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Lipids to the Top of Hair Biology

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Abstract

Little attention has been given to the impact of lipid metabolism on hair follicle biology and pathology. Three recent papers (one in the current issue) describe a major effect of altered lipid metabolism on hair growth. A direct link was made to at least one form of cicatricial alopecia, but the role lipids play in other follicular pathologies, such as the acneiform conditions, are inadequately explored and must be tested.

Because hair follicles originate within an organ whose primary role is barrier to water loss, one would assume that hair follicle structure and function must also be dominated by lipid components: lipids to repel water, lipids to maintain the permeability barrier, lipids to maintain structure, and lipid messengers. Yet, when serious attention is given to this deceptively simple appendage, the focus is usually on its protein structure and peptide signaling. Where lipids have been implicated in hair follicle pathology, the findings have been made serendipitously (e.g., Sundberg *et al.*, 2000; Moulson *et al*., 2003; Westerberg *et al.*, 2004; Lee *et al.*, 2007; Shimomura *et al*., 2009), without a deep understanding of the finding within the big picture. For those of us who live with the follicle, it is satisfying to note that in the past 3 years as many papers have appeared describing fundamental lipid pathways, which, when perturbed, cause severe hair follicle injury.

In 2007 Wan *et al*. described a mammary gland–specific peroxisome proliferator–activated receptor-γ (PPARγ) knockout mouse that showed no phenotype itself. But pups suckling on the mutant dam developed an alopecia induced by oxidized lipids carried in the milk. Once weaned and freed of the toxin-containing milk, the pups regained their hair. The affected skin exhibited abnormal follicle growth and cycling, dilated pilary canals, follicle arrest in an abnormal catagen/telogen, and a dermis housing inflammatory cells. The contribution made by Karnik *et al.* (2009) related to the association of PPARγ deficiency with a form of human cicatricial alopecia. By gene array analysis and real-time PCR, this group demonstrated the downregulation of PPARγ and PPARγ-regulated genes required for cholesterol biosynthesis, lipid metabolism, and peroxisome biogenesis in patients with lichen planopilaris (LPP). When these investigators knocked out PPARγ expression in the stem cells of mouse hair follicles, not only did the mutation recapitulate many of the gene expression and histological findings of LPP, it also induced follicle cyst formation, dystrophic catagen/telogen forms, and dermal inflammation.

The current issue of the *Journal of Investigative Dermatology* features work from a group with long-term interest in cholesterol metabolism. Cholesterol has been suspected of playing

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CONFLICT OF INTEREST
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a role in normal hair biology, as illustrated by the hair loss suffered by some patients taking cholesterol-reducing statins. In the current study, Evers *et al*. (2010) asked the inverse question. They studied the effect of an upregulated cholesterol synthesis pathway in mouse hair follicles by knocking out the expression of Insig proteins, inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-limiting enzyme of cholesterol biosynthesis. Insig proteins normally control cholesterol synthesis by decreasing it whenever sterol levels are high. In this model, sterol precursors accumulated in the hair follicle epithelium, causing distortion of whiskers and hair shafts; ectatic, keratin-plugged distal follicles; and abnormally arrested catagen/telogen forms.

The approaches taken in the three studies have fundamental differences, such as in the expression site of the hair follicle mutation: the mammary gland, hair follicle stem cell lineage, and epidermis and hair follicle sheath. The cells expressing the mutation also differ: endothelial/hematopoietic cells (Wan *et al*., 2007), hair follicle epithelial stem cells (Karnik *et al*., 2009), and oral epithelium/epidermis/hair follicle outer root sheath (Evers *et al*., 2010). Nonetheless, many of the changes observed are remarkably similar. For example, hair shaft distortion, distal follicle ectasia (pseudocyst), keratin plugging of the pilary canal, dystrophic catagen/telogen forms, and dermal inflammation are found to a variable degree in all three studies. In addition, the phenotype in the first two studies is dramatically reversible, so, despite significant follicle distortion, under the proper rescue therapy normal follicles reform, a feature no doubt reflecting the regenerative power of the follicle itself.

Equating the phenotypic similarities of the three mutants with the data at hand may perhaps be a stretch in logical thought, although the downstream factors accumulating in the absence of PPARγ are common, including the upregulated prostaglandin and lipoxygenase pathways and downregulated lipid metabolic pathways. None of the studies defines a mechanism to explain how the cellular follicular changes occur: why do the distal follicles dilate, why does the follicle lumen fill with keratin, why do the hairs crimp? What causes dermal inflammation? What is the link between altered lipid metabolism, inflammation, and disrupted hair follicles? The three studies clearly show an apparent toxic effect on hair follicle cycling—the pathology is clear. The role of these lipid metabolic pathways in normal hair follicle biology and the mechanism by which changes in these pathways cause the pathological phenotype remain unclear, and such questions need attention.

A trivial explanation for the common features of the variants in these reports might be that upon insult the hair follicle can muster only one, or a few, cell responses to injury. One such response would be the inflammation induced by proinflammatory lipids or sterols. We now know that there is an extensive, delicately balanced interaction between the immune and metabolic pathways, an interaction that is dysfunctional in chronic metabolic diseases such as type 2 diabetes and atherosclerosis (Hotamisligil, 2006; Wellen *et al*., 2007). Although there are short-term compensatory and adaptive measures that keep this delicate balance in check, the outcome could be detrimental if one arm overwhelmed the other in the long run. For example, Karnik *et al*. (2009) have reported that LPP includes a chronic disturbance of metabolic homeostasis in hair follicle cells due to inactivation of PPARγ. The PPAR and liver X receptor families of transcription factors seem to be crucial for modulating the intersection of metabolic and inflammatory pathways (Bensinger and Tontonoz, 2008). Activation of these transcription factors inhibits the expression of several genes involved in the inflammatory response, with the implication that loss of activation of these factors will not only disturb metabolic homeostasis but also induce inflammatory damage to tissues, such as the hair follicle.

A second cellular response to disturbed lipid homeostasis could be organelle stress. The endoplasmic reticulum (ER), mitochondria, and peroxisomes are important sites for the

metabolism of lipids, especially phospholipids and cholesterol, and for the monitoring of their intracellular status (Murphy *et al.*, 2009). For example, cholesterol sensing is initiated at the ER membrane through the transcription factor sterol-regulatory-element-binding protein (Colgan *et al.*, 2007). Organelle stress induced by chronic disturbance of metabolic homeostasis in hair follicle cells could lead to the generation of reactive oxygen species by the ER and mitochondria, leading to activation of stress and inflammatory signaling cascades and oxidative damage (Ron and Walter, 2007; Todd *et al*., 2008). If ER and mitochondrial homeostasis were not restored, the organelles could activate apoptotic pathways in the hair follicle, destroying it.

A third mechanism linking lipid homeostasis to the hair follicle is lipid modification of signaling proteins such as Hedgehogs (Hhs) and Wnts, which are necessary for hair follicle morphogenesis and cycling. The N-terminus of Hh becomes modified by the fatty acid palmitate on a conserved cysteine residue, whereas the C terminus is cholesterol modified. Wnt molecules are palmitoylated on the first conserved cysteine (C77), a residue that is present on all Wnts. Genetic data suggest that lipid modification localizes the Wnt and Hh proteins to membranes, a requirement for Wnt and Hh protein activity (Nusse, 2003). A site-directed mutation in one of the endogenous *Hh* genes in the mouse (*sonic hedgehog*) demonstrated that loss of cholesterol modification attenuates the range of Hh activity, and perhaps even a loss, of Hh activity (Lewis *et al*., 2001). Alterations in fatty acid metabolism or cholesterol biosynthesis as a result of PPARγ loss (Wan *et al.*, 2007; Karnik *et al*., 2009) or sterol precursor accumulation (Evers *et al*., 2010, this issue) could prevent appropriate lipid modification of Wnt and Hh and thereby interfere with hair follicle morphogenesis and cycling.

Evers *et al*. postulate that disruption of the Sonic Hh pathway might have been caused by the high concentrations of tissue sterols observed, although the possibility that other morphogenetic pathways, such as Wnt (Bazan and deSauvage, 2009) and Notch (Demehri and Kopan, 2009), are also affected by tissue sterols could not be ruled out. We have observed similar histological changes in mutants ranging from a *stearoyl coenzyme A desaturase* gene mutant in the asebia mouse (Sundberg *et al*., 2000) to the follicle changes in a mouse with *Sox 9* gene knockout (VPJ Vidal, personal communication, 2006). Nevertheless, any or all of the mechanisms discussed may plausibly connect the toxic insult and the cellular changes observed.

A parallel for some of the pathological changes described in these models can be found in several forms of clinical cicatricial alopecia as well as in acne vulgaris. On the basis of the observations reported by Evers *et al*., we would predict that lipids play a significant role in hair follicle morphogenesis and cycling and that alterations in lipid pathways underlie many clinical hair follicle disorders.

Clinical Implications

- Although lipids are a small part of hair composition, cholesterol plays important roles in hair biology.
- In animal models, genetic errors in lipid metabolism cause both inflammation and abnormal hair growth, resembling several dermatological disorders.
- Opportunities for pharmacological intervention in hair disorders may be derived from new knowledge about lipid metabolism.

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