Phylogeny of the Hair Follicle: The Sebogenic Hypothesis

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TO THE EDITOR

All hair follicles form and function in association with a sebaceous gland (Sokolov, 1982; Bell, 1986; Wheatley, 1986). Although sebaceous glands may form and function in the absence of a hair follicle (for example, in the eyelid, the vermilion surface of the lips, the nipples and areolae, prepuce, labia minora; Montagna and Parakkal, 1974), hair follicles are not formed, nor do they function, normally in the absence of a sebaceous gland (Williams and Stenn, 1994; Philpott *et al.*, 1996; Sundberg *et al.*, 2000; Porter *et al.*, 2002; Allen *et al.*, 2003; Vidal *et al.*, 2005). The independence of one and not the other suggests that one structure (the sebaceous gland) may have developed before the other (the hair follicle). In this study, we propose an hypothesis suggesting that the hair follicle developed in a primitive multicellular oil gland and that the hair shaft growing from that follicle served initially merely as a wick to draw the product of the gland to the skin surface to fortify the primitive permeability barrier. At the outset, we share with the reader our uneasiness regarding the shadowy relationship we are trying to draw between the structures we see today in all mammals and that structure which our synapsid reptilian ancestor bore, as there is no obvious hair follicle precursor in the extant animal kingdom, which would serve to make a logical and convincing connection (Carroll, 1988). Although there is a wide literature focusing on the phylogeny of the hair follicle (as reviewed by Danforth, 1925; Elias and Bortner, 1957; Maderson, 2003; Wu *et al.*, 2004), our discussion here is limited to the topic of this hypothesis. It has been a surprise to us how rare the sebaceous gland is considered in the discussion of hair follicle evolution and its belittlement regarding skin biology in general (e.g., Kligman, 1963).

For the simplest invertebrates (for example, the worms or insects), the integument consists of a single layer of epithelium overlying loose mesenchymal tissue. Interspersed in the epithelial cells may also be glandular cells, which liberate mucous, chitinous, or calcareous deposits serving to enhance the protective property of the skin surface (Bereiter-Hahn *et al.*, 1984). With the development of the vertebrates, the surface epithelium became multilayered, a property which now allowed the formation of multicellular glands. For primitive water-based animals—the fish and amphibia—the surface is covered with a rich mucous layer; however, as the early tetrapods left the water-saturated environment for dry land, it became critical for the skin to serve as a barrier to water loss, resisting the new, harsh, desiccating surroundings of dry land (Wrench *et al.*, 1980; Maderson, 2003; Jablonski, 2006). To make this adaptation, the epidermis exploited lipid components to generate a permeability barrier (Menon, 2004; Elias, 2005; Lillywhite, 2006). As it is assumed that the initial structural epidermal barrier was inefficient and thus incomplete, the structural barrier function was augmented by glandular oily secretions (Rothman, 1954; Gordon and Olsen, 1995; Maderson, 2003); this feature is actually found in some amphibians today (Lillywhite, 2006). Fundamental to the sebogenic hypothesis is the conclusion that early land dwellers could only have survived on dry land if their epidermal barrier were enhanced by gland-produced lipid. The evolutionary origin of sebaceous glands, like the hair follicle itself, is obscure. Initially, the primary lipid glands were thought to be small, but there would be an evolutionary advantage for those species which had (1) greater oil gland production capacity and (2) an efficient means of conveying lipids to the skin surface. Those animals with more lipid on its surface would have a more complete water barrier. To produce more lipids and retain its protective properties, an epidermis would most advantageously produce a large deep-lying lipid gland. To enhance the release of lipid, from the deep-lying gland, onto the dry skin surface, a wick would be needed. At first that wick might have been a simple, thin, multicellular keratin plug, which would have projected out of the lipid gland duct. With time that wick would develop layers improving its efficiency in growth, formation, and lipid-bearing capacity. Above all, it would be optimal for the wick to have a surface that would provide a direction and a support for lipid flow. Such is found in the cuticle of all hair where the cells making up the cuticle of the wick, or shaft, points downward (Jones, 2004), allowing that shaft exterior to scoop the lipid up to the skin surface. The wick concept is also invoked in the evolution of another cutaneous structure. Oftedal (2002) points out in support of his thesis on the evolution of the mammary gland that a hair shaft egresses from the mammary gland of current day monotremes. Although this wick is lost in the mammary gland of marsupials and the placental mammals, its use as a means of drawing milk fluids to the dry skin surface is well illustrated. By the same argument, a small sebaceous gland or a gland situated on a warm wet surface would not need the wick and that gland could be wickless or hairless.

With time and the need for more efficient homeothermy, those animals with a longer, denser population of wicks would have an advantage. This argument is consistent with the current

notion that thermoregulation developed independent of fur formation (Ruben and Jones, 2000), suggesting that the earliest hair structures generated for another purpose. Nevertheless, once it was fully developed in its lipid transport function, the glandular wick could now serve a role in temperature regulation, in sensation, in protection from the environment, and as a tool for communication with the environment (Maderson, 1972).

Some cellular and molecular works suggest that formation of the hair follicle and the sebaceous gland are very closely related—as the sebogenic hypothesis would predict. Prouty *et al.* (1997) and more recently Y. Zheng (unpublished) found that weak hair-inductive dermal cells will produce sebaceous glands without hair follicle formation. These studies suggest that there is a dose–response and that a low dose gives rise to the sebaceous gland and a stronger dose to both hair follicles and associated sebaceous gland. Experimentally also, by manipulating specific signaling pathways, induction of differentiated sebaceous glands without associated hair follicles have been observed (Allen *et al.*, 2003). Molecular studies also suggest a dose–response effect in sebaceous gland and hair follicle formation. For instance, reducing the Wnt pathway suppresses hair differentiation and gives rise to sebocyte differentiation (Merrill *et al.*, 2001). Recently, it has been shown in transgenic mice that *Smad7* is capable of shifting the skin differentiation program from one forming hair follicles to one forming sebaceous glands by antagonizing WNT/β-catenin signaling (Han *et al.*, 2006). Similarly, inhibiting WNT target genes using a dominant-negative *Lef-1* promotes sebocyte development while inhibiting differentiation of hair lineages (Silva-Vargas *et al.*, 2005). These few cellular and molecular studies suggest that in development certain weak growth factor signals support sebaceous gland formation, whereas only a stronger one induces hair follicle formation. One would suspect that the weak signal would be the earlier one to appear phylogenetically and that the sebaceous gland would appear first.

There are several implications to this hypothesis. The first relates to follicular biology. If the sebaceous gland and hair follicle coevolved, it would appear logical that they would have co-adapted to each other and even become dependent on each other for optimal function. To that end, understanding hair follicle growth must require insight into sebaceous gland growth and vice versa. The second relates to disease. Could it be that in some hair follicle disorders, the malfunction rests in the sebaceous gland and, conversely, in some sebaceous gland disorders, the malfunction rests in the hair follicle? Regarding the former, some evidence has been presented that a sebaceous gland defect might underlie the cicatricial alopecias (the evidence is very sound for the phenotype in the mouse) (Williams and Stenn, 1994; Philpott *et al.*, 1996; Sundberg *et al.*, 2000; Porter *et al.*, 2002; Allen *et al.*, 2003; Vidal *et al.*, 2005). The pathological implication might be that a normal sebaceous gland is critical to the exit of a shaft from the pilary canal (for example Stenn *et al.*, 2006). For alleged sebaceous gland disorders, the primary problem could be in the resident hair follicle; for example, in acne vulgaris. In this disorder, the sebaceous component of sebaceous follicles becomes enlarged. Could the disease result because the resident hair follicle is neotonous (heterochronic): hair follicle growth does not keep up with the rapid and dominant growth of the gland? In one form of acne, Goldsmith (Apert syndrome, Zouboulis *et al.*, 2005) has argued that the observed downregulation of *noggin*, a molecule important to hair growth (absent in the patient), might play a role in the pathogenesis of this disorder. So, for hair follicle physiology, we would argue that a sebaceous gland is needed for normal hair shaft egress and for sebaceous gland physiology, we would argue that a normal shaft is needed for normal sebum egress to the epidermal surface.

In summary, the sebogenic hypothesis states that under the drying conditions of the new land environment, the earliest tetrapods required a lipid cover to enhance the poorly developed epidermal permeability barrier. The lipids making up that cover arose in part from a primitive sebaceous gland. The most efficient gland was large, deep, and had a wick that enhanced lipid spread over the epidermal surface. That wick, the original shaft, arose in the context of a sebaceous gland. Those animals with a strong and prominent sebaceous gland wick would more efficiently transfer lipids from a large, deep, oil gland to the surface and thus more efficiently prevent water loss from its surface. With time animals were selected for more adaptive advantages bestowed by the wick, now the hair shaft, which offered protection from trauma, heat loss, and radiation.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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Activity and Safety of Pegylated Liposomal Doxorubicin as First-Line Therapy in the Treatment of Non-Visceral Classic Kaposi's Sarcoma: A Multicenter Study

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TO THE EDITOR

While several studies have been published regarding AIDS-related Kaposi's sarcoma (KS), and standard first- and second-line treatments exist for those patients (Di Lorenzo *et al.*, 2007), no such standard treatment has been established for Classic KS (CKS). Two randomized trials showed that pegylated liposomal doxorubicin (PLD) is more effective than the doxorubicin–bleomycin–vincristine combination (Northfelt *et al.*, 1998) and the bleomycin–vincristine combination (Stewart *et al.*, 1998). Although PLD has been approved for use in patients with AIDS-associated KS, only a few case reports and small retrospective studies have described the use of PLD in CKS (Gottlieb *et al.*, 1997; Kreuter *et al.*, 2005; Di Trolio *et al.*, 2006; Ezquerra *et al.*, 2006; Di Lorenzo *et al.*, 2008). We conducted an international multicenter retrospective analysis to evaluate the activity and safety of PLD in patients with CKS who had not received previous systemic chemotherapy.

Between 1998 and 2007, eight institutions treated 55 patients with CKS with PLD, as first-line chemotherapy. Median age was 70 years and 15 patients (27%) were older than 75 years (Table 1). A total of 610 cycles of PLD were administered. The schedule of every 3 weeks resulted in a mean received dose intensity of 19.2 mg m^{-2}, or 96% of the planned dose intensity. A dose reduction of 20% was made in 70 cycles (12%) because of grade 3 neutropenia, anemia, or thrombocytopenia. The median number of cycles administered was nine (range, 3–30).

Complete and major responses were observed in 16 (29%) and 23 (42%) patients, respectively, giving an overall response rate of 71%. Minor response was observed in 6 (11%), whereas stable disease and disease progression occurred in six (11%) and four (7%) patients, respectively. Median time to response was 4 months (range, 1.4–7 months) and median duration of response was 25 months (range, 1–55 months). There was a statistically significant correlation between complete response and baseline stage. In fact,

Abbreviations: CKS, Classic KS; KS, Kaposi's sarcoma; PLD, pegylated liposomal doxorubicin