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Common skin conditions and disorders

Hair physiology and its disorders

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Hair follicles are complex skin appendages, the perturbations of which have an impact on human health and emotional welfare disproportionate to their small dimensions. Changes to the parameters of hair follicle size, numbers per unit area of skin, and growth cycle time duration determine hair coverage and fundamentally underlie the diagnosis of an individual with alopecia or hypertrichosis. Here we review the hair follicle's physiology, its disorders and principles of hair disorder treatment development.

Introduction

The skin, the second largest organ in the body after the skeleton, is of primary importance to the survival of mammalian life [1]. The skin structure is derived from the embryonic ectoderm and mesoderm, which give rise to the epidermis and dermis, respectively [2]. Within these generalized layers of the integument are specialized structures also derived from the ectoderm and/or mesoderm including sensory nerves, sweat glands and hair follicles [3].

Humans have over 2 million hair follicles, which collectively may have significant positive and negative influence on skin health [4]. Most follicles produce short, rapidly cycling, fine and nonpigmented vellus hairs. Eyebrow, eyelash and scalp follicles produce long, slowly cycling, coarse, pigmented, terminal hairs from birth. However, follicles retain a degree of plasticity with respect to the type of hair produced and a number can transform from vellus into terminal hair production and *vice versa*. This is particularly seen during puberty when androgen-

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responsive vellus hair follicles are promoted into terminal follicles [5].

The perturbation and loss of hair follicles and alterations in hair fiber production in humans is generally not a life-threatening event, but does have a dramatic impact on quality of life and emotional wellbeing [6,7]. As such, hair disorders are a significant issue for many individuals. The hair follicle physiology, changes during the development of hair disorders and potential modes of treatment development are examined here.

Hair follicle development

Hair follicles first start to form in the skin of a human embryo from the 8th to 12th week of gestation. Hair follicle formation typically begins on the face and then progressively spreads ventrally and caudally over the body. The development and differentiation of hair follicles during embryogenesis is classically divided into eight stages characterized by distinct morphologies [8].

This formation of hair follicle appendages requires a complex and currently poorly understood sequence of autocrine, paracrine and endocrine signals to occur both within and between the epithelium and dermis. How these regulators interact with each other, their relative significance, the degree of redundancy in the signaling system, and how these signals determine the development of such a complex structure, its size, its distribution and subsequent growth cycle characteristics are still largely unknown [9]. However, multiple signaling and signal transduction pathways have been

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proven significant for the correct development and geographical distribution of hair follicle formation through the skin [10].

Of particular note, Wnt gene products and associated intracellular mediators of cell signaling, β -catenin and LEF1 have been shown to be fundamental to hair follicle embryogenesis [11,12]. The subsequent cascade of activated signaling pathways mediated by β -catenin and LEF1 include ectodysplasin A (EDA), noggin, transforming growth factor beta 2 (TGF β 2), TGF β R-II, β 1 integrin and neural cell adhesion molecule (NCAM) among others. Experimental induction of their respective expression induces hair follicle formation suggesting a significant role for these factors in hair follicle development. By contrast, multiple inhibitors of hair follicle placode formation, such as bone morphogenic protein (BMP)-2, BMP-4, p75NTR and activin β a are also expressed in the embryonic skin and may serve to regulate the distribution pattern and size of hair follicles [10].

It has previously been asserted that no new follicles develop after birth and that the immense regenerative capacity within hair follicles serves only to induce anagen formation and epithelial repair following wounding. Recently some hair follicle inductive capacity has been identified following wounding and again Wnt expression seems important in determining cell fate as epithelial cells migrate out of hair follicles to participate in wound repair [13].

Hair follicle morphology

Hair follicles are formed with multiple epithelium- and mesenchyme-derived cell layers each performing unique functions and together comprising more than 20 distinct cell populations. The hair follicle, along with the sebaceous gland and the arrector pili muscle, form the so-called 'pilosebaceous unit' [14]. The relative proportions of individual components within the pilosebaceous unit vary between different hair follicle types but the fundamental structure essentially remains the same. In the scalp skin, terminal hair follicle units comprise groups of three to five individual follicles that are surrounded by a fibrous sheath and may share a common arrector pili muscle.

The hair follicle can be divided into a permanent superficial structure and a transient cycling region, which includes the hair bulb. The dividing line between the permanent and transient parts of a hair follicle lies immediately below the hair follicle bulge region and the insertion point of the arrector pili muscle. The bulge region has particular importance in hair follicle growth. It is a specialized compartment of the outer root sheath in which epithelial and neuroectodermal stem cells are believed to reside [15].

Hair fiber and inner root sheath growth is a consequence of rapid proliferation of keratinocyte transit amplifying cells that reside in the bulb region adjacent to the dermal papilla during an anagen growth phase. The dermal papilla

condensate of specialized mesenchymal cells has important inductive and hair growth regulatory properties [3]. In fact, surgical removal of the dermal papilla and the lower dermal sheath prevents hair growth, which indicates the importance of these specialized mesenchymal cells as a key signaling center in hair follicles [16].

Hair follicle growth cycling

Three main phases of the growth cycle are recognized – a growth phase (anagen phase I–VI), regression phase (catagen) and resting phase (telogen) [4]. The time duration of each phase depends on the type and location of the hair follicle. Under physiological conditions, approximately 85% of scalp hair follicles are in anagen while 15% are in a telogen phase [5]. The duration of anagen in healthy scalp hair follicles is typically two to six years and is the principle determinant of hair length. The anagen phase is followed by a short resting phase, catagen. Catagen is characterized by a cessation of protein and pigment production, involution of the hair follicle and a fundamental restructuring of the extracellular matrix. In telogen, the hair follicle regresses to less than half its anagen phase size. Morphologically, all that remains is a peg of epithelial cells overlying a cluster of quiescent dermal papilla cells. Hair cycle synchronization is lost after the second moult wave shortly after birth. Hereafter hairs cycle independently and seasonal moulting is not seen in humans [3].

Recent research suggests that hair fiber shedding is an active and highly controlled process, which differs from the quiescence typically found throughout much of the telogen phase. The term 'exogen' has been introduced to identify the hair fiber shedding event as a separate process during hair follicle cycling [17]. The morphology of the hair root suggests that the exogen process involves a proteolytic event in the cells of the telogen shaft base. The nature of this shedding process remains to be identified. However, desmoglein 3 appears to have a role in maintaining telogen hair anchorage within the follicle and loss of desmoglein 3 is associated with exogen [18]. Empty hair follicles after shedding of the hair fiber, but before the onset of renewed anagen, are in a stage termed 'kenogen'. Kenogen can be observed in healthy skin, but the frequency and duration are significantly greater in individuals with androgenetic alopecia [19].

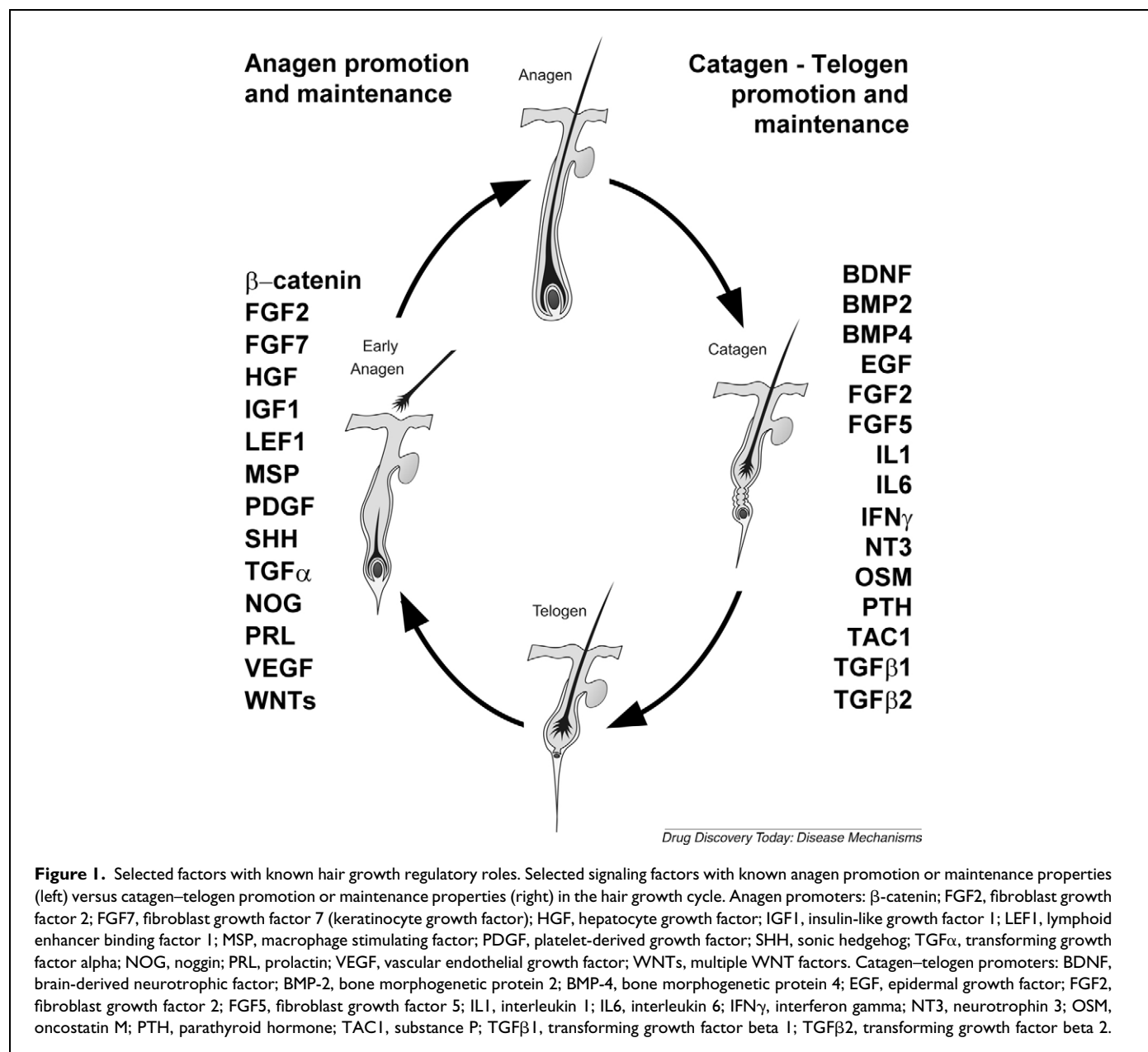
Under normal physiological conditions, each hair follicle will continue to cycle throughout life. These cycles are regulated by specific changes in the local signaling milieu, based on changes in the expression of cytokines, hormones, neurotransmitters and their receptors as well as transcription factors and enzymes, which act via endocrine, paracrine or autocrine routes. What determines the clock mechanism and the duration of anagen in individual hair follicles is not known, although many hypotheses have been suggested [4].

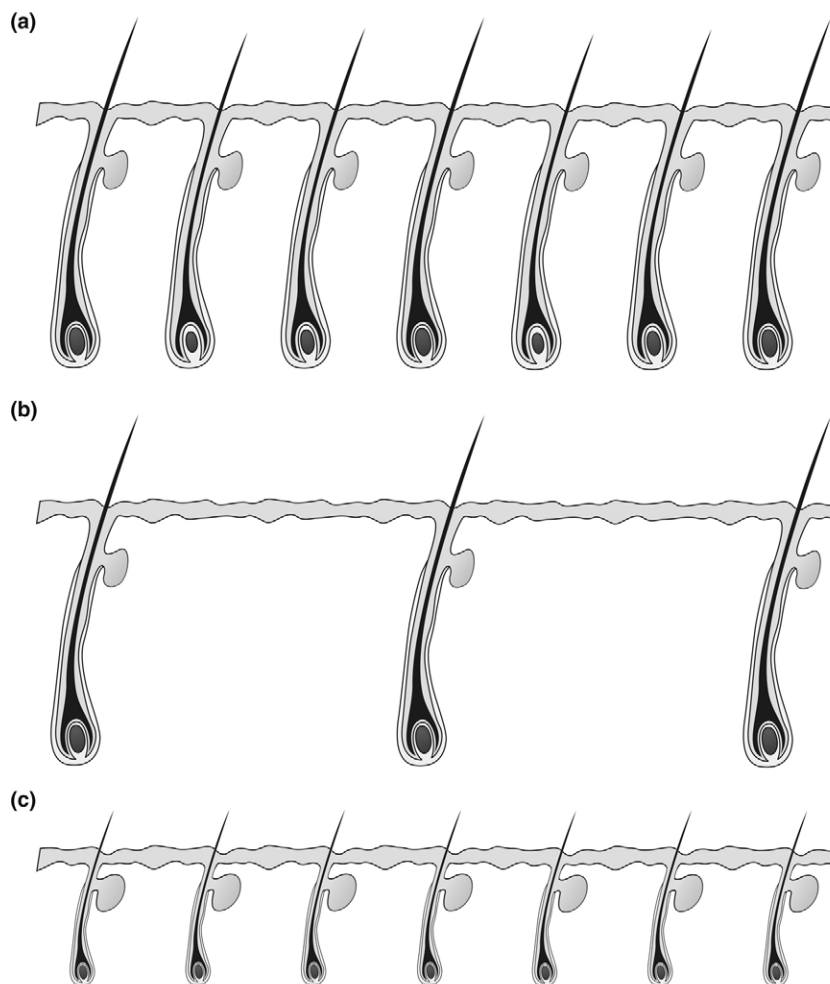
Hair growth and onset of a new anagen growth phase recapitulates hair follicle embryogenesis and reutilizes similar molecular signaling pathways. As with hair follicle embryogenesis, the primary initiators (as currently known) for the start of a new hair growth cycle and onset of anagen involve Wnt/ β -catenin signaling pathway interaction. WNT proteins are strongly expressed in hair follicle bulge epithelial cells adjacent to the dermal papilla at anagen onset. Several studies have demonstrated that the perturbation of Wnt signaling inhibits cell proliferation and dermal penetration events subsequent to anagen initiation. Overexpression of Wnt and Wnt-associated proteins such as sonic hedgehog (Shh) induces anagen in telogen stage hair follicles [20,21]. Many other molecules are believed to be involved in hair cycle regulation including multiple fibroblast growth

factors (FGFs) and hairless, a mediator of Wnt signaling [10] (Fig. 1).

Hair biology applied to hair disorders

The biological properties of hair follicles contribute to our perceptions and definitions of what is a hair disorder. Alopecias or hypertrichoses are, in essence, an observation of too little or too much hair fiber over an area of skin significantly different from the norm as defined by society. In other words, changes to the parameters of hair follicle number per unit area of skin, changes in hair follicle size and growth cycle time duration determine cosmetic hair coverage and whether or not an individual has a hair disorder (Figs 2,3). One or more of these factors may lie behind the development of a hair growth disorder and the net impact of involvement





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Figure 2. Changes in hair follicle parameters associated with hair disorder development. All hair loss disorders can be reduced to three essential mechanisms that involve hair follicle density, hair follicle size and hair growth cycle duration. Compared to a normal hair follicle density **(a)**, a reduction in the density of hair follicles per unit area can reduce the apparent coverage of skin by hair **(b)**. A reduction in the size of the hair follicles in an area of skin can also result in reduced hair coverage **(c)**.

of more than one factor may be greater than the sum of the parts.

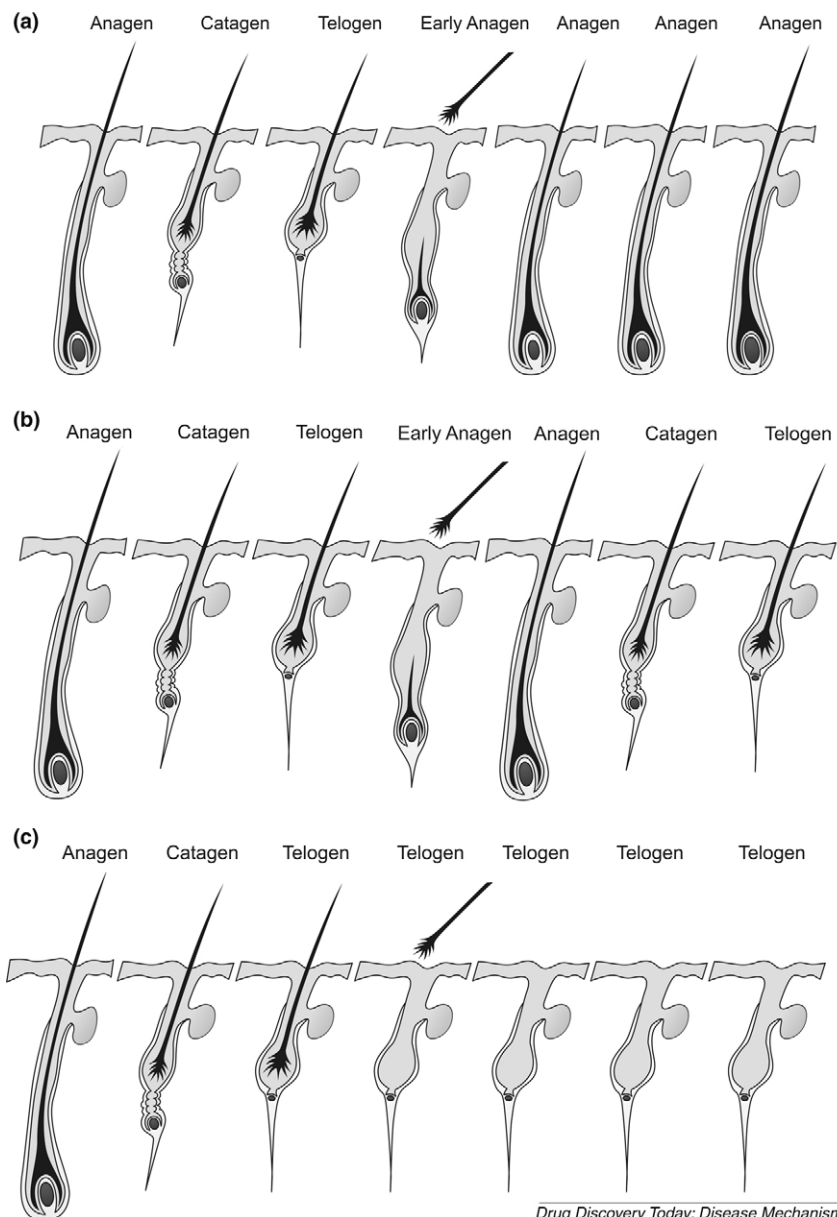
Congenital disorders of hair growth

Congenital disorders of hair growth are almost always genetic rather than environmental. Fundamentally a congenital alopecia or hypertrichosis is because of a problem in the correct embryogenic formation of hair follicles. As hair coverage is defined by hair follicle density, size and growth cycle, embryogenic modifications to these parameters can result in congenital hair growth disorders.

The most obvious embryogenic modification possible is a reduction in the number of hair follicles formed per unit area of skin. Aplasia cutis congenita, in which regions of skin fail to form correctly, is an example. Several forms of congenital hypotrichosis may also involve a failure of development of the full complement of hair follicles. However, more typically

hair follicle formation does occur at a normal density, but the hair follicles fail to regenerate following their second or third catagen. Congenital atrichia and Marie Unna hypotrichosis are good examples where hair follicles form and grow hair in their first full cycle, but fail to survive and successfully enter subsequent hair growth cycles. Such conditions involve mutations in one or more genes that are functionally significant for cohesive hair follicle structure maintenance. The late onset, patterned destruction of hair follicles in Marie Unna hypotrichosis makes this condition unique.

Whether hair follicles are terminal or vellus in nature and their number and distribution are at the root of congenital hypertrichosis. *In utero*, babies are covered from head to toe by a uniform coat of fine lanugo hair about 1 cm in length. Shortly before full-term the scalp hairs elongate into terminal hairs, the eyebrows remain unchanged, while the remaining involute into vellus hairs. The expected norm is terminal hair



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Figure 3. Changes in hair growth cycles associated with hair disorder development. Changes to the hair growth cycle that elicit hair growth disorders can take one or more of three key presentations. Compared to a normal hair growth cycle time course (a), changes to the hair growth cycle can occur such that the duration of anagen is truncated yielding brief production of short and fine hair fibers (b). Equally, changes to the hair growth cycle can involve a prolongation of the resting telogen phase after the hair from the previous growth cycle is shed (c).

follicle distribution restricted to the scalp and eyebrows and vellus hair follicles to cover the face and body in newborns. When terminal hair follicles form beyond these limits and take the place of vellus hair follicles on the face and elsewhere, the consequence is diagnosed as congenital hypertrichosis. In this event the density of hair follicles is presumed to be unaltered. Rather, the size of the hair follicle that develops is inappropriate for the skin region.

Finally, the hair growth cycle duration can play a role. Congenital hypertrichosis lanuginosa is a disorder in which the duration of the anagen growth phase is prolonged beyond the norm in vellus hair follicles, the net result being

long, fine, unpigmented hair growth. Again, the density of hair follicles has not been altered and the distribution of terminal and vellus hair follicles is correct. The problem is one entirely based on an unusually long duration of anagen growth in facial and body vellus hair follicles. FGF5 knockout mice have an angora phenotype and are thought to be the animal correlate of congenital hypertrichosis lanuginosa [4].

Acquired disorders of hair growth

Acquired disorders of hair growth are more complex in their nature and the hair biology parameters involved.

Fundamentally though, the three factors of hair follicle density, size and growth cycle parameters underlie acquired disorders.

Which of these biological hair growth factors is predominant varies with different diagnoses. In telogen effluvium, for example, changes to the hair growth cycle predominate. Hair follicle density remains the same and a switch in hair follicle size from terminal to vellus does not occur. By contrast, cicatricial alopecia development relies more or less exclusively on loss of hair follicle density through follicle destruction.

The most common alopecia, androgenetic alopecia, produces a patterned baldness that is a good example of a condition that involves complex changes in more than one biological parameter. Arguably, changes to hair growth cycling are the dominant issue in early pattern baldness. The development of pattern baldness involves a reduction in the percentage of scalp hair follicles in anagen, a reduction in the anagen growth phase duration, and a corresponding increase in the percentage of hair follicles in telogen and an increase in the duration of telogen. These alterations, in combination with a shift in the exogen phase from primarily occurring in early anagen to initiation primarily during telogen, result in thinning hair coverage [4].

The predominant biological hair growth factor involved also varies over time for the same diagnosis. In pattern baldness, while the initial dominant biological factor in the disorder is a change in hair growth cycling, later the switch in hair follicle size from terminal to vellus dominates. Ultimately, some loss of hair follicle density occurs as vellus hair follicles are destroyed. This loss of hair follicle density contributes less to a loss of meaningful hair coverage given the hair follicles are vellus in nature, but the loss in hair follicle density reduces options for treating pattern baldness. If hair follicles survive in some form there is the potential to correct their aberrant size or growth cycle. Once they have gone, scalp reduction surgery, hair transplantation, or in the future hair follicle replication, are the only options.

Alopecia areata, the second most common alopecia seen in dermatology clinics, is a particularly complex acquired hair disorder. Loss of hair follicle immune privilege and exposure of hair follicle autoantigens are believed to lead to infiltration of inflammatory cells and premature termination of the anagen phase, respectively. Transmission of the signal to neighboring follicles sets up a molt wave emanating from the central focus that most commonly peters out and results in a circular patch of bald scalp. Hair follicle miniaturization is a prominent feature of alopecia areata, however, although the histology of these miniaturized hairs is indistinguishable from those seen in androgenetic alopecia; these hairs maintain the capacity to rapidly revert into terminal hairs once the inflammatory signals die out [22].

Principle biological objectives of hair disorder treatments

Hair disorders are fundamentally caused by the changes in hair follicle density, size and/or changes to the hair growth cycle. The principle of any hair disorder treatment should be to directly modulate one or more of these parameters. What approach is taken depends in part on the nature of the hair growth disorder. Where the underlying cause of the changes to hair growth density, size and growth cycle is known, the most obvious approach is to target the initiating disease mechanism. Treatment to remove the disease-initiating event, while not directly acting on the affected hair follicles, may enable the damaged hair follicles to recover through their inherent regenerative capacity. The range of possible hair disease initiating mechanisms involved varies significantly from hormonal activity and stress, to inflammatory responses and genetic mutation. The considerable heterogeneity of hair disorder pathogenesis cannot be reviewed here. However, given many hair disorders involve changes to hair follicle distribution, size and growth cycle, it is potentially possible to treat multiple disorders through the development of treatments modulating one or more of these parameters.

Hair follicle density replication

For disorders in which hair follicle density is the predominant concern, such as end stage androgenetic alopecia, scarring alopecia or congenital hypotrichoses, the primary objective in new treatment development should be to generate new hair follicles from adult skin. On initial consideration such an idea might be rejected as absurd; however, a long history of evidence suggests such an event is possible. Various terms *hair replication*, *hair multiplication*, *hair cloning* and *follicular neogenesis*, the creation of new hair follicles has been demonstrated. Cultured dermal papilla cells or dermal sheath 'cup' cells from the bulbar region of hair follicles can be implanted and shown to regenerate new hair follicles as well as to enlarge resident hair follicles [23]. This cell-based therapeutic approach is currently an active area of commercial research by several companies.

Initiation of hair follicle formation in postnatal skin by molecular and genetic manipulation might also be possible. For some time it has been speculated that hair follicle formation could occur in response to wounding. Recent research has demonstrated that such an event can occur and is Wnt signaling dependent [13]. However, given the significant potential danger of initiating unregulated skin neoplasia growths with such an approach it remains to be seen whether a molecular- or genetic-based treatment to induce hair follicles to form is feasible. In practical terms, the development of drug-based treatments is more likely to focus on modifying the size and growth cycle of resident hair follicles as opposed to inducing new hair follicle formation.

Hair follicle size manipulation

Hair follicle size determines the size of the hair fiber produced and hair follicle size has been linked to the size of the dermal papilla. Larger dermal papillae dictate thicker hair fiber growth. In androgenetic alopecia, the switch from large terminal hair

follicles to miniaturized vellus-like hair follicles correspondingly results in a switch from terminal hair fiber to vellus hair fiber production. This switch in size seems to be the consequence of dermal papillae responding to androgen hormones with a reduction in cell numbers. Consequently, a focus of hair

Table 1. Targets and related therapies

	Strategic approach to target	Expected outcome of intervention at target	Who is working on the target	Therapies in trial	Refs
Drug promotion of hair growth	Minoxidil-based treatments in multiple topical formulations	Increased duration of anagen hair growth and increased hair follicle size	McNeil-PPC, Inc.	All trials complete, commercially available	[24,27]
Drug inhibition of androgen-mediated hair loss	Oral finasteride inhibitor of Type II 5 alpha reductase	Reduced action of dihydrotestosterone in androgenetic alopecia. Increased duration of anagen hair growth and increased hair follicle size	Merck & Co., Inc.	All trials complete, commercially available	[24,25]
Drug inhibition of androgen-mediated hair loss	Blockade of androgen production or androgen receptors using antiandrogen drugs (spironolactone, cyproterone acetate)	Reduced action of testosterone and dihydrotestosterone in androgenetic alopecia. Increased duration of anagen hair growth and increased hair follicle size	Multiple	Limited clinical studies complete, commercially available	[29,30]
Drug inhibition of androgen-mediated hair loss	Oral dutasteride inhibitor of Type I and Type II 5 alpha reductase	Reduced action of dihydrotestosterone in androgenetic alopecia. Increased duration of anagen hair growth and increased hair follicle size	Glaxo Smith Kline, Inc.	Phase III trials active	[26]
Drug modification of hair follicle size	Activation of the sonic hedgehog (Shh) gene pathway using agonists	Increased duration of anagen hair growth and increased hair follicle size	Curis, Inc.	Preclinical research	[28]
Drug modification of hair follicle size	Ammonium trichloro (dioxoethylene- <i>O,O'</i> -) tellurate compounds	Increased duration of anagen hair growth and increased hair follicle size	BioMas Ltd	Phase II clinical trials planned for 2008	[31]
Drug modification of hair follicle size	Tetrapeptide aldehyde proteasome inhibitors	Increased duration of anagen hair growth and increased hair follicle size	Neosil, Inc.	Phase II clinical trials planned for 2008	ClinicalTrials.gov Identifier: NCT00418730
Hair follicle formation	New hair follicle induction using promoters of WNT gene activity	Increased number of new hair follicles per unit area	Follica, Inc.	Phase I clinical trials planned for 2008	[13]
Hair follicle regeneration	Hair follicle replication and/or reactivation using cell implantation	Increased number of new hair follicles and/or increase size of miniaturized hair follicles	Aderans Research, Inc. Intercytex, Inc. Phoenix Bio Co., Ltd	Pilot clinical trials complete Phase II clinical trials planned for 2008 Unknown	[23,32]
Hair follicle redistribution	Surgical transplantation of hair follicles from donor regions to alopecic scalp skin	Modification of hair follicle density in alopecic scalp regions	Multiple	Available commercially	[33]

disorder development research has been on preventing dermal papilla cell responses to androgens or overcoming their response by an increase in hair follicle growth activity. Finasteride and dutasteride both block conversion of testosterone into the more biologically active derivative dihydrotestosterone and administration to balding men arrests and partially reverses hair follicle miniaturization [24–26] (Table 1).

Minoxidil is a hair loss product with the ability to increase the size of miniaturized hair follicles in addition to initiating anagen growth in telogen stage hair follicles [24,27]. Its specific mechanism of action is unclear but as a potassium channel opener, it has a significant positive effect on dermal papilla cells. By promoting increased dermal papilla cell activity, minoxidil might increase the dermal papilla cell signaling to the rest of the pilosebaceous unit resulting in an increase in size. More recently, commercial development of Shh signaling as a method of increasing hair follicle size and modifying the growth cycle has also been reported [28]. It is probable that several other molecular approaches to hair follicle enlargement remain to be discovered.

Hair follicle growth cycle modulation

The key event in the hair growth cycle that contributes to alopecia is the relationship of exogen hair shedding to anagen and telogen. If exogen occurs in a typical sequence during early anagen then old telogen hair fiber is shed but replaced quickly with new anagen hair fiber. By contrast, if exogen occurs predominantly during telogen then the shed hair is not immediately replaced. The result is a hair follicle that does not contain any hair fiber. As such it does not contribute to hair coverage. The longer the duration of telogen perhaps the greater the chance of exogen occurring during telogen. The longer the duration of kenogen when a hair follicle is devoid of any hair fiber, the lack of hair coverage is maintained [4]. Consequently, a priority in the development of treatments for several alopecias is the development of growth cycle modulators that reduce telogen and prolong anagen duration.

Anagen can be induced and prolonged using hair growth promoters including minoxidil, immunophilin ligands (cyclosporine, tacrolimus), and analogs of known hair growth mediators such as keratinocyte growth factor, hepatocyte growth factor, macrophage stimulating protein, Shh and others. By contrast, an anagen to catagen/telogen transition can be activated by toxins, cytostatic drugs, stress and inflammation, and catagen can be induced with numerous endogenously produced mediators [10]. Some of these factors are under active investigation as potential hair growth promoters or inhibitors, though research has yet to reach the clinical trial stage.

Conclusions

Research and development of treatments for hair growth disorders is a relatively small area of interest to the pharma-

ceutical industry despite the considerable commercial potential. In part, the reluctance to enter the field may be because of the complexity of the hair follicle unit and the many issues to be addressed in the development of an effective treatment. Our understanding of how hair follicles function and why changes to the hair follicle density, size and growth cycle occur during disorder development is poorly understood. As a result, no clear avenue of investigation has emerged. However, several biotech companies have been formed in recent years, primarily driven by academic scientists with an interest in hair biology. With time these companies may develop new treatment approaches to hair loss and hypertrichosis.

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