Aesth Plast Surg (2019) 43:253–266
https://doi.org/10.1007/s00266-018-1248-1

ORIGINAL ARTICLE SPECIAL TOPICS

Review of Human Hair Follicle Biology: Dynamics of Niches and Stem Cell Regulation for Possible Therapeutic Hair Stimulation for Plastic Surgeons

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Received: 1 June 2018 / Accepted: 19 September 2018 / Published online: 15 October 2018

Abstract Plastic surgeons are frequently asked to manage male- and female-pattern hair loss in their practice. This article discusses the epidemiology, pathophysiology, and current management of androgenetic alopecia and emphasizes more recent knowledge of stem cell niches in hair follicles that drive hair cycling, alopecia, and its treatment. The many treatment programs available for hair loss include newer strategies that involve the usage of growth factors, platelet-rich plasma, and fat to stimulate follicle growth. Future research may clarify novel biomolecular mechanisms that target specific cells that promote hair regeneration.

Level of Evidence V This journal requires that authors assign a level of evidence to each article. For a full description of these Evidence-Based Medicine ratings, please refer to the Table of Contents or the online Instructions to Authors www.springer.com/00266.

Keywords Hair follicles · Hair cycle · Androgenetic alopecia · Stem cell niches · Treatment strategies

Introduction

Schofield [1] first proposed the term, "niches," in hematopoietic tissues to describe specialized, discrete, and slow cycling stem cell domains in microenvironments that regulated cell identity, self-renewal, and differentiation. During normal homeostasis, stem cells often leave their niches and evolve into transit-amplifying (TA) cells, which dynamically proliferate and commit to terminal differentiation [2, 3]. Since then, considerable characterization of stem cell niches has been reported in invertebrate systems [4, 5]. In contrast, the definition and interaction of stem cell niches in the mammalian system have been less well defined because of their complexity and lack of specific markers. Despite these limitations, extensive investigations [6–8] have described the architecture and cycling of de novo and postnatal hair follicles in pigmented, albino, and mutant strains in mice. Notwithstanding species-to- species differences, the study of intact human hair follicles remains particularly attractive because they represent the only mini-organs that exhibit morphological and cyclical transformations, embracing recapitulation of its embryonic development from growth (anagen), apoptotic regression (catagen), to quiescence (telogen). These events are driven by compartmentalized cell types and their signaling molecules that regulate de novo hair formation in embryonic skin and new hair growth cycling in adult skin switching from dormancy to rapid cell division during cycling. Our current incomplete understanding of the molecular controls of follicle induction and morphogenesis is almost entirely based on analysis of invertebrates and mutant mice. Therefore, caution is advised in assuming that exactly the same controls occur in human hair follicle development [9]. This review investigates recent findings on these complex putative niches and their cross-talk that reveal important new insights and strategies to understand hair follicle biology, enrichment of inductive cell populations, and development of innovative therapies for hair stimulation and treatment of associated disease states. Relevant articles were identified through systematic searches through MEDLINE and Cochrane Library with

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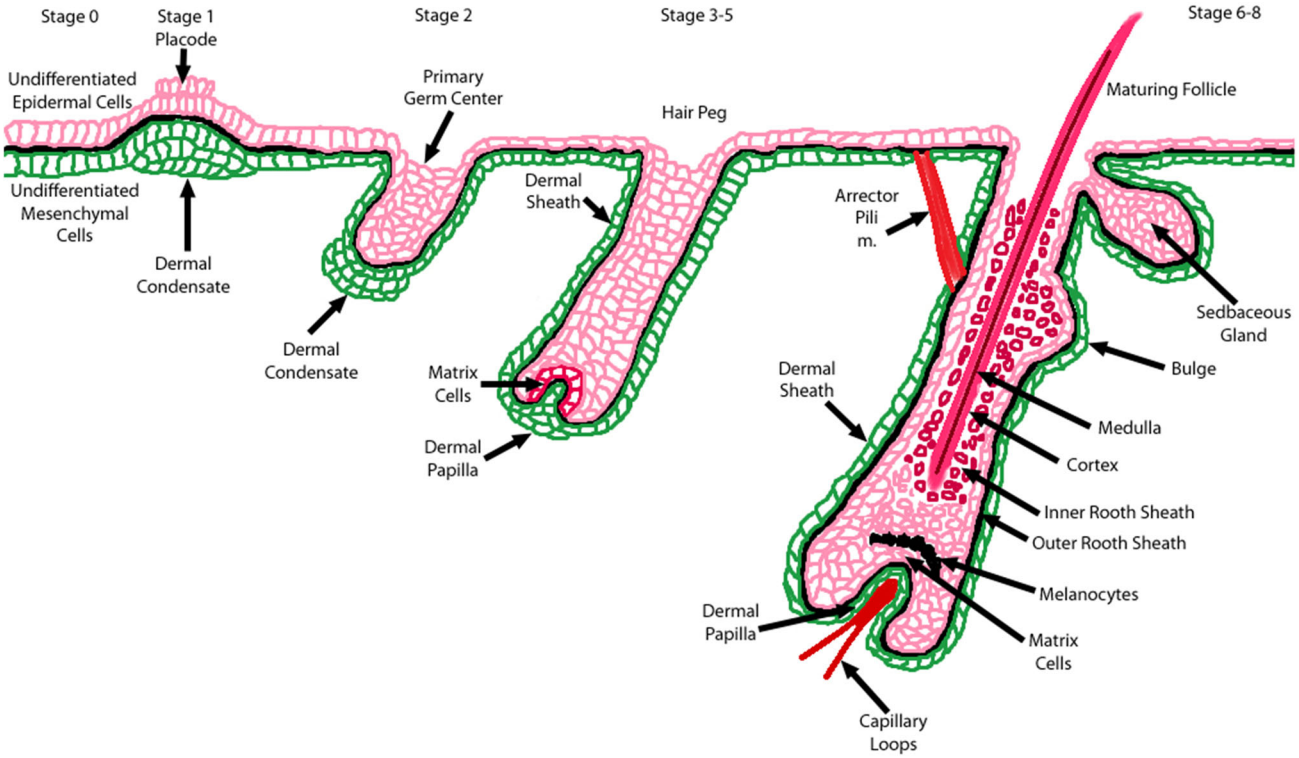

Fig. 1 Schematic representation of nascent hair follicle morphogenesis during embryogenesis by specialized epithelial and mesenchymal stem cells and their niches from Stage 0 to Stage 8

additional publications from the reference lists of the review articles (1990–2018). Search terms included but were not limited to androgenetic alopecia, female-pattern hair loss, follicle stem cells and niches, platelet-rich plasma, fat grafting, stromal vascular fraction, and medical and surgical treatments.

Stem Cell Niches of Nascent Hair Follicles

Hair follicles are organized into a number of heterogeneous cell types arranged in multiple epidermal (epithelial), dermal (mesenchymal), and neuroectodermal stem cell habitats that interface with each other in a hierarchical manner for embryonic morphogenesis and postnatal cycling [10, 11]. Eventually, these quiescent stem cells proliferate and differentiate into epithelial lineages (sebocytes, eccrine cells, keratinocytes, trichocytes of the outer and inner root sheaths), mesenchymal lineages (fibroblasts of the dermal papilla and dermal sheath, arrector pili muscle), and neural crest lineages (melanocytes). Generally, mesenchymal cells are believed to play dominant roles as inducers, whereas epithelial cells act as responders during the process of nascent and cycling follicle formation through reciprocal and complex signaling molecules (in CAPITALS) by transcription factors (*in italic*) [12].

Epithelial Contributions to Nascent Hair Follicle Development

In a review by Schmidt-Ulrich and Paus [9], de novo initiation of follicle development in mice embryos has been found to be contingent upon reciprocal communications under key roles of canonical WNT via *β-catenin* pathways and other regulatory activating or inhibitory proteins (transcription factors, receptors and ligands, and adhesion molecules) between the single-layered primitive epidermal ectodermal cells and dermal mesenchymal cells [13, 14]. It remains unclear, however, when and how embryonal stem cell niches become established and whether their gene expressions by transcription factors are functionally transferred to progeny cells in stem cell niches of the first and subsequent postnatal cycles.

Initially, undifferentiated ectodermal cells begin to gather, elongate, and organize mainly under EDaA1/EDaR/*NF-κβ* and NOGGIN/*Lef-1* pathways [15, 16] into microscopically identifiable *placodes* which are transformed chiefly by sonic hedgehog (SHH) activation of *Gli2* pathways into *primary hair germ centers* [17] (Fig. 1). In vivo pulse-chase mice experiments [8, 18] have demonstrated that a population of quiescent histone H2B-GFP label-retaining cells (LRCs) with specified stem cell markers, such as Sox9 protein, are localized within the *primary germ*

centers of epithelial cell clusters early in nascent Stage 2 developing follicles. Sox9 protein has emerged as a key regulator of stem cell identity in niche centers that govern de novo follicle formation. Recent elegant embryonic pulse-chase studies [9, 19] established that early LRC Sox9 cells are direct precursors of LRCs that reside in both the embryonic and adult *bulge* niches (see below). Without the presence of Sox9-positive cells, normal morphologic development of nascent follicles and cycling of postnatal follicles not only fail to occur, but impaired epidermis does not normally recover after injury.

As epithelial columns plunge downward, regulated by a myriad of ill-understood signaling pathways [11] (SHH/*Gli2, WNT/β-catenin, NOGGIN/Lef-1, TGF-β2*) and enter into the *hair peg* phase of Stages 3–5, LRC Sox9-expressing cells concentrate in a developing layer and proliferate principally under similar signaling pathways to develop into the *outer root sheath* [20]. As subsequent structural layers occur to form the lower portion of the nascent mature follicle, a trail of H2B-GFP-positive LRC cells extends toward the proximal base of hair *bulb*. During Stages 6–8, progeny of LRC Sox9-derived cells [21, 22] differentiate ultimately into *trichocytes* and highly proliferative, transit-amplifying *matrix cells*, both of which play leading roles through to the eventual formation of the shaft and other structures in the nascent follicle.

Another specialized epithelial Sox9 stem cell niche, called the *bulge* [23, 24], develops as a subjacent extension from the *outer root sheath* and is located proximal to the presumptive sebaceous gland units opposite the point of insertion of the arrector pili muscle. Mice experiments [25] have demonstrated that *bulge* LRC Sox9 stem cells develop early, but are not required for embryonic follicle development which depends critically on progeny of Sox9 cells derived from the *outer root sheath*. However, progeny of LRC Sox9-derived *bulge* stem cells is a requirement for formation of the sebaceous lineage and also encompasses most if not all cells in the later described *secondary hair germ* [26, 27], both of which promote cyclic phases of postnatal follicles in the nude mice model [6]. At the late cytodifferentiated Stages 6–8 of follicular maturation, a variety of transcriptional factors has been suggested to regulate lineages that form the eventual *inner root sheath, cortex, and medulla* of the nascent hair shaft. Data for the exact hierarchical cascade of signals are incomplete, but implicate a central role for the transcriptional repressor CCAAT, a displacement protein CDP, Cutl1, and the zinc finger transcription factor GATA3 [28, 29]. In developmental waves [30], melanocytes arrive to produce pigmentation granules in the central core of the hair shaft, accompanied by migrating hematopoietic cells and neurotrophin-induced nerve cells which form, respectively, capillary loops and nerve innervations located around and within the mesenchymal-derived dermal papilla. At the proximal base of the follicle, the mass of undifferentiated *matrix cells*, melanocytes, and cells of the proximal outer root sheath finally congregate into the onion-shaped *bulb* which partially surrounds the capillary and neural network.

Mesenchymal Contributions to Nascent Hair Follicle Development

Once epithelial *placode*s have formed in Stage 1, epithelial cues from placode cells are needed to induce the assemblage of mesenchymal cells, as *condensates,* beneath the *placodes/primary hair germ centers* [31] (Fig. 1). Dermal mesenchymal cells in their niches play pivotal roles in de novo and cycling hair formation through release of their own first molecular message of signals and transcription factors for support of proper formation of placodes [11, 15, 25] and induction of epithelial downward growth during early Stage 2 by fibroblast growth factors (FGFs) and bone morphogenetic proteins (BMPs) inhibitor (NOGGIN) [32, 33]. The complex and bewildering composition and actions of the epithelial and dermal cues are being determined and may involve certain members of the WNT family, SHH/*Gli2*, and PDGF-A (platelet-derived growth factor A) [34–36]. Through initiating cross-talking molecular signals between these two compartments, mesenchymal cells in the *dermal condensates* begin their journey downward during Stages 3–5, external to the advancing epithelial columns, and eventually form into the *dermal sheath* and proximal *dermal papilla* at the base of the nascent follicle [14].

The *dermal sheath,* composed of three collagen layers with specialized fibroblasts of mesenchymal origin [37], lies outside of the *external root sheath* from the *bulge* level downward and becomes contiguous with the base of the *dermal papilla*. The dermal sheath cells have been considered a cellular reservoir for dermal papilla cells and can regenerate a new dermal papilla after its loss [38, 39]. There appears to be a two-way cellular talk and cellular migration between the dermal papilla and dermal sheath whose exact signaling mechanisms (*Pl3K-Akt pathway*) await further elucidation [40]. The *dermal papilla* stem cells eventually reside in a complex and diverse cellular niche of the *bulb* at the base of the nascent follicle and participate in epithelial–mesenchymal cross-talk through its unique gene signature molecules with surrounding epithelial cells of the matrix, outer root sheath, as well as mesenchymal cells of the dermal sheath, to induce de novo follicle development.

Stem Cell Niches of Postnatal Cycling of Hair Follicles

The cycling postnatal hair follicle undergoes dramatic morphological and architectural structural transformations driven by quiescent and proliferative niche stem cells during the anagen phase of growth and homeostasis, transitioning to catagen phase of apoptosis and shrinking of the lower follicle, and ending in telogen phase of quiescent miniaturization [4] (Fig. 2). The regulatory mechanisms by which stem cells in independent subpopulated compartments become activated and mobilized are essential to follicle homeostasis.

Catagen phase highlights the important apoptotic signals from exhausted, short-lived TA matrix progeny that initiates the start of regressive miniaturization of the follicle. During catagen, the *dermal papilla* cells provide transcriptional signals to activate the *secondary germ* niche that plays a critical role during catagen's regressive phase in losing the lower portion of the follicle to a thin epithelial strand. The strand is retracted upward to the base of the permanent portion of the follicle leaving the bulge region with the small *secondary germ* center which remains dormant during telogen resting phase [41]. Although the cellular relationship of the *bulge* and the *secondary germ* remains unclear, single cell lineage tracing experiments and BrdU labeling studies suggest, respectively, that bulge cells migrate to or transform into the *secondary germ* [42] which then proliferate during telogen-to-anagen transition to form the inner root sheath and hair shaft of the new terminal hair [24, 41].

After a short telogen period, a remarkable regeneration of the miniaturized follicle is contributed from three stem cell niches (*secondary germ, bulge, and dermal papilla*) to recapitulate an entire new lower follicle and hair shaft. Investigators [7] believe that the signaling mechanisms involved in the renewing cyclic phases mimic those implicated during the embryonic morphogenic stages of development. Toward the end of telogen, *secondary germ* cells burst with activity fueling the release two key-step signaling pathways initiate cycling from telogen to anagen: stabilization of β-catenin for WNT signaling via transcriptional cofactor for *Lefl;Tcf* proteins [41, 43]; bone morphogenetic protein (BMP)-positive or BMP-negative signaling, respectively, for induction of dermal papilla and bulge cell quiescence [44]; or initiation of morphologic and cyclic stimulation [45]. During the brief surge of *secondary germ* activities, the bulge transcriptional output remains relatively stable favoring cycle inhibitors and signaling repressors. Following the onset of early anagen, however, *bulge* cells then unleash transcriptional and proliferative signals by elevated levels of *β*-catenin [46] and are employed more sparingly to stimulate *outer root sheath, matrix cells, and inner root sheath* for the new follicle throughout anagen [47]. In summary, the *secondary germ* cell niche is believed to fuel primarily the initial stages of telogen–anagen regeneration and is the first responder to *dermal papilla* signals, while the *bulge* niche acts more as the engine that maintains progression of the hair cycle and is the reservoir of long-term stem cells [48]. The molecular mechanisms regulating cross-talk between secondary germ cells and mesenchymal dermal papilla cells remain unclear during telogen–anagen regeneration, but most likely involve the activities of BMP inhibitors, FGFs (fibroblast growth factors), and WNT effectors via *β-catenin* stimulation [41].

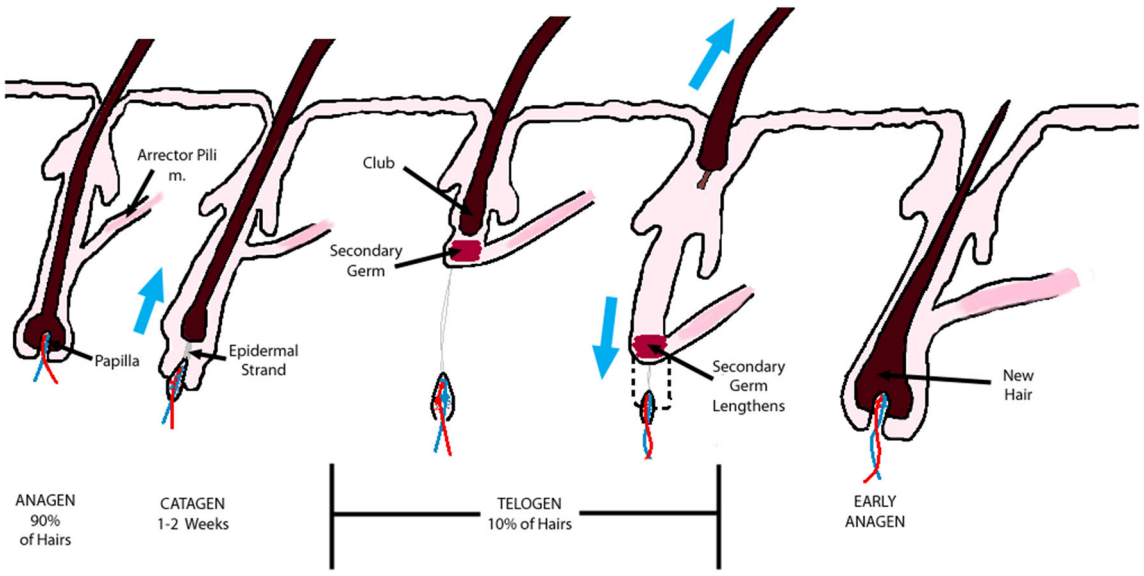

Fig. 2 Schematic representation of normal mature follicle growth cycling from anagen growth, catagen regression, and telogen quiescence

Extrinsic Regulation from Adipose Tissue for Follicle Cycling

Skin-associated white adipose tissue collections formed postnatally and existed as "intradermal fat depots" surrounding hair follicles that were distinct from subdermal/subcutaneous adipose layers [49]. These intradermal adipocytes regenerated with faster kinetics than other adipose tissue depots, and their cellular dynamics parallels with the hair cycle, suggesting that an interplay existed between follicles and adipocytes [50]. During cycling morphogenesis, for example, intradermal adipocytes expanded either by cell hypertrophy or by hyperplastic adipogenesis, doubling the skin's thickness [51] as the follicle entered into anagen growth phase and then receded during telogen [52]. Recent studies [53, 54] suggested that intradermal adipose depots increased primarily by adipogenesis, requiring the upregulation and transcriptional activity of the nuclear receptor, PPARγ, in preadipocytes. Through BrdU pulse-chase mice studies [55], additional data demonstrated that preadipocyte proliferation was low during early to mid-catagen, but increased during late catagen to generate a sufficient population of mature adipocytes to induce a fourfold surge during anagen induction. Preadipocyte numbers returned to baseline levels during homeostasis of the matured anagen phase. Taken together, these investigations indicated that there exist exquisite, but incompletely understood, regulatory mechanisms that control the stimulation or inhibition pathways for hair cycling via signals from preadipocyte precursor cells and adipocytes.

To clarify the signaling importance of adipocyte–follicle interactions, a genetic mice model, lacking *Early β-cell factor 1 (Ebf1$^{-/-}$)* expression in intradermal adipocytes, sebaceous glands, and *dermal papilla* of anagen follicles, has been shown to have less adipose-derived stem cells and, therefore, reduced intradermal mature adipocytes [56]. In these mutant mice, miniaturized follicles failed to cycle into anagen and lingered instead in late catagen-telogen, suggesting the requirement of adipose-derived stem cell transition to mature adipocytes for anagen induction through the activation of the bulge stem cells. When these defective mutant mice are transplanted with WNT/*β-catenin*-expressive preadipocytes, anagen induction occurred implying the need for specific adipocyte precursor lines [55]. The complicated cellular regulation for signals and transcription factors during proliferation and differentiation of adipose tissue was updated in a recent review in plastic surgery [57].

Mature intradermal adipocytes and the dermal papilla also contribute other signaling and transcription molecules that regulate bulge stem cells during the cycling process. Recent studies [58, 59] have shown that mature intradermal adipocytes periodically released bone morphogenetic protein (BMP2) mRNA, an inhibitory signal, that suppressed bulge cell activity during quiescent cycling phases in early telogen and late anagen. Once BMP2 signals are extinguished, follicles became responsive to WNT/*β-catenin* activation signals, enabling them to complete telogen and re-enter anagen. The competing balances between BMP and WNT signals appeared to synchronize transitions from quiescence to proliferation.

Androgenetic Alopecia (AGA)

Androgenetic alopecia (AGA), commonly known as male- and female-pattern loss of hair, affects more than half of men and women populations in the USA over age 50 [60, 61] with significant psychosocial effects in both sexes [62, 63]. Although the significant impact of androgen presence and genetic propensity is mandatory for male AGA, much more has to be elucidated. Male AGA is believed to be due to a polygenic mode of inheritance and the presence of dihydrotestosterone (DHT) [64]. Several lines of circumstantial evidence demonstrated supportive roles of androgens in male AGA: (1) the absence of AGA in eunuchs and pseudohermaphrodites [65], lacking in functional androgen receptors (AR) and 5α-reductase enzyme, respectively, (2) castrated postpubertal men terminating progression of AGA [66], (3) elevated levels of 5α-reductase, DHT, and AR in the balding male scalp [67], and (4) mitigation of hair loss with finasteride by inhibiting type II 5α-reductase activity [68]. Two isoenzymes for 5α-reductase type I (5αR1) and type II (5αR2) are believed to mediate the conversion of testosterone to DHT. 5αR1 is concentrated to sebaceous glands and linked in the exacerbation of acne vulgaris, while 5αR2 has been recovered in higher levels in follicles with male AGA [69].

Although the testosterone-receptor mechanism is not well understood, DHT has been suggested to activate epidermal AGA keratinocytes in the production of *caspase-1* and *IL-1β*, regulated at the inflammasome, immune transcriptional levels, to facilitate follicular miniaturization and apoptosis with each successive cycle [70, 71]. Recent studies supported these findings by demonstrating that (1) testosterone reduced TLR4 expression of immune–inflammatory mechanisms in monocytes and macrophages [72] and that (2) *caspase-1* mediated an inflammatory cell death cycle of pyroptosis [73]. Such contributing data in male AGA suggest that underlying androgenic mechanisms of inflammation and innate immunity may play significant roles in the formation of smaller, thinner, and finer apoptotic male-pattern alopecia, as defined in Norwood's classification of hair loss [74]. Hair loss in men is progressive

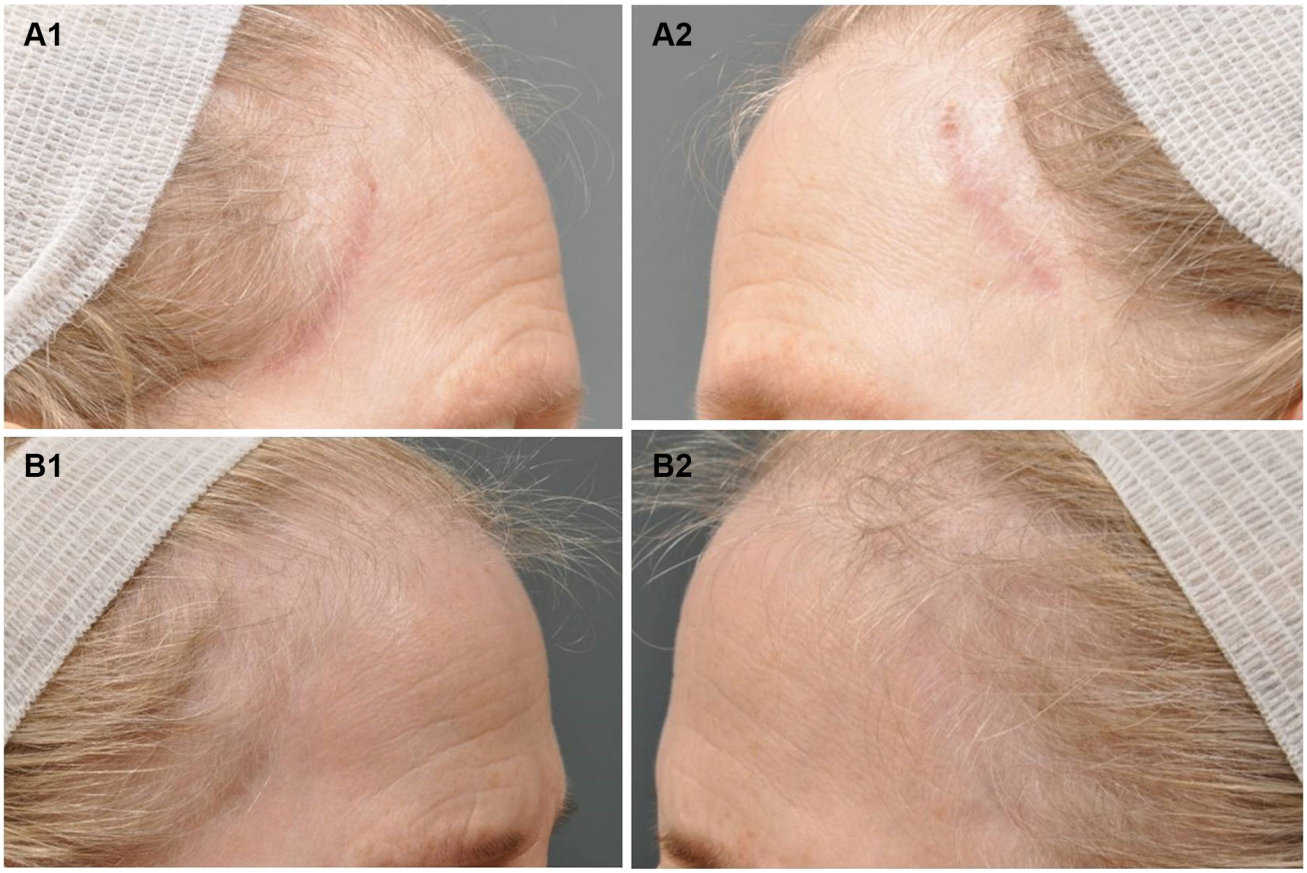

Fig. 3 **a** This 63-year-old Caucasian female presented with telogen effluvium after a lateral brow lift through post-trichial incisions 1 cm behind the anterior temporal hair lines. The patient was not on any hormonal replacement therapy and has never been on minoxidil treatments. The exposed scars were visible and of cosmetic concern. **b** The patient underwent one session of micro-needling (three stampings at 1.5 mm, 1.0 mm, and 0.5 mm depths) to the entire fronto-temporal hairline and extending about 5 cm into the hair-bearing scalp and simultaneous injection of 4 ml PRP (0.1 ml/1 cm^2; 40–50 marked treatment squares, 2.4 × 106 platelets/μl; Harvest-Terumo Technologies Corp., Plymouth, MA). Xylocaine 0.5% with epinephrine (25 ml) was injected in the subdermal space as the local anesthesia prior to the procedure. New vellus and terminal hair growth were observed anterior to the surgical scars and within the fronto-parietal scalp about 1 year after the procedure

with recession of the frontal hairline and hair loss over the frontal and vertex scalp regions. Miniaturization can abruptly occur after a few hair cycles such that the hair does not penetrate the scalp surface.

Female-pattern hair loss (FPHL) remains a poorly understood complex in which a number of factors, such as heredity, inflammation, hormonal or vascular influences, are under current investigation for deleteriously affecting follicles [75–77]. While androgenic alopecia 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 [78, 79]. FPHL can often be precipitated and exacerbated by drugs, acute stress, diet, hormonal changes, weight loss, and partum [80]. 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 [61]. Such changes lead to diffuse loss of hair density, affecting primarily the vertex and frontal scalp, defined by different grading systems [81, 82].

Chronic telogen effluvium (CTE), on the other hand, is believed to occur in apparently healthy women [83] and is attributed to an asynchronization disorder whereby generalized hair shedding (teloptosis) of greater than 20% existed than observed in FPHL [84]. Although combination occurrences of FPHL and CTE represent the most common manifestations of female hair loss, other presentations, such as cycle delays and lag phases [85], complicate diagnoses and treatments as they may possess slightly different variant mechanisms of hair loss.

Recent global gene expression studies [86–88] reported that a defect in conversion of stem cells to daughter progenitor stem cells in the bulge area might play a role in the pathogenesis of male AGA. In haired male humans [88], isolated bulge and their progeny secondary stem cells

possessed high levels of preferential expression of the intermediate filament protein KRT [14] and cell surface markers $CD200^+$, $CD34^+$, and $ITGA6^+$. At the end of normal cycling during catagen, secondary germ cells arose as progeny from bulge stem cells; expressed similar KRT15 filament proteins and $CD200^+$, $CD34^+$, and $ITAG6^+$ bulge cell markers; and were immediately responsible for the formation of the new lower hair follicle at early anagen. In bald male humans, however, isolated cell populations of secondary germ progenitor cells were greatly diminished, possibly due to the lack of replenishment from bulge cells, and potentially resulted in reduced populations of matrix stem cells which were responsible for hair shaft production. The roles of these genomic mechanisms in the pathogenesis of male AGA have yet to be identified in FPHL and CTE conditions [89].

Evaluation of Hair Loss

The human scalp is predetermined to have approximately 100,000 terminal hair follicles at birth. At any time, most follicles are in either the growing anagen phase (90–95%), regressive catagen phase ($< 1\%$), or quiescent telogen phase ($\simeq 10\%$). At the end of telogen, about 100 miniaturized shafts are shed and the same number entered the anagen cycle.

The diagnosis of male AGA, female FPHL, or CTE is based primarily on the basis of medical history, physical examination, context of age and occupation, and clinical importance with the need for biopsies rarely needed. Because of their less common occurrence, the reader is referred to other reviews [90] for further discussion of diffuse alopecia areata, an autoimmune disease, cicatricial traumatic alopecia, and other less infrequent diseases.

Medical Treatment Options

Current treatments for managing androgenetic alopecia range from noninvasive medical approaches to follicular unit transplantation using donor punch or strip harvesting techniques performed manually or by robotic-assisted surgeries [91–93]. Today, surgical transplantation remains the gold standard, but is generally not recommended for patients with early stages of alopecia, diffuse thinning, thin donor sites, and scarring or immunogenic forms of hair loss. Multiple surgeries are costly and can be associated with a number of complications [94]. Although hair transplantation or surgical reduction procedures, and hairpieces are viable options for some patients, a number of non-approved US Food and Drug Administration (FDA) treatments for AGA have been available that included topical formulations, oral supplements, and prescription medications and low-level light [92–95]. Although their individual mechanisms of action have not been fully elucidated with few clinical controlled trials [96–98], they are offered as monotherapy or as combination therapies. Two FDA-approved drugs have been available, however, for the treatment of male- and female-pattern hair loss, but differ in mechanisms of action and route of administration. They are prescribed as stand-alone treatment options to maintain as much coverage as possible or combined with hair transplantation surgery to reduce telogen shedding. Although both drugs retard hair loss and stimulate anagen growth, neither restores hair loss completely and results in hair loss upon termination of their usage.

Minoxidil, a piperidinopyrmidine derivative, was reported to produce unexpectedly hypertrichosis in 24–100% of patients who were being treated for refractory cases of hypertension as an oral medication in the 1970s [99–101]. Subsequent dose-dependent placebo-controlled studies determined that the FDA-approved marketing of topical 2% or 5% concentrated foam preparations was safe and effective for temporary AGA improvement in males [102] and females [103] and for post-hair transplantation [104], appearing to prolong the duration of anagen, reverse miniaturization, and reduce postsurgical telogen effluvium. The precise mechanisms of action may be attributable to the conversion of minoxidil to its active form of minoxidil sulfate by sulfotransferase enzymes [105], localized selectively in the lower outer root sheath to its active form (minoxidil sulfate) [106] that produced arteriolar vasodilation as a potassium channel opener [107], increased Doppler cutaneous blood flow up to an hour after application [108], stimulated vascular endothelial growth factors [109], and promoted dermal papilla cells proliferation [110]. Although debate continues about whether minoxidil prolongs anagen or shortens telogen, clinical studies in balding men have shown increased anagen–telogen ratios after 12 months [111], as well as improved mean hair diameters after 12 months at 4 months [112]. Reversible side effects such as contact dermatitis and unwanted hair in both men and women have been well documented [113–116].

Finasteride, a member of the azasteroid family, was originally introduced for the treatment of benign prostatic hypertrophy and was FDA-approved in 1997 [117, 118] in a 1-mg oral dose for male-pattern AGA. Initial randomized placebo-controlled trials demonstrated prolonged hair growth to the balding vertex [119, 120] and frontal scalp [121]. The mechanisms of action have been ascribed to its selective inhibition of type 2 5α-reductase isoenzyme that converts testosterone to DHT. The 60–70% reduction in DHT [122] is believed to reduce miniaturization and increase the anagen–telogen ratios [123]. Finasteride was

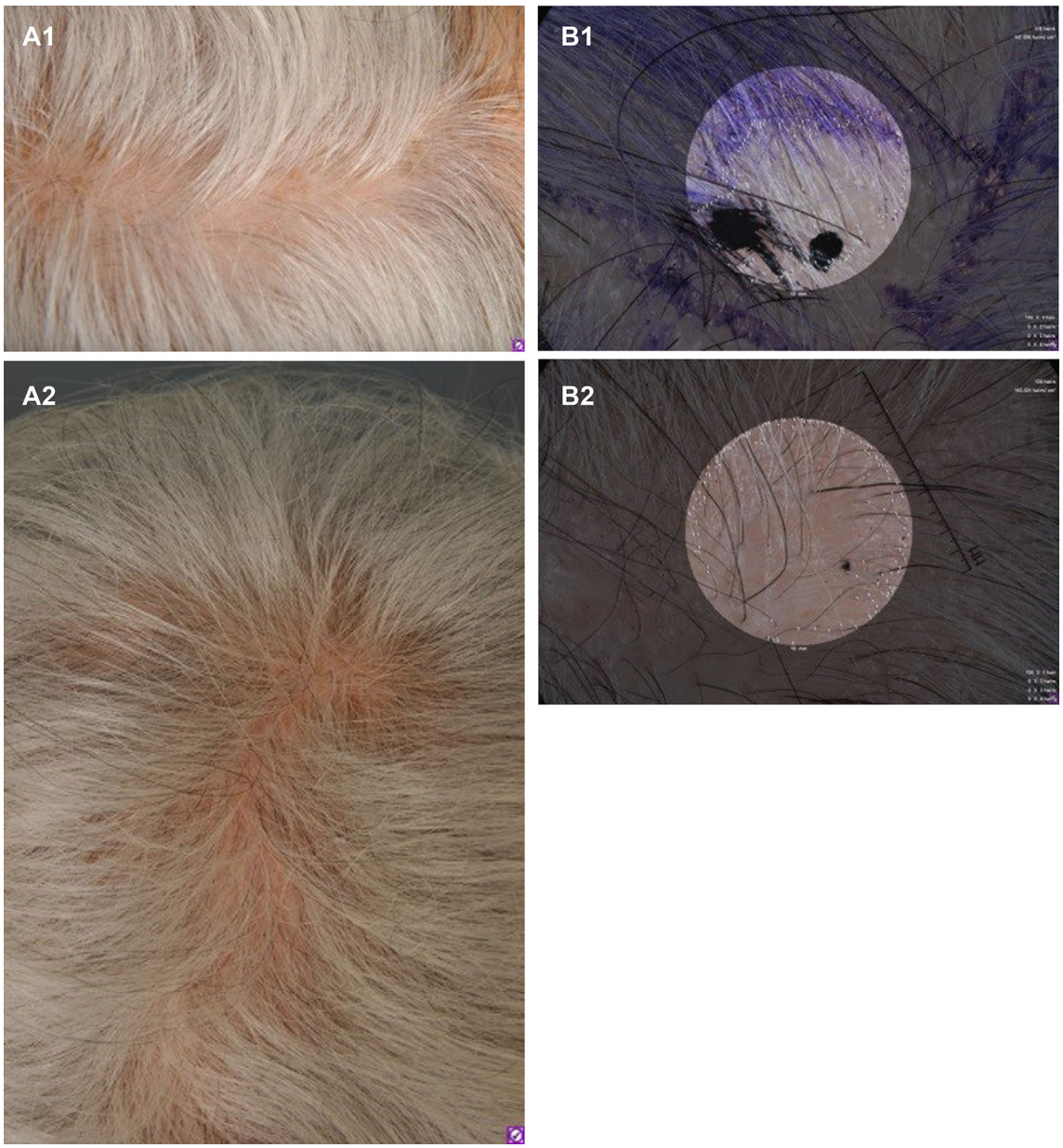

Fig. 4 **a** This 64-year-old African-American female presented with chronic telogen effluvium to the entire scalp, especially to the vertex. The patient was on Premarin replacement therapy and had never received minoxidil treatments. **b** The patient underwent one session of micro-needling (three stampings at 1.5 mm, 2.0 mm, and 2.5 mm depths to the entire fronto-temporo-parietal and vertex scalp). Immediately thereafter, 30 ml of fat, harvested at the hip rolls by a Lipogems system (Lipogems International S.R.L., Milan, IT) was combined with 3 ml of PRP (1.2 × 106 platelets/μl, Harvest-Terumo Technologies Corp., Plymouth, MA) and injected in the subaponeurotic plane (0.2 ml/1 cm^2) under 150 marked treatment squares. Xylocaine 0.5% with epinephrine (35 ml) was injected in the subaponeurotic space prior to the procedure. At 6 months, new vellus and terminal hairs were observed throughout the treated scalp with an increased hair count by computerized microscopy (Canfield Imaging, Parsippany, NJ)

suggested to induce not only the prolongation of anagen hairs [124], but also the reduced expression of caspases and apoptosis inhibitors to activate anagen growth [125, 126]. The prolonged use of finasteride resulted in minimal side effects as compared to placebo except for a slight increase with sexual complaints of less libido and erectile/ejaculatory dysfunctions [119, 120] and unwanted hair in both sexes [124–127]. The Prostate Cancer Prevention Trial for patients taking finasteride 5 mg/day reported a relative reduction in the prevalence of prostate cancer, but higher Gleason scores on positive biopsies [128]. Currently, there is no FDA approval for its use in the treatment of alopecia in women. Finasteride is contraindicated in child-bearing aged females, unless effective birth control measures are

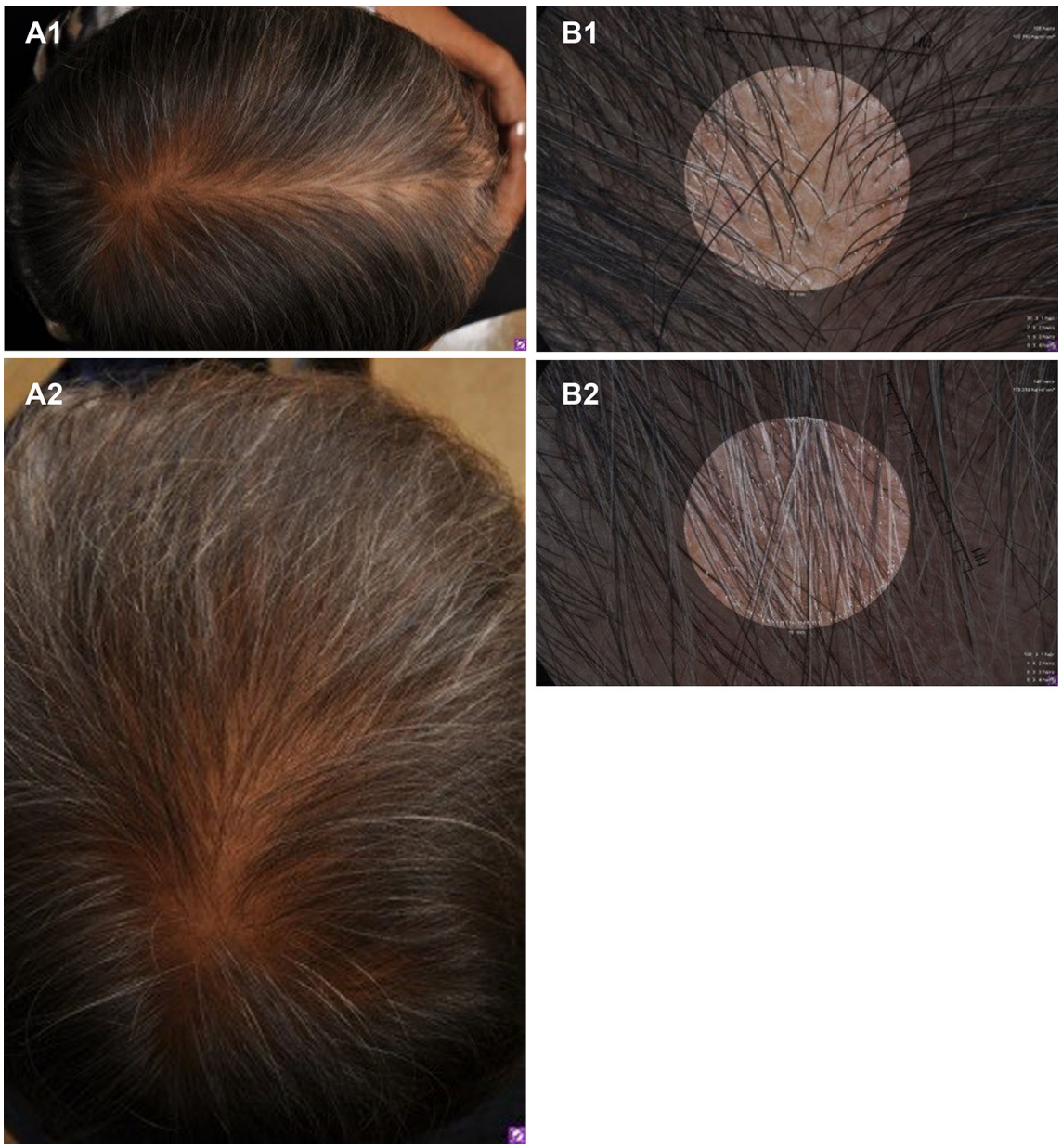

Fig. 5 **a** This 72-year-old Caucasian female presented with chronic telogen effluvium to the entire scalp since her mid-twenties. The patient was not on hormone replacement therapy and had never received minoxidil therapy. **b** The patient underwent one session of fat grafting combined with stromal vascular fraction (SVF) to the thinning scalp. A 3–4-mm blunt-tip Mercedes cannula collected about 300 ml of lipoaspirate in 60 ml Toomey syringes. Five milliliter of SVF was obtained by enzymatic separation (Cytori Therapeutics, Inc., San Diego, CA). An aliquot of the lipoaspirate was processed in the PureGraft Filter system (PureGraft, San Diego, CA) to obtain about 30 ml of purified fat. The PureGraft-processed fat was combined with 5 ml SVF and injected in 0.2 ml aliquots/1 cm^2 and injected in the subaponeurotic space under approximately 100 marked treated squares. Xylocaine 0.5% with epinephrine (35–50 ml) was injected in the subaponeurotic space prior to the procedure. New vellus and terminal hairs were observed 1 year after treatment with an increased hair count by computerized microscopy (Canfield Imaging, Parsippany, NJ)

used, because of feminization of a male fetus. Some but not all FPHL-affected women respond to 5α-reductase inhibitors, indicating the relative minimal significance of DHT as a primary cause of hair thinning in women [79].

Controversial Growth Factor Approaches for AGA

With interest in stem cell niches [129] and their growth factors [130] for cellular proliferation and differentiation, new current strategies have begun to focus on either

platelet-rich plasma (PRP) [131–134] or adipose tissue containing natural stem cell populations [55, 129, 130] for the treatment of female and male AGA. Although the signaling and transcriptional factors of growth factors have been studied in nascent and adult phases of the germinal hair cycle, there have been few clinical controlled trials to verify the safety and efficacy of such protocols.

Platelet-rich plasma contains a high number of platelet particles that are concentrated above levels normally found in whole blood. Experimental studies [135, 136] have demonstrated that activated platelets release a number of potent growth factors that include platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), transforming growth factor (TGF), vascular endothelial growth factor (VEGF), epithelial growth factor (EGF), and insulin-like growth factor (IGF). Growth factors are believed to be generally responsible for angiogenesis [137], stem cell proliferation and differentiation [138, 139], and anti-apoptotic properties [140], but specifically for hair follicles, anagen induction [133], proliferation of dermal papilla cells [141], cyclic growth [142], and follicle development [143]. Furthermore, Guisti's in vitro dose-dependent study [144] indicated the optimal concentration of activated platelets in PRP to stimulate angiogenesis occurred between 1.5 and 3.0 $\times$ 10^6 cellular particles/μl.

Although a few published clinical trials without remarkable side effects have reported (1) improved survival and density of PRP-transplanted hair follicles in males [131], (2) increased thickness of PRP–dalteparin/protamine-stimulated follicles in thinning hair in both sexes [132], or (3) increased mean numbers and diameters of CD34 + PRP stimulated follicles in male- and female-pattern hair loss patients [134], a recent randomized, single-blinded clinical PRP trial demonstrated a statistically significant increase in hair counts, caliber shaft diameters, and satisfaction outcomes at 6 months with three consecutive monthly sessions with one booster session 3 months later than after two sessions 3 months apart [145, 146]. Further larger, controlled, standardized split-scalp studies will need to be completed to substantiate the safety and clinical efficacy in both male and female patients with different stages of hair loss (Fig. 3).

The use of autologous fat grafting with or without enhancement with growth factors from PRP or stromal vascular fractions (SVFs) has been anecdotally reported (Figs. 4 and 5). Based on encouraging published results with PureGraft®-purified adipose tissue and KerastemCelution®-derived ADRCs (Solano Beach, CA) [147], a Kerastem phase II multicenter clinical trial (STYLE) is currently underway to study dosing ADRC requirements to achieve positive hair stimulation in early-stage hair loss in female and male subjects. Currently, there exist no FDA-approved adipose stem cells isolation devices, procedures, or clinics in the USA.

Conclusion

The goals of the present chapter was to provide an overview of the importance of stem cell niches in both epidermal and mesenchymal lineages that give rise to specific structures within the nascent mammalian hair follicles and subsequent postnatal follicles. This orchestrated design of recapitulation through triggering of molecular cross-talking signals and transcription factors regulates the various defined cycling stages from miniaturized to fully developed hair follicles. As differential expressions of stem-cell-associated markers are identified and more functionally understood, an accumulated body of information will provide researchers and clinicians an improved understanding of normal cycling, androgenetic hair loss, and more uncommon entities as autoimmune types of alopecia. It is anticipated that evidence-based treatments will continue to be developed with safe and reliable drugs, growth factors and possibly, in the near future, FDA-approved approaches utilizing PRP and stem cells to address hair loss and emotional stress for millions of men and women.

Acknowledgements The author wishes to thank Evelyn Avanessian, RN, Brigette Ibarra, LVN, for technical assistance in PRP isolation and cell counting; Sharon Cuellar, CST, for surgical assistance; Melissa Avitea, MA, for her IRB assistance; and Margaret Gaston, BS, for creating the artwork and providing the statistical and photographic assistance.

Compliance with Ethical Standards

Conflict of interest The author is an unpaid consultant to Harvest Technologies Corp and MicroAire Surgical Instrument and declares no conflicts of interest with respect to the authorship and publication of this article. The author has neither financial nor investigational interests with Cytori Therapeutics, Inc. The author received no financial or equipment support from any of the device companies in this study. No financial support was provided for the writing of the article.

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