Molecular Basis of Hair Growth Control

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While to refer to it as a "revolution of" may be rather strong, or as a "bare beginning" rather modest, we are, nonetheless, embarking on a new phase in our understanding of hair biology. Recent advances can be found in terms of concepts, systems for study, mechanistic insights, and molecular and genetic aspects of hair follicle growth control. The progress is best documented in the many studies that *associate* cellular and molecular phenomena with aspects of hair growth (Stenn *et al*, 1996; Paus, 1996), attendant with the uncertainties inherent in associative studies.

To support this progress it has been necessary to develop quantifiable systems. Productive animal laboratory models include the pigmented mouse (Paus *et al*, 1989) and the macaque (Uno, 1987). The mouse model allows easy analysis of factors that turn on or suppress anagen growth. The macaque provides a model for studying hormone-dependent patterned alopecia. For organ culture, the system of Philpott (Philpott *et al*, 1990) has been extensively used throughout the research community and applied to rat (Philpott *et al*, 1992), sheep (Bond *et al*, 1994; Williams and Stenn, 1994), goat (Ibraheem *et al*, 1994), and horse (Williams *et al*, 1996) follicles. This organ culture system measures anagen hair growth. Systems for studying telogen follicles in culture or the vellus-to-terminal follicle switch are sorely needed. Although models for studying cells derived from hair follicles have been less successful, such cells can be grown, passaged (Limat *et al*, 1991), immortalized (Weinberg *et al*, 1993; Prouty *et al*, 1996), and analyzed in culture. With notable exceptions (Ihara *et al*, 1991), though, it has not been easy to reform follicles from the dissociated follicle cells in culture. Recently, Lichti and colleagues were able to demonstrate follicular regrowth from dissociated follicle-derived cells by placing the dissociated follicle cells in a subcutaneous skin chamber on the back of nude mice (Lichti *et al*, 1993). These reassembled follicles appear morphologically and functionally normal. Finally, the ultimate model for testing molecule function, the transgenic mouse, is being used in upregulated, downregulated, or null gene animals. The latter approach has, in many cases, led to significant insights into follicular function; in fact, to the dismay of those of us in the field, some of the most spectacular results in transgenesis and hair biology have been made serendipitously by investigators who never thought of hair except as a nuisance on the way to their target organ (e.g., Veis *et al*, 1993; Hebert *et al*, 1994).

As the follicle is the only periodically and regularly regenerating organ system throughout the lifetime of the mammalian adult, hair follicle biology is attracting the attention of researchers as a model system for investigating epithelial-mesenchymal interactions, pattern formation, organogenesis, differentiation, and cycling. Several important lessons are apparent from these collective studies: (i) There are many molecules involved in the control of follicle growth, many of which we have undoubtedly not yet discovered — witness recent reports of newly defined genes for *nude* (Nehls *et al* 1994), *hairless* (Begoña *et al*, 1994), and anhidrotic ectodermal dysplasia (Kere *et al*, 1996). (ii) Many of the genes functioning during *Drosophila* development have homologs that are associated not only with limb bud formation and tooth and feather development in vertebrates, but follicle formation, indicating evolutionary conservation in the molecular mechanisms of morphogenetic signaling. Recent examples include *Msx-1* (Noveen *et al*, 1995; Reginelli *et al*, 1995), *patched*, *sonic hedgehog* (Bitgood and McMahon, 1995; Goodrich *et al*, 1996), homeobox cluster (Bieberich *et al*, 1991; Kanzler *et al*, 1994), and BMP-2/BMP-4 (Lyons *et al*, 1990; Jones *et al*, 1991) genes. (iii) Many of the genes associated with follicle development and cycling are proving to be tools of development, which are used over and over again, phylogenetically and ontogenetically. Obviously, because such genes are fundamental to early development and then again, later, in hair follicle morphogenesis and cycling, the experimentalist must use highly specific, timed, and targeted gene disruptions in order to assess relevance to follicle development and cycling. (iv) Work with null mutant mice have illustrated an important principle regarding hair follicle growth in that there appears to be much less molecular and pathway redundancy in the follicle as compared to other organ systems. While knocking out a pathway in the brain appears to have other back-up systems, knocking out the same pathway in hair follicles leads to significant growth and morphologic changes (e.g., Hebert *et al*, 1994). (v) Tissue localization studies (Goodrich *et al*, 1996), transgenic animal approach (Blessings *et al*, 1993), and differential gene screening (Yu *et al*, 1995) have identified certain molecules at certain regions of the follicle during certain phases of its cycle. Such studies have implicated specific candidate genes in the process of anagen induction (e.g., Paus *et al*, 1994; Danilenko *et al*, 1995), in catagen induction (Hebert *et al*, 1994), and in the pigmentation cycle (Vrieling *et al*, 1994; Millar *et al*, 1995). From these studies it appears that several gene families are particularly important to follicle formation, growth, and cycling, namely, the transforming growth factor-β, fibroblast growth factor, insulin-like growth factor, and epidermal growth factor families (Stenn *et al*, 1996).

Illustrative of the molecular associative studies being made in the field is that of Takakura *et al* (1996), reported on page 770 of this issue, which implicates the platelet-derived growth factor (PDGF) gene and its receptor in follicle development and cycling. Having produced a specific antibody directed against the mouse PDGF receptor, PDGFRα, they find that the receptor is detected and thus is expressed in early newborn, but not fetal, mouse epidermis. In neonatal skin, PDGFRα and its ligand manifest contiguous expression: the ligand is expressed in sebaceous and follicular epithelia, and the receptor is expressed in the surrounding mesenchymal cells. So, from these data we have learned: (i) a new association between dynamic follicle development and the expression of the PDGF receptor and ligand, and (ii) another example of the above-stated principle regarding the repeated use of the same molecular tool, over time and space, in sculpting biologic systems. Takakura and colleagues take the experiment one step further. When they injected antibody to the PDGF receptor into newborn mice, follicle development was delayed, hair canal formation was suppressed, and incidental to our focus here, kidney collecting duct formation was altered, implicating an apparent function for this receptor/ligand system in these systems. Although the conclusions drawn appear

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logical, it appears that a negative control was not described: it would be interesting to know what effect an irrelevant skin-directed antibody might have on hair formation in this model. Nevertheless, if the perturbation produced by the antibodies on follicle growth is specific, we can now begin to ask how the action of the PDGF system affects follicle formation.

When the Takakura *et al* report is combined with other such associative molecular studies, we can envision an environment of molecules that appears important to hair formation and cycling. We are led to believe that these molecules primarily influence follicle health. Another side of the issue, however, has not been addressed, namely, the fact that the follicle is a central part of the skin organ. In most studies the possibility that the follicle might influence basic epidermal and dermal dynamics is not considered despite the fact that it has long been recognized in rodent skin that the whole skin organ changes within the cycle: there is whole organ thickening in anagen and thinning in telogen (Hansen *et al*, 1984). In this respect it is pertinent to ask how other elements of the skin might influence the follicle and how the follicle might influence the skin. Through the molecular analyses of hair growth we hope to have, in the near future, some insight into the latter issue as well as a sufficient understanding of our patients' hair diseases to enable us to forge the tools of effective treatment.

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