

Research Update

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The management of cicatricial alopecia currently centers on the working classification of primary cicatricial alopecia that separates two main groups: those with predominantly lymphocytic inflammation and those with predominantly neutrophilic inflammation. This is based on examination of scalp biopsies with light microscopy, which cannot separate the various clinical subtypes in these groups.

It became clear that molecular studies were needed to understand the cicatricial alopecias. Microarray analysis of lichen planopilaris (affected and unaffected scalp biopsies) was compared to normal control biopsies. These studies revealed major biological pathways that were up-regulated, including inflammatory and cell-death pathways, whereas lipid metabolic and hair follicle cycling pathways were down-regulated. Abnormal lipid metabolism and cholesterol biosynthesis, and buildup of pro-inflammatory (toxic) lipids were noted in both affected and unaffected scalp biopsies in lichen planopilaris (LPP), whereas the inflammatory changes and hair follicle and sebaceous gland destruction were marked in affected scalp biopsies only. This suggested that the inflammatory changes may not represent the primary events in the pathogenesis of LPP. Amongst the down-regulated genes in LPP was the significantly decreased expression of the peroxisome proliferator-activated receptor gamma (PPAR gamma) in hair follicles and sebaceous glands. Further experiments pointed to a key role for PPAR gamma in the pathogenesis of LPP.

The role of PPAR gamma in the hair follicle changes in LPP was supported by the creation of a mouse model. Targeted deletion of PPAR gamma in hair follicle stem cells in mice resulted in a progressive, pruritic, scarring alopecia. These studies all suggested that PPAR gamma is crucial for healthy pilosebaceous units, and it is the loss of this function that triggers the pathogenesis of LPP (Karnik et al, 2009). However, the triggers for initiating this loss, such as environmental, genetic, microbial, or dietary triggers, are not known.

In frontal fibrosing alopecia (FFA), another predominantly lymphocyte-mediated cicatricial alopecia, similar PPAR gamma dysfunction was noted in gene expression studies. In central centrifugal cicatricial alopecia (CCCA), PPAR gamma was not decreased, although a co-activator of PPAR gamma was decreased. In the predominantly neutrophilic primary cicatricial alopecias, further molecular study is needed.

Other studies have also pointed to the importance of normal lipid pathways in maintaining healthy hair follicles. The nursing pups of mice that had targeted deletion of PPAR gamma in their mammary glands developed hair loss, whereas the mothers themselves had no visible changes. The PPAR gamma deficiency caused toxic lipid accumulation in the lactating mammary gland, and the

inflammatory lipids in the milk caused hair loss in nursing pups. When the pups were weaned, their hair loss was reversed (Wan et al, 2007).

Gene expression profiling at Case Western Reserve University is continuing for all types of cicatricial alopecia. The clinical variants of the lymphocytic and neutrophilic groups probably reflect differences in the underlying gene expression patterns. In future, a new classification of the cicatricial alopecias may be possible based on molecular features:

- a) Disorders with abnormal lipid/metabolic changes due to decreased PPAR gamma expression (LPP, FFA). This may lead to uphill treatment strategies with the use of PPAR gamma agonists (Mirmirani et al, 2009).
- b) Other nuclear receptor or metabolic changes.

Recent observations suggest that some collective brainstorming might be helpful to unravel the cicatricial alopecias. One striking observation is the increased incidence of FFA since it was first described in Australia by Kossard in 1994. The recent increase has been noted worldwide. Another observation is that the aryl hydrocarbon receptor is up-regulated in microarray analysis. This xenobiotic receptor (receptor for foreign substances), in response to dioxin-like substances, is known to suppress PPAR gamma.

Dioxin is generated from automobile emissions, industrial waste and forest fires. Dioxins seem to accumulate in animal fat and fish, and food seems to be the major source of dioxin exposure in humans. Once in the body, it has a slow rate of metabolism and remains for long periods. Agent Orange is dioxin and causes loss of sebaceous glands. These observations suggest that plotting zip codes and cicatricial alopecia, specifically FFA, may be informative.

Karnik P, Tekeste Z, McCormik TS, Gilliam AC, Price VH, Cooper KD, Mirmirani P. Hair follicle stem cell-specific PPAR gamma deletion causes scarring alopecia. *J Invest Dermatol* 129; 1243-57, 2009.

Wan Y, Saghatelian A, Chong LW, Zhang CL, Cravatt BF, Evans RM. Maternal PPAR gamma protects nursing neonates by suppressing the production of inflammatory milk. *Genes Dev* 21:1895-908, 2007.

Mirmirani P, Karnik P. Lichen planopilaris treated with a peroxisome proliferator-activated receptor gamma agonist. *Arch Dermatol* 145: 1363-66, 2009.