

Hair Follicle Biology, the Sebaceous Gland, and Scarring Alopecias

OF ALL structures in or on the mammalian body, the hair follicle has one of the most complex functions. It must produce, on the skin surface during a long period, a multicellular product, the hair shaft, and yet preserve in the deep dermis an "epithelial finger" that produces the shaft. The cells making up the shaft contain the machinery to produce strong cytoskeletal and cellular adhesions and to be molded by the inner root sheath. The combined hair shaft-inner root sheath structure moves outward as a unit, sliding along a slippage plane provided by the innermost layer of the outer root sheath. The outer root sheath remains behind and intact. The shaft is liberated from the sheath at a level just below the sebaceous duct, and it exits the pilary canal as a sheath-free hair fiber.

Early researchers recognized that removal of the sheath from the shaft was a crucial event in hair processing, without which the shaft could not easily exit the skin. Because sheath dissolution occurs just below the sebaceous duct, it was postulated that the sebaceous gland, or the region of the follicle at this level, might be responsible for its separation.¹⁻³ Experimental evidence for this conclusion was found serendipitously during a study of sheep hair follicle growth in culture,⁴ in which it was demonstrated that the sebaceous gland (or the midfollicular region) was necessary for the dissolution of the sheath from the shaft. Subsequently, this phenomenon was corroborated in human^{4,5} and horse follicles.⁶ These findings implicated an important role for sebaceous glands in skin besides synthesizing and liberating its emollient.

What the active agent might be in sebum that causes sheath dissociation is not known but is under current investigation.

We tested the idea that the sebaceous gland is central to hair biology by asking the question, What happens to hair follicles in an animal that has defective sebaceous glands? This question led us to the *asebia* mouse mutant,⁷ a mouse that forms hair follicles with markedly hypoplastic sebaceous glands. After the first hair cycle, this mouse has progressive hair follicle loss and striking scarring alopecia. In a detailed histological study,⁸ we found that cornified plugs in the hair canal apparently impede hair shaft egress. The histological findings suggested that the shaft, prevented from exiting the pilary canal, pushes the follicle in reverse toward the dermis, giving rise to the abnormally long and deep anagen structures seen. In support of the idea of distal pilary canal resistance, we could demonstrate that the shaft often perforated the bulb (the proximal follicle) in association with follicle-destructive chronic inflammatory and foreign body reactions. In the absence of normal sebaceous gland function, then, not only is sheath inadequately separated from shaft, as we found experimentally, but there is also follicle destruction and dermal scarring.

Although chronic, progressive alopecia develops in all 3 spontaneous *asebia* mutations (*ab*, *abJ*, and *ab2J*), scarring alopecia in association with sebaceous gland pathology is not unique to the *asebia* mouse mutant. Images published of the *bareskin* mouse mutant (mapping to mouse chromosome 11) indicate that the inner root sheath is retained much higher into the pilary canal (in-

fundibulum) than normal; moreover, in this mouse mutant, sebaceous glands are morphologically abnormal.⁹ Harlequin ichthyosis mice also show alopecia associated with thick epidermal scales.¹⁰ These mice have hypoplastic sebaceous glands and manifest large and compact cornified plugs within their pilary canal (infundibulum). These mice die at 10 to 12 days of age, prior to the anticipated onset of a true scarring alopecia.

Observations with these mouse mutants led us to reconsider the role of the sebaceous gland in human scarring alopecias. Most of the inflammatory, scarring alopecias in humans show an intense inflammatory cell reaction about the follicle at the level of the isthmus and upper infundibulum. Since tissue destruction in this region might include the "bulge" zone, the putative site of follicular stem cells has been implicated as the mechanism for follicular destruction seen in these disorders.¹¹ In fact, in most if not all forms of the "classic" inflammatory, scarring alopecias (alopecia mucinosa, lupus erythematosus, lichen planopilaris, pseudopelade of Brocq, follicular degeneration syndrome, and scleroderma), the sebaceous glands appear to be a common victim during the early course of the disease. Similar observations have been made with sebaceous adenitis with hyperkeratosis in dogs and cats.¹²⁻¹⁴ It is generally believed that the sebaceous gland is destroyed before the follicle—the sebaceous gland is lost first. The mechanism for sebaceous gland loss may be multifold. One such mechanism is that sensitized lymphocytes might attack the proliferating basal cells of the sebaceous gland as observed in graft-vs-host disease.¹⁵

As a representative example of a scarring alopecia, the earliest changes in the follicular degeneration syndrome consist of sebaceous gland loss in the presence of a relatively intact hair-forming epithelium.¹⁶ The hair-forming epithelium is eventually destroyed late in the disease course, but this appears as a sequel to the sebaceous gland loss.

Our studies and those of the literature do not explain why the sebaceous gland is lost in the early phases of the human scarring alopecias or even if there is a cause-and-effect relationship. In the case of the mouse, however, the data are compelling. The asebia mouse has shown us that the mutation of a gene unique to sebaceous gland function leads to a scarring alopecia.^{9,17}

In conclusion, the hypothesis we are proposing is that many of the scarring alopecias, which have proven to be mechanistically obscure, are based on primary sebaceous gland pathological features. In vitro studies indicate an important role of the sebaceous gland–isthmus in dissociating the internal root sheath from the shaft. Several mouse mutants showing pathologic features of the sebaceous gland manifest keratinous follicular plugging. If inadequate sebaceous gland function could lead to hair follicle destruction, perhaps we should

reassess our treatment protocols and give more attention to the superficial-lying sebaceous gland than to the deeper-lying anagen follicle.

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REFERENCES

1. Auber L. The anatomy of follicle producing wool-fibres, with special reference to keratinization. *Trans R Soc Edinburgh*. 1951;62:191-254.
2. Straille WE. Possible functions of the external root sheath during growth of the hair follicle. *J Exp Zool*. 1962;150:207-224.
3. Gemmell RT, Chapman RE. Formation and breakdown of the inner root sheath and features of the pilary canal epithelium in the wool follicle. *J Ultrastruct Res*. 1971;36:355-366.
4. Williams D, Stenn KS. Transection level dictates the pattern of hair follicle sheath growth in vitro. *Dev Biol*. 1994;165:469-479.
5. Philpott MP, Sanders DA, Kealey T. Whole hair follicle culture. *Dermatol Clin*. 1996;14:595-607.
6. Williams D, Siock P, Stenn K. 13-*cis*-Retinoic acid affects sheath-shaft interactions of equine hair follicles in vitro. *J Invest Dermatol*. 1996;106:356-361.
7. Gates AH, Karasek M. Hereditary absence of sebaceous glands in the mouse. *Science*. 1965;148:1471-1473.
8. Sundberg J, Boggess D, Sundberg BA, et al. Asebia (*ab2J*) a mouse mutation with sebaceous gland hypoplasia, dermal scarring, and lipid abnormalities: characterization and comparison with asebia-J. *J Invest Dermatol*. In press.
9. Sundberg JP, King LE. Mouse models for the study of human hair loss. *Dermatol Clin*. 1996;14:619-632.
10. Sundberg JP, Boggess D, Hogan ME, et al. Harlequin ichthyosis: a juvenile lethal mouse mutation with ichthyosiform dermatitis. *Am J Pathol*. 1997;151:293-310.
11. Lavker RM, Miller S, Wilson C, et al. Hair follicle stem cells: their location, role in hair cycle, and involvement in skin tumor formation. *J Invest Dermatol*. 1993;101:16S-26S.
12. Baer K, Shoulberg N, Helton K. Sebaceous adenitis-like skin disease in two cats. *Vet Pathol*. 1993;30:437.
13. Power HT, Ihrke PJ, Stannard AA, Backus KQ. Use of etretinate for treatment of primary keratinization disorders (idiopathic seborrhea) in cocker spaniels, West Highland white terriers, and basset hounds. *J Am Vet Med Assoc*. 1992;201:419-429.
14. Rosser ER, Dunstan RW, Breen PT, Johnson GR. Sebaceous adenitis with hyperkeratosis in the standard poodle: a discussion of 10 cases. *J Am Anim Hosp Assoc*. 1987;23:341-345.
15. Murphy GF, Lavker RM, Whitaker D, Korngold R. Cytotoxic folliculitis in GvHD: evidence of follicular stem cell injury and recovery. *J Cutan Pathol*. 1991;18:309-314.
16. Sperling LC, Sau P. The follicular degeneration syndrome in black patients: "hot comb alopecia" revisited and revised. *Arch Dermatol*. 1992;128:68-74.
17. Zheng Y, Eilertsen KJ, Ge L, et al. Stearoyl CoA desaturase gene is expressed in mouse pilosebaceous apparatus and is defective in the asebia mutant mouse. *J Invest Dermatol*. 1999;112:550.