Hair Sciences

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The hair follicle is in the unique position of going through dynamic cyclical changes that allow hairs to be replenished and hairs on different parts of the body to grow to different lengths. In this edition we look at hair cycling through the well-known stages of anagen, catagen, and telogen. In particular we will address the shedding phase during which club fibres are released. I have asked Dr. Gillian Westgate, a well-respected cell biologist, who has worked for many years in research into regulation of hair growth, to give us some insight into current thinking on this subject.

The hair cycle discussed with Dr. Gilliam Westgate

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1. At which point in the anagen phase do androgens act—for example, the beginning as well as the end (i.e., anagen VI)? We know that hair growth inhibitors such as DKK-1 are increased after dermal papilla cells from balding male hair follicles are treated with DHT: Are these only present at certain parts of the cell cycle?

The role of androgens in transforming hair growth through puberty is well-known, however, just as childhood vellus follicles are triggered to become terminal follicles at puberty, pattern baldness, which returns these large follicles back to their vellus state, is also driven by androgens. However, two key questions remain: First, what are the molecular pathways that drive androgen-dependent follicle transformation and, second, do androgens play an active part in the regulation of the normal (non-balding) hair growth cycle? The examination of these questions has revealed insulin-like growth factor 1 (IGF1), Dickkopf-1 (DKK1), and transforming growth factor beta (TGF-beta) as candidate downstream effectors of androgen action.[1,2,3,4] The inhibition of proliferation in the anagen hair follicle bulb matrix has been shown to be driven by androgen induced DKK1 and TGF-beta, which suggests that anagen VI is the target state of the follicle for androgen action in a paracrine fashion. DKK1 is also induced by factors associated with stress; it inhibits the Wnt signaling pathway, which is known for its role in hair growth induction.[5,6] Therefore, any locally elevated DKK1 expression in the dermal papilla in late telogen or very early anagen might also delay or limit the development of the subsequent follicle. However, the subsequent development of a new follicle that is either larger (puberty) or smaller (balding) than the previous one, suggests that early anagen might also be a site of androgen action. The link between androgens, DKK1, and reduced Wnt signaling might influence current debates on de novo hair follicle induction.[6] The androgen responsiveness of the tissue might have an impact on successful development of new technologies in this area by biotechnology companies.

Editor's note: *The current research work on Wnt signaling will be the subject of a future article. It would be interesting to know if the follicular neogenesis stimulated in balding areas would be androgen sensitive or if these hair follicles actually bypass local tissue-dependent androgen effects and even revert to neonatal.*

2. Is there a quantitative way to tell how severe balding will be? For example, do those with later stages of balding have a larger amount of growth inhibitors?

The answer to this question is difficult because balding is a complex process with several factors, both genetic and non-genetic, driving the changes. Furthermore, not every follicle is affected at the same time or to the same extent and follicle transformation can take place for some people within a few years, or may take decades for others. Isolation of dermal papilla cells from transformed vellus balding follicles has been reported with these cells showing altered behavior from non-balding cells.[7,8] Others have investigated and found gender differences for factors such as 5-alpha-reductase and aromatase,[9] which may explain the differences in patterning of hair loss between men and women. Recent genetic studies have found that certain polymorphisms in the androgen receptor gene may predispose to increased risk of developing baldness, and screening tests are already becoming available. Clearly a simple quantitative test is not going to be sufficient to predict the extent of balding, however, as more genetic markers are found and family history is taken into account, it is likely that some predictive ability will become genuinely possible.

3. Exogen has been described as the empty telogen follicle. Is exogen a separate phase in the cell cycle or is it simply the action of telogen hair removal from the hair follicle?

Exogen is now acknowledged as a distinct phase of the hair growth cycle.[10] Exogen does not describe the empty follicle; this state has been labeled kenogen.[11] Exogen is defined by the time between the formation of a telogen club hair and its eventual expulsion from the follicle (termed teloptosis). In most animals, retention of the telogen club hair in the skin is very important to maintaining the fur/coat and the cycle is activated, for example, to change coat colour with season. Human body hair has a longer telogen than scalp hair,[12,13] again suggesting that there is a separation between the processes of telogen and exogen.

4. Is exogen a passive phase or is there an active process that occurs? What evidence is there for each proposal?

There is no definitive answer to this question. While a mechanical (passive) theory seems logical, the growing tip of the new hair fibre occupies a separate epithelial silo from the previous club hair, suggesting that pushing out is too simple an explanation. It is more likely that exogen includes signal-

ling and adhesion factors involved in both active retention and active release of the club hair fibre. This "exogen" terminology can be used to describe club fibres in all types of follicles, enabling a distinction between the status of the club fibre and the status of the follicle. In support of the timing of exogen being regulated, the loss of hair even in man can be linked to seasonal molting,[14] which implicates a timing mechanism in release of the club hair. In rodents, the plucking of the old club hair triggers anagen to be started earlier than normal, however, this is not known to be the case in man.

5. Can we tell from the appearance of the club hair when exogen has commenced?

Figure 1. Club hairs with attached capsules

In pluck trichograms two types of telogen hair can be seen: a club hair with an attached capsule of partially viable cells (Figure 1) or a club hair with little or no material attached (Figure 2). Van Neste recently described a histochemical method to stain plucked hairs that differentiates these two types of club hair.[15] The relative proportions of hairs with these two phenotypes may be used to relate shedding of hair to disorders of the scalp such as dandruff.[16]

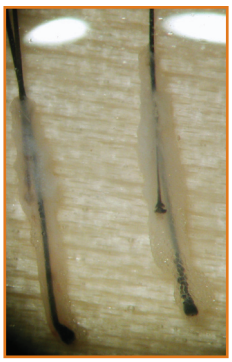

Figure 2. Club hairs with little or no cells attached

6. Does exogen occur prior to the formation of a new hair follicle, that is, before the next anagen phase in humans?

In human scalp tissue, only rarely do we see an example of a telogen club hair still resident in a follicle that has re-entered anagen. However, the rarity of seeing these follicles may be also because telogen follicles are already in low numbers in scalp skin and the transitions are reasonably rapid (weeks) as opposed to anagen, which lasts years. Such follicles are readily apparent in pelage skin in animals.

In a new review on exogen, Higgins, et al., have proposed different models of exogen and the circumstances when each scenario might be important. In human scalp, where hair grows continuously for months and years, the requirement for retained telogen club hairs may be less important.[17] However, early release of the club hair without the follicle re-entering into anagen means overall loss of hair density, which is undesirable. This period of follicle emptiness (latency) was found to increase in time and prevalence with degree of balding in men,[18] and may be overcome either by triggering the follicle back into anagen or delaying exogen.

7. We know that with the initial use of minoxidil telogen effluvium occurs. What is the mechanism?

Minoxidil affects hair growth by triggering the re-entry of telogen follicles into anagen. The clinical benefit from minoxidil usage is that the anagen to telogen ratio is increased as well as overall hair density. As balding is associated with a rise in the proportion of telogen follicles, the shedding seen is more likely to reflect the change from telogen to anagen, than minoxidil affecting the mechanisms of exogen per se. The effluvium seen does, however, suggest that initiation of anagen might be linked to initiation of exogen, and while this seems entirely logical, there is no direct evidence for this.

8. Is there a way to delay exogen? Is this how progesterone works in the pregnant woman or does progesterone prevent anagen to catagen transformation? Do you think that by either delaying or expediating exogen new therapeutic agents could be developed?

The molecular pathways of exogen itself are not understood. It is possible that exogen may proceed with similar cellular differentiation pathways involved in the laying down of the club hair and trichilemma to those involved in maturation of the stratum corneum and subsequent desquamation. There is some evidence for this, as described by Higgins, et al., in a new review on exogen.[17] In scalp, retaining the telogen club hair for longer would clearly offer a benefit of increased hair density—two hairs for each follicle! However, when changes in shedding are observed, they are normally associated with an alteration in the dynamics of the whole hair cycle, and in particular the length of anagen. As anagen duration increases, the proportion of telogen hairs decreases, hence shedding decreases, too, and this is thought to be what happened in pregnancy. The end of pregnancy is followed by a larger than normal shedding event as follicles, held in anagen, proceed to telogen. Maintaining an environment around a club hair such that it is retained for the maximum time within the normal constraints of the follicle cycle and follicle architecture, would be a useful target for intervention. However, education of the consumer or patient as to the role of shedding within the normal hair cycle and its relationship with the length of anagen would also help to reduce concerns about, what for many people, is probably normal hair shedding.

Editor's note: *In the past there have been studies performed by hair transplant surgeons where hair-free skin has been transplanted, with the theory that empty follicles are present that contain germinal centers. These studies have by and large been unsuccessful. While a direct link between shedding of scalp hair and induction of the next anagen remains unproven, in balding sites, there are increased numbers of hairless "latent" telogen follicles that are lacking the intrinsic signaling to induce anagen. As Dr. Westgate and her colleagues write in their full article, "It is essential for animals to grow new hairs before the old club fibers fall out to ensure they are never naked or without key sensory apparatus such as the whisker." This would clearly be beneficial in humans to reduce the impact of hair thinning and suggests that a fruitful link between induced activation of dormant telogen follicles with retention of club fibers would seem a promising area of research to pursue.*

For more information on exogen the following review paper has been accepted for publication in the Journal of Investigative Dermatology *and will soon be available:*

From Telogen to Exogen: Mechanisms underlying formation and subsequent loss of the hair club fibre. Claire Higgins, Gillian Westgate, Colin Jahoda.

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Dr. Gill Westgate, cell biologist and biochemist, obtained a PhD in Regulation of Hair Growth from the University of Utrecht in 1997. Her industry experience was obtained at Unilever Research in the U.K., where she led their Hair Biology research programme. Gill has published many papers on aspects of hair biology and works in collaboration with scientists and Dermatologists in Industry in Academia. Since 2003, Gill has worked as a consultant, combining her experience and knowledge of this area of science with the needs of R&D in Industry to help clients scope, design, and implement projects. Gill is an Honorary Visiting Senior Lecturer with Bradford University, U.K., and is currently working with them to establish the new Centre for Skin Sciences at Bradford. She is also a member of and Secretary to the Board of the European Hair Research Society.