characterized by its typical bitemporal recession, balding to the vertex and crown areas, and occipital sparing, as defined in Hamilton-Norwood's classification [30], whereas diffuse thinning with an intact frontal hairline is referred to as an FPHL variant in men. A common pathway of follicular miniaturization occurs with progressive reduction of anagen duration, prolongation of telogen, and minimal inflammatory fibrosis with associated clinical findings of a mixture of terminal, intermediate, and vellus-sized hairs and a negative Pull Test in long-standing AGA.

Hair transplantation or surgical reduction procedures, and hairpieces are viable options for some male patients. Both the FDA [31] and a European consensus group [32] recommended only finasteride, a competitive inhibitor of type II 5α-reductase enzyme, and topical minoxidil, a potassium channel opener and vasodilator, for MPHL based on sufficient evidence base medicine data. Recent articles have summarized each of their bio-pharmacological actions [3,33] and adverse events [3,34].

FEMALE PATTERN HAIR LOSS AND TREATMENT

FPHL remains a poorly understood complex, especially about the roles that genetic factors, inflammation, or hormonal or vascular influences play [35]. Although androgen dependency is generally the most common form of hair loss in men, the involvement of androgens in patterned or nonpatterned hair thinning or loss has not been as well established in women [36]. FPHL often can be precipitated and exacerbated by drugs, acute stress, diet, hormonal changes, weight loss, and partum [37]. FPHL, described as regressive or senescent alopecia, is characterized by progressive shortening of the anagen phase, a lengthening of the latency period, and miniaturization into villus-like hair [38]. Such changes lead to diffuse loss of hair density, affecting primarily the midline vertex and centrofrontal scalp, defined by different grading systems [33]. Minoxidil dose-dependent placebo-controlled studies [39] determined that the FDA-approved marketing of topical 2% or 5% concentrated solutions was safe and effective for temporary AGA improvement in men and women and for post-hair transplantation [40,41], appearing to prolong the duration of anagen, reverse miniaturization, and reduce postsurgical telogen effluvium.

TELOGEN EFFLUVIUM AND TREATMENT

Telogen effluvium (TE) is believed to occur in apparently healthy women and is attributed to an

asynchronization disorder whereby generalized hair shedding (teloptosis) of greater than 20% existed than observed in MPHL or FPHL [42]. TE can start 2 weeks after a trigger but peaks between 6 and 8 weeks and then improves approximately 2 months after the trigger is removed or treated. Bouhanna and Bouhanna [43] clearly summarized etiologic triggers, diagnostic tests, and treatment prognoses in acute and chronic (longer than 6 months duration) cases.

NOVEL APPROACHES TO ANDROGENETIC ALOPECIA

Regenerative medicine, in which the patient's own platelet-rich plasma (PRP), stem cells, adipose tissue, growth factors, conditioned media, and low-level light therapy has now become viable alternatives to conventional therapies. Although the FDA has approved these medical devices through a 510K regulation, the status simply demonstrates safety rather than efficacy. As yet, there are no approved indications or pathways for their usage in alopecia.

PLATELET-RICH PLASMA

Platelets release more than 20 types of growth factors that include platelet-derived growth factor, fibroblast growth factor, hepatocyte growth factor (HGF), transforming growth factor, vascular endothelial growth factor, epithelial growth factor, and insulin-like growth factor. Growth factors are believed to be generally responsible for angiogenesis [44], stem cell proliferation and differentiation [45], and antiapoptotic properties [46], but specifically for hair follicles, anagen induction [47], cyclic growth [48], follicle development [49], and proliferation of dermal papilla cells [50].

There are several recent clinical studies [51–54] suggesting a benefit of PRP for the treatment of AGA. A video of PRP and low-level light therapy treatment accompanies this article.

ADIPOSE TISSUE AND STROMAL VASCULAR FRACTION

Recent reports [55,56] suggest that adipose tissue is an integral part of the normal hair cycle, and that its reduction parallels hair loss and prolongation of the telogen phase. A recent pilot study [57] suggests that scalp stromal vascular fraction–enriched fat grafting may represent a promising approach for AGA.

CONDITIONED MEDIA

The use of secretory factors in cluster differentiation (CD) from adipose-derived stem cell cultures for hair loss has advantages of transportable packaging and the absence of tissue matching between donor and recipient [58]. A few clinical trials [59] have suggested a promising strategy for AGA with no significant side effects.

LOW-LEVEL LIGHT THERAPY

Several devices on the market have reported to improve AGA by using multicentered, sham-controlled, double-blind approaches [60–62]. Further studies will be required to confirm its role in the treatment of hair loss.

SUMMARY

Although practitioners in their clinical practice strive to practice evidence-based medicine, the successful management of MPHL, FPHL, and TE is based on astute judgment and experience. Strategic planning varies according to the clinical stage of AGA and responses to approved medico-surgical treatment options. Fundamental to the Good Practice of Medicine for alopecia consist of a profound understanding of follicular biology, stem cell functions and dysfunctions, incorporation of useful tests, and a flexible approach to approved options. Practitioners should be open to novel treatments that possess significant therapeutic potentials from on-going trials under the auspices of the FDA.

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