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Commentary

Mechanism of Apoptotic Regulation of Follicular Regression

Toward Understanding the Molecular Basis for Tissue Remodeling and Regeneration

George F. Murphy

From Departments of Pathology and Dermatology, The Center for Dermatopathology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania

"There are one hundred and ninety-three living species of monkeys and apes. One hundred and ninety-two of them are covered with hair. The exception is a naked ape self-named* Homo sapiens*."
—Desmond Morris, *The Naked Ape* (1967)

Perhaps one of the last outposts of cutaneous biology is the hair follicle. Depending on regional anatomy, the hair shaft in humans often represents either an adornment or unwanted vestige, and conventional scientific wisdom has regarded the hair follicle to be of little pathophysiological value. Recent data, however, challenge such beliefs and suggest that study of hair follicles may provide new insights into phenomena as diverse as skin immunity, pigmentation, and tissue remodeling and regeneration. Aside from the endometrium, the hair follicle is unique in its ability to display cyclic regression and regeneration. This amazing feat encompasses intimate interplay between mesenchyme and epithelium. It also involves repeated involution and regeneration that originates from a permanent portion of the follicular apparatus and culminates in generation of an amazingly complex temporary follicular apparatus capable of manufacture of a pigmented hair shaft. But why do we have follicles, why must they cycle, and what can we learn from this regression and regeneration that has for so long been ignored by the scientific community? Only 150 years ago, Virchow averred in reference to the process of desquamation that the epidermis is ultimately "in itself an inert mass, which is gradually removed."[1] Of course, we now know the epidermis to be a factory for manufacture of cytokines and growth factors, and a reservoir for dynamic interactions between keratinocytes, pigment cells, antigen presenting cells, unmyelinated axons, and those T cells that constantly percolate up from the underlying dermis.[2,3] Rather than considering hair follicles to represent passive and pedestrian receptacles for hair shafts, we now are learning of their potential to be extraordinarily informative about the most basic biological processes. Even in those primates that are naked, or nearly so.

Follicular Structure and Function: The Machinery of Cyclic Regeneration

Students of normal or pathological anatomy have long known that the hair follicle is amazingly complex. Hair follicles on the scalp are of substantial length, spanning between the epidermal surface into the subcutaneous fat. The deepest portion (proximal from the vantage point of trichogenesis), or bulb, is rooted in a mast cell- and axon-rich fibrovascular mesenchyme embraced by a claw of basaloid epithelial cells that together form the follicular papilla and hair matrix, respectively. From this emerge multiple distinct layers of specialized epithelium devoted to genesis and support of the hair shaft. Progression of the follicle upward toward the epidermal surface reveals the insertion site of the arrector pili muscle and origin of the sebaceous duct and gland from the wall of the follicular canal. In this general region, a functionally critical yet structurally subtle structure resides, the follicular bulge. It is within this aggregate of relatively undifferentiated and unimpressive basaloid epithelial cells that the ability of the underlying pilar apparatus to regenerate in a cyclic manner appears to reside. Cotsarelis and co-workers[4–7] have convincingly demonstrated this

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Address reprint requests to Dr. George F. Murphy, Jefferson Medical College, Dept. of Pathological Anatomy and Cell Biology, 545 JAH, 1020 Locust St., Philadelphia, PA 19107.

bulge region to represent a stem cell-rich repository that is capable of giving rise to mature anagen follicles after the dramatic involutional phases termed catagen and telogen. In this way, mature anagen hairs periodically yet temporarily regress, a process involving apoptosis whereby entire follicles retract dramatically upward toward the epidermal layer. As the base of the foreshortened follicle approximates the bulge region, the hair shaft is no longer supported by the nutrient-rich anagen bulb, and the hair shaft eventually ejects from the resting telogen follicle, making room for the a new shaft that will result during anagen regeneration. Were it not for the ability of the resilient and persistent bulge to give rise to a new anagen follicle and hair shaft, not entirely dissimilar to the root system of a perennial plant, an inert telogen follicle would be but a gravestone marking the site where a previously healthy hair shaft flourished.

The follicular bulge and what lies above it may therefore be regarded as a permanent portion of a normal follicle, whereas the subjacent canal and shaft are cyclically expressed in relation to the hair cycle. The superficially located infundibulum forms much of what is regarded as the permanent portion of the follicular canal. Incapable of hair shaft formation by itself, the infundibulum is a reservoir for melanocytes and dendritic immune cells that reside in a microenvironmental niche relatively protected from noxious macroenvironmental agents that predominate more superficially. It is therefore not surprising that early repigmentation in treated vitiligo often begins about follicular ostia, and that Langerhans cells that resist depletion by chronic exposure to sunlight tend to cluster in the recesses of infundibular epithelium.[8,9] Indeed, if a time were to come when naked apes are authentically alopecic, one might suspect that the infundibula will persist long after the loss of trichogenic capacity of human follicles.

Why Cycle? Hair and Survival

Lessons as to why the hair cycle is necessary may be learned from an imagined scenario whereby hair follicles are frozen in the anagen phase, incapable of regression into catagen and telogen. Because the length of the hair shaft is primarily determined by the growth rate during anagen (a fraction of a millimeter/day) and the length of anagen (in humans, in the general range of 1000 days), a species in continuous anagen could have the peculiar ability for limitless hair growth. This would result in hair shafts limited in length only by traumatic or intentional excision. From the standpoint of most modern day homo sapiens, with ready accessibility to coiffeurs, this may not seem to pose much of a problem. But from the perspective of a ravenous cheetah pursuing a gazelle at high ground speed, a 10-foot pelage would likely pose significant problems for efficient locomotion. Of course, hair cycles of lower vertebrates are probably even more complex than those in humans, with variations related to seasonal molts and implications for insuring adequate insulation against vicissitudes of climate. However, the fact remains that the hair cycle seems to in part represent nature's built-in form of haircut, and implications for survival in the animal kingdom are not trivial ones.

Pathological Consequences of Follicular Targeting

Neurohormonal and immunological factors are key elements in pathological loss of human hair. Interestingly, disorders characterized by cell injury at or near the region of the stem cell-rich follicular bulge, such as lupus erythematosus and lichen planopilaris, often result in permanent hair loss.[10] In contrast, targeting of the follicular bulb expressed during anagen, as occurs in alopecia areata, results in premature progression of follicles into catagen and telogen stages. Other disorders in which the follicular cycle is perturbed, resulting in abnormal entry into regressive phase of the hair cycle, include adrogenetic alopecia and telogen effluvium, the latter a peculiar yet relatively common condition whereby an inordinately large number of follicles synchronously enter into catagen/telogen, resulting in often massive hair loss. The psychosocial implications of hair loss in humans cannot be underestimated, ranging from potentially devastating issues of self-image in children to expenditure of billions of health care dollars annually by adults for remedies that all too often are, at best, ineffectual. Thus, with regard to the potential biological insights presently encrypted within the hair follicle, as well as the more immediate psychosocial and economic implications, understanding the pathophysiological basis of follicular regression and renewal is of utmost importance.

Molecular Mechanisms of Follicular Regression

It is in this context that the report by Botchkarev and co-workers[11] in this issue of *The American Journal of Pathology* is so exciting. Here convincing data are presented indicating that the transcription factor, p53, is involved in apoptosis-driven regression of hair follicles. In addition to demonstrating co-localization of p53 and apoptotic markers in catagen follicles, Botchkarev and colleagues reasoned that if p53 is important in follicular regression, then p53 knockout mice should exhibit predictable defects in catagen involution. Indeed, their data indicate that knockout animals show retardation of catagen as well as alterations in Bax, Bcl-2, and insulin-like growth factor binding protein-3, all putatively involved in control of catagen and encoded by p53 target genes. This, of course, raises key questions concerning the potential therapeutic efficacy of manipulation of molecular pathways involved in apoptotic follicular involution.

Suddenly, the study of the hair follicle no longer seems trivial or unimportant. In the final analysis, understanding molecular regulation of follicular involution and regression will be paramount to eventual elucidation of the genetic strategies that dictate physiological anagen renewal. And anagen renewal may hold clues that will impact on why organogenesis and tissue remodeling are so much more difficult for humans. . . than for those truly

hairless members of the animal kingdom, like planaria and salamanders!

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